PHIL DAVF: STUDY OF PHIL® EMBOLIC SYSTEM IN THE TREATMENT OF INTRACRANIAL DURAL ARTERIOVENOUS FISTULAS

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PHIL DAVF: STUDY OF PHIL® EMBOLIC SYSTEM IN THE TREATMENT OF INTRACRANIAL DURAL ARTERIOVENOUS FISTULAS

Clinical Protocol
Protocol Number: CL11005
IDE Number: G170203

Principal Investigators:
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Alan Boulos, MD

Study Sponsor: MicroVention Inc.

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Sponsor Signatures:

Signature: _____ Date: _____

Robert Gash / Senior Director, Clinical Operations

Signature: _____ Date: _____

Shiela Warner / Director, Medical Affairs

Signature: _____ Date: _____

Sapna Singh / Director, Regulatory Affairs

CONTENTS

LIST OF ABBREVIATIONS

AE	Adverse Event
CDA	Confidentiality Agreement
CFR	Code of Federal Regulations
CMP	Clinical Monitoring Plan
CRO	Contract Research Organization
CTA	Computed Tomography Angiography/Angiogram
CV	Curriculum Vitae
dAVF	Dural Arteriovenous Fistulas
DMSO	Dimethyl Sulfoxide
DSA	Digital Subtraction Angiography/Angiogram
eCRFs	Electronic Case Report Forms
EDC	Electronic Data Capture
FAS	Full Analysis Set
FDA	Food and Drug Administration
ICF	Informed Consent Form
ICH	Intracranial Hemorrhage
IDE	Investigational Device Exemption
IFU	Instructions For Use
IRB	Institutional Review Board
ISO	International Organization for Standardization
MRA	Magnetic Resonance Angiography/Angiogram
mRS	Modified Rankin Scale
nBCA	N-Butyl-Cyanoacrylate
NHND	Non-Hemorrhagic Neurological Deficits
NIHSS	National Institute of Health Stroke Scale
HEMA	Hydroxyethyl Methacrylate
PHIL	Precipitating Hydrophobic Injectable Liquid
PI	Principal Investigator
PVA	Polyvinyl Alcohol
QOL	Quality of Life
SAE	Serious Adverse Event
SRS	Stereotactic Radiosurgery
UADE	Unanticipated Adverse Device Effect

INVESTIGATOR AGREEMENT

I. **Conduct of the Study**. As the principal investigator for the clinical study, I hereby agree to:

1. Provide Sponsor with a current copy of my curriculum vitae, which includes my relevant experience including dates, locations, extent and type of experience.
2. Certify that ☐ **I have** / ☐ **I have not** been involved in a study or other research that was terminated (attach to this signed agreement a written explanation of the circumstances that led to such termination)
3. Conduct the study in accordance with this Agreement, the investigational plan, 21 CFR Part 812 and other applicable Food and Drug Administration (FDA) regulations, as well as the conditions of approval imposed by the reviewing Institutional Review Board (IRB) and/or FDA
4. Change the protocol only by agreement with Sponsor, the IRB and the FDA except when necessary to protect the safety, rights or welfare of subjects. If such a change occurs, I will promptly inform the Sponsor of this event
5. Appoint only qualified sub-investigators to assist in the conduct of the study.

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6. Supervise all testing of the device involving human subjects
7. Permit the investigational device to be used only with study subjects under my or a sub-investigator's supervision
8. Ensure that the requirements for written informed consent under 21 CFR Part 50 are met;
9. Disallow any subject to participate in the clinical study before obtaining IRB and FDA approval
10. Protect the rights, safety, and welfare of subjects under my care
11. Promptly notify Sponsor of any adverse effects during the study
12. Provide sufficient accurate financial disclosure information to Sponsor as required by 21 CFR Part 54 and to promptly update this information if any relevant changes occur during the study and for one year following completion of the study
13. Refrain from supplying the investigational device to any person not authorized under 21 CFR Part 812 to receive it
14. Return to Sponsor any remaining supply of the investigational device or otherwise dispose of the device as the sponsor directs

II. **Records**. I also agree to maintain the following accurate, complete and current records relating to the clinical study:

1. All correspondence with another investigator, an IRB, Sponsor and its agents, the monitor, and FDA
2. Records of receipt, use or disposition of the investigational device that relate to (a) the type and quantity of the device; (b) the dates of receipt, (c) the batch number, lot number or code mark; (d) the names of all persons who received, used, or disposed of each device; and (e) why and how many units of the device have been returned to Sponsor, repaired, or otherwise disposed of

3. Records of each subject's case history and exposure to the device, including signed and dated consent forms, medical records, progress notes of the physician, individual hospital charts and nursing notes
4. Documents that evidence informed consent and, for any use of a device without informed consent, any written concurrence of a licensed physician and a brief description of the circumstances justifying the failure to obtain informed consent
5. Copy of the protocol and all amendments
6. Written documents showing the dates of and reasons for each deviation from the protocol
7. Any other records that Sponsor, the IRB or the FDA may require to be maintained by regulation or by specific requirement.

III. **Record retention**. I agree to maintain all records required by Section II above during this study and for a period of two years after the later of the following two dates: a.) the date on which the study is terminated or completed, or b.) the date the records are no longer required for purposes of supporting a premarket approval application or a notice of completion of a product development protocol. Should I choose or need to withdraw from the responsibility to maintain the records as required by this Section and transfer custody of the records to any other person who will accept responsibility for them under this Section, I shall provide notice of transfer to Sponsor and FDA no later than 10 working days after the transfer occurs.

IV. **Inspections**.
1. I agree to permit authorized FDA employees, at reasonable times and in a reasonable manner, to enter and inspect any of my premises where devices are installed, used or implanted, or where records of results from use of the devices are kept.
2. I agree to permit representatives of Sponsor, the monitor, the IRB, and the FDA, at reasonable times and in a reasonable manner, to inspect and copy all records relating to the study

V. **Reports**. I agree to report the following:
1. Unanticipated adverse device effects, to Sponsor and the reviewing IRB as soon as possible, but in no event later than 10 working days after discovery;
2. Withdrawal of approval by the reviewing IRB;
3. Progress reports, to Sponsor, the monitor, and the reviewing IRB, at least annually;
4. Emergency deviations from the investigational plan to protect the life or physical wellbeing of a subject, to Sponsor and the reviewing IRB as soon as possible, but in no event later than 5 working days after the emergency occurred;
5. Use of the investigational device without informed consent, to Sponsor and the reviewing IRB within 5 working days after the use occurs;
6. A final report, to Sponsor and the reviewing IRB, within 3 months after termination or completion of the study or my part of the study;
7. Accurate, complete, and current information about any aspect of the study, upon request, to the reviewing IRB and the FDA.

Investigator name	Date
Investigator signature	DD/MMM/YYYY

PROTOCOL SUMMARY

Study devices:	PHIL® (Precipitating Hydrophobic Injectable Liquid) Embolic System (PHIL™-25% / 30% / 35%)
Title:	PHIL DAVF: Study of PHIL® Embolic System in The Treatment of Intracranial Dural Arteriovenous Fistulas
Study design:	The study is a prospective, multicenter, single-arm, clinical study evaluating outcomes in subjects with intracranial dural arteriovenous fistulas treated with PHIL® device.
Study purpose:	To evaluate the safety and probable benefit of MicroVention, Inc. PHIL® Liquid Embolic material for the treatment of intracranial dural arteriovenous fistulas.
Number of subjects:	Up to 75 subjects may be enrolled and treated with the PHIL® device to ensure follow-up is available for 60 subjects in the United States.
Number of sites:	Up to 25 study sites
Duration of study:	Enrollment duration: approximately 36 months Subject follow-up: 6 months following completion of intracranial dAVF treatment. Expected subject participation: up to 9 months Total study duration: approximately 45 months
Primary measured outcomes	• Safety: The proportion of subjects with neurological death or ipsilateral stroke within the first 30 days following completion of the first PHIL treatment procedure. Neurologic death is subject death reported as having resulted from a neurologic cause. Stroke is defined as a new focal neurological deficit in a defined vascular distribution of abrupt onset with symptoms persisting for >24 hours AND a neuro-imaging study or other quantitative study that does not indicate a different etiology. This includes ischemic and hemorrhagic strokes. It is expected that fewer than approximately 15% of subjects will experience neurologic death or an ipsilateral stroke within the first 30 days following completion of the first PHIL procedure treatment. • Probable benefit: Angiographic occlusion of the pre-specified target vessel intended for treatment at procedure following completion of the first PHIL treatment procedure. Angiographic occlusion of the pre-specified target vessel is defined as cessation of flow at the point of embolic agent administration at the target vessel. It is expected that approximately 60% of the subjects will achieve cessation of flow of the pre-specified target vessel when treated with PHIL.
Secondary measured outcomes	The following outcomes will be measured: • The proportion of subjects with neurological death or ipsilateral stroke within the first 30 days following completion of all PHIL treatments. • Angiographic occlusion of the pre-specified target vessel intended for treatment at procedure following completion of all PHIL treatments. • New-onset or worsening of permanent morbidity at 6 month follow-up. • New-onset Intracranial hemorrhage (ICH) at6 month follow-up.

	• New-onset of cranial nerve palsy at 6 month follow-up • Clinically significant technical events during the PHIL embolization procedure(s) including but not limited to reflux of embolic material, migration of the embolic material, catheter entrapment or damage, and vessel dissection. • Device-related adverse events at procedure and 30 days. • Device-related mortality at procedure and 30 days. • Procedure related adverse events including complications of arterial puncture, contrast-induced nephropathy, radiation-induced injuries, renal and anesthesia-related complications. • New-onset of device- or procedure-related neurological deficit or adverse event, or worsening of a previous neurological complaint, disorder, deficit, or adverse event that is unresolved at 6 month follow-up even if not associated with a change in mRS.
Additional measured outcomes	The following outcomes will be measured: • Improvement of neurological symptoms • Number of procedures required to treat the fistula at 6 month follow-up • Procedure time (defined as first to last fluoroscopic or digital subtraction angiographic acquisitions) • Radiation exposure (dosage and time) • Injected volume of PHIL • Neurological modified Rankin Scale (mRS) at 3 and 6 month follow-up • Self-reported QOL questionnaire, EQ-5D at 6 months follow-up • Unplanned adjunctive treatments
Inclusion criteria	1. Subject is ≥22 and ≤80 years of age. 2. Subject is willing and capable of complying with all study protocol requirements, including specified follow-up period. 3. Subject or authorized legal representative must sign and date an IRB approved written informed consent prior to initiation of any study procedures. 4. Subject has an intracranial dAVF that can be treated by embolization with PHIL without the need for other liquid embolization products (e.g., Onyx, nBCA). 5. Subject has an intracranial dAVF that is deemed appropriate for embolization with PHIL without significantly increased risk to collateral or adjacent territories.
Exclusion criteria	<u>General</u> 1. Subject has a modified Rankin Scale of >3 or has another neurological deficit not due to stroke that may confound the neurological assessments. 2. Subject having multiple dAVFs to be treated. 3. Subject has dAVF requiring pre-planned treatment with adjunctive treatments (i.e. embolic coils, surgical resection, etc). 4. Subject presents with an intracranial mass or is currently undergoing radiation therapy for carcinoma or sarcoma of the head or neck region. 5. Subject has known allergies to DMSO (dimethyl sulfoxide), iodine or heparin. 6. Subject with a history of life threatening allergy to contrast media (unless treatment for allergy is tolerated). 7. Subject is experiencing (or has experienced) an evolving, acute, or recent disabling ischemic stroke, has conditions placing them at high risk for ischemic stroke or has exhibited ischemic symptoms such as transient ischemic attacks, minor strokes, or stroke-in-evolution within the prior 3 months timeframe. 8. Subject has had an acute myocardial infarction within 30 days prior to index procedure.

9. Subject has had or plans to have any major surgical procedure (i.e. intra-abdominal or intrathoracic surgery or any surgery/interventional procedure involving cardiac or vascular system) within 30 days of the index procedure.
10. Subject is currently participating in another clinical study which may interfere with outcome measurements for this study.
11. Female subject is currently pregnant.
12. Subject has an acute or chronic life-threatening illness other than the neurological disease to be treated in this study including but not limited to any malignancy or debilitating autoimmune disease
13. Subject has existing severe or advanced comorbid conditions which significantly increase general anesthesia and/ or surgical risk including but not limited to advanced COPD, uncontrolled hypertension / diabetes, congestive heart failure, chronic or acute kidney disease.
14. Subject has evidence of active infection at the time of treatment.
15. Subject has dementia or cognitive or psychiatric problem that prevents the patient from completing required follow-up.
16. Subject has co-morbid conditions that may limit survival to less than 24 months.
17. Subject has a history of bleeding diathesis or coagulopathy, international normalized ratio (INR) greater than 1.5, or will refuse blood transfusions.

<u>Angiographic</u>

1. Subject has severe calcification or vascular tortuosity that may preclude the safe introduction of the sheath, guiding catheter, or access to the lesion with the microcatheter.
2. Subject has a contra-indication to DSA, CT scan or MRI/ MRA
3. Subject has a history of intracranial vasospasm not responsive to medical therapy
4. Subject has extra-cranial stenosis or parent vessel stenosis > 50% proximal to the target lesion to be treated.

Study visits and assessments

Visits		Screening / Baseline	PHIL procedure(s)	Discharge(s)	30-day follow-up[1]	3-month Follow-Up[1]	6-month Follow-Up[1]	Unscheduled
Assessments	Method	Office / clinic	Hospital visit		Office/clinic	Office/clinic	Office/clinic	Office/clinic/hospital
Informed consent		X						
Assess inclusion / exclusion		X						
Demographics and medical history		X						
dAVF information (classification)		X						
modified Rankin Scale score		X			X	X	X	X
NIH Stroke Scale score		X			X[2]	X[2]	X[2]	X[2]
Hunt and Hess Stroke Scale score[3]		X			X	X	X	X
Physical exam (dAVF symptoms)		X		X[4]	X	X	X	X
Clinical chemistry & hematology		X		X	X	X	X	
QOL (EQ-5D)		X[5]					X	
dAVF and embolized vessel data			X					
Irradiation Information			X					
PHIL procedure			X					
Device usage			X					
Angiography		X[6]	X[7]		X[8]	X[8]	X	X[9]
Adverse event / technical event			X	X	X	X	X	X

	1. Follow-up to be scheduled after completion of the last PHIL treatment. 2. Required at any time point if signs of new-onset neurological deficit are present. 3. Required in the case of presenting hemorrhage. 4. This exam should be completed within 2-days post-procedure. 5. To be performed within 7 days in advance of the procedure. 6. DSA preferred but CTA/MRA can performed depending on subject health status. 7. Must include a pre-treatment and post-treatment angiogram. 8. Required if subject presents with symptoms relating to the treated dAVF (DSA, CTA or MRA acceptable). 9. Standard Care imaging (DSA, CTA or MRA acceptable).
Statistical analysis:	Descriptive statistics will be used to summarize the data collected in this study.

REVISION HISTORY

Revision	Effective Date
A	18 Jan 2018
B	26 Apr 2018
C	19 Mar 2020
D	14 Jul 2020
E	03 Apr 2023

SUMMARY OF CHANGES

REVISION D TO REVISION E

Section	Change	Rationale
Protocol Summary, Section 3.2 and 7	Added secondary measured outcome: New-onset of device- or procedure-related neurological deficit or adverse event, or worsening of a previous neurological complaint, disorder, deficit, or adverse event that is unresolved at 6 month follow-up even if not associated with a change in mRS.	To reflect the correct secondary measured outcome.

KEY ROLES

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1 BACKGROUND INFORMATION

1.1 INVESTIGATIONAL PRODUCT

The PHIL® device is a non-adhesive liquid embolic agent comprised of a Triiodophenol-(lactide-co-glycolide) acrylate and hydroxyethyl methacrylate (HEMA) co-polymer dissolved in DMSO (dimethyl sulfoxide). An iodine component is chemically bonded to the co-polymer to provide a radiopacifier element during fluoroscopic visualization. The PHIL® Liquid Embolic System consists of a sterile, pre-filled, 1.0 mL syringe of PHIL® liquid embolic, a sterile, pre-filled 1.0 mL syringe of DMSO, and microcatheter hub adaptors.

1.2 CLINICAL BACKGROUND

Arteriovenous fistulas are a type of arteriovenous malformation whereby blood is shunted directly from the arterial system to the venous system, bypassing the capillary bed. Dural arteriovenous fistulas (dAVFs) are a rare type of acquired intracranial vascular malformation consisting of a pathologic shunt located within the dura mater of the brain.[1] These lesions have been categorized by Awad et al[2], Borden et al[3], and Cognard et al[4] according to their locations and patterns of venous drainage. Dural arteriovenous fistulas (dAVFs) can be observed anywhere on the dural layer meninges of the cranium and spine. This condition accounts for 10-15% of all intracranial arteriovenous malformations diagnosed.[5] These fistulas can be congenital or acquired diseases. When observed as acquired diseases, they are most often encountered in males between the age of 50 and 60 years old. DAVFs present with a wide spectrum of symptoms or none at all, and come with varying range of risk of clinical sequalae. A thorough evaluation of the anatomy and venous drainage is crucial to determining the best treatment strategy. Acute presentation with intracranial hemorrhage occurs in up to 65% of patients, and patients with a previous intracranial hemorrhage may have up to a 35% risk of another neurologic event within 2 weeks.[6] Endovascular embolization has become the primary treatment approach for DAVFs. The goal of endovascular therapy is to achieve complete obliteration of the fistulous point between the feeding arteries and the draining veins. This can be safely accomplished by occluding the draining veins, which often results in complete closure of the lesion, unlike in cerebral arteriovenous malformations.

1.2.1 LOCATION OF DAVFS

DAVFs can be observed anywhere on the meninges of the cranium and spine, however, the most frequent locations are the transverse sinus, cavernous sinus, tentorium cerebelli, and superior sagittal sinus. Other frequent locations include the anterior cranial fossa, Torcular, vein of Galen and straight sinus, superior or inferior petrosal sinus, foramen magnum, and condylar vein.

1.2.2 PATHOGENESIS

The pathogenesis of the dAVFs is not fully understood. Most of the lesions are believed to initiate from thrombosis of a dural venous sinus. This occlusion causes venous congestion and subsequent venous hypertension. Over time, this increased venous pressure dilates small capillaries, which open direct shunts between dural arteries and veins, creating dAVFs.[7]

The fistulas will initially drain into larger venous sinuses. However, with increased venous pressure, the veins will undergo remodeling with hyaline deposition and intimal proliferation. This remodeling will cause blood to reflux into the cortical veins instead of solely flowing into the venous sinuses.[7] Unlike drainage into the dural sinuses, cortical veins are not protected by the dura and cannot withstand high arterial pressure.[8] Therefore, DAVFs with cortical drainage are at a higher risk for Intracranial hemorrhage (ICH).

Several antecedent events have also been cited as causing the development of DAVFs. The most common referenced preceding event is head trauma. Other events that have been reported include craniotomy, acupuncture, cerebral infarction, hormonal alterations observed in pregnancy and menopause, increased systemic thrombotic activity, otitis, sinusitis and tumors. [7]

1.2.3 CLASSIFICATION

The Borden classification system (Table 1 is based on the site of venous drainage (dural sinus and/or cortical vein) if cortical venous drainage is present. In this classification system, Type I DAVFs drain directly into the dural venous sinus without cortical venous reflux. Type II DAVFs drain into a dural sinus with Cortical Venous Reflux. Type III lesions drain completely into a cortical vein. Patients with Type II and III DAVFs are at highest risk of ICH and/or neurologic deficits. [9, 10]

TABLE 1 CLASSIFICATION OF DAVF

Type	*Borden System* *Pattern of venous drainage*
I	Drainage directly into dural venous sinus
II	Drainage into dural venous sinus with cortical venous reflux
III	Drainage directly into cortical veins only

In this study, the Borden System (Figure 1), will be used to classify dAVFs.

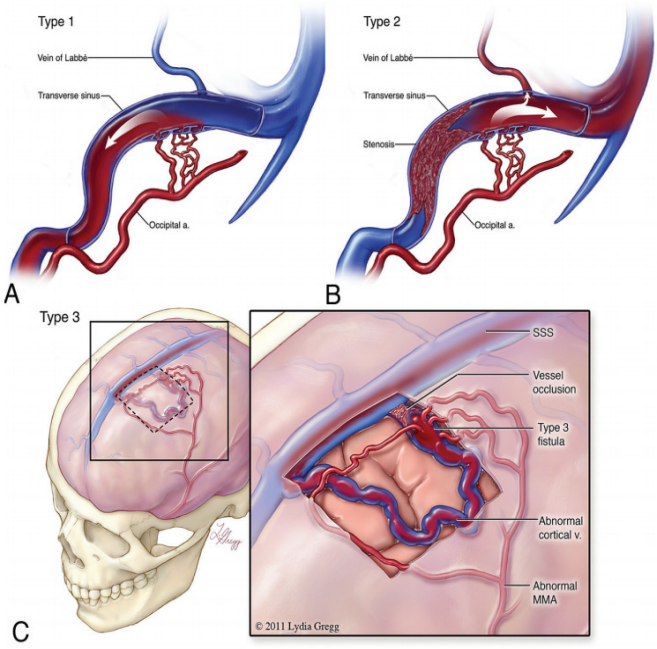

FIGURE 1 BORDEN SYSTEM

1.2.4 SYMPTOMS/CLINICAL PRESENTATION

DAVFs can be asymptomatic or present with symptoms that range from Pulsatile Tinnitus (low risk/benign) to Intracranial Hemorrhage and Severe Neurologic Deficits (aggressive/high risk) (Table 2). Their clinical and angiographic presentation dictate the urgency of the treatment.

TABLE 2: CLINICAL PRESENTATIONS OF DAVFS

Clinical group	*Manifestation*
Low risk (benign)	Pulsatile tinnitus Orbital symptoms
Aggressive / high risk	Intracranial Hemorrhage (ICH) Seizures Altered mental status, dementia Hydrocephalus Cranial Nerve Palsies Loss of motor functions

Benign dAVFs tend to be found in the transverse sigmoid sinus and cavernous sinus. Patients with transverse sigmoid sinus fistulas develop pulsatile tinnitus. Patients with cavernous sinus fistulas often develop orbital symptoms, including chemosis, proptosis and conjunctival infection. [10] Aggressive/high-risk dAVFs may present with hemorrhage, non-hemorrhagic neurological deficits or even death. Patients with superior sagittal sinus fistulas develop symptoms of global venous congestions as seizures, hydrocephalus and dementia. Patients with brainstem dAVFs can develop symptoms of cranial nerve palsies and loss of motor functions. [10]

The more aggressive neurological symptoms occur in cases of dAVFs with retrograde cortical venous drainage (Type II to III). Van Dijk et al. reported that the persistence of cortical venous drainage yields an annual mortality rate of 10.4%. Excluding events at presentation, the annual risk for hemorrhagic or non-hemorrhagic neurological deficits during follow-up was 8.1% and 6.9%, respectively, resulting in an annual event rate of 15%. [11] Duffau et al. reported a 35% rebleeding rate in the two weeks following an initial hemorrhage. [6] Davies et al. reported a 20% annual mortality and morbidity rate. [12]

1.2.5 TREATMENT OF DAVFS

The decision to treat DAVFs must be based on the patient's clinical presentation, current status (age, medical condition, comorbidities), and type of lesion (location, classification, and angiographic features) and the clinical judgement of the treating physician. The primary goal of the treatment is complete excision/obliteration of the fistula and interruption of all feeding arteries. [13] This will eliminate the cortical drainage and the resulting risk of hemorrhage. High-grade lesions should be treated early to avoid the risks of hemorrhagic and non-hemorrhagic neurological deficits (NHND). Close follow-up is necessary to assess the development of new symptoms or progression of existing ones. [9]

DAVF with Cortical Venous Reflux (CVR) carries a high risk of ICH or ischemic venous infarction due to arterialization of the draining veins. Optimal treatment involves complete shunt occlusion as soon as possible. Before the use of surgical or radiosurgical treatments, the present consensus is to first attempt to treat such fistulas by using an endovascular approach. [14, 15, 16, 17]

The therapeutic armamentarium for the treatment of dAVFs includes conservative monitoring, endovascular therapy, surgical excision and radiation therapy (Sections 1.2.5.2 - 1.2.5.5). Some cases may use a combination of the above for treatment. Based on the published literature (Table 3), the majority of dAVF treated with liquid embolic

material are treated with single procedure (52%-88%). After treatment with liquid embolic material, some patients are referred for adjunctive therapies include coiling (4%-12%), surgery (6%-10%) or radiosurgery 5%-15%).

TABLE 3 SINGLE EMBOLIZATION VS ADJUNCTIVE THERAPIES FOR DAVF

Author	N	Agent	Single embolization N (%)	Adjunctive therapies N (%)
Abud (2011)	42	Onyx	27 (64%)	Coils - 5 (12%) Surgery - 4 (10%)
Baltsavias (2014)	170	nBCA	145 (85%)	Coils - 13 (8%)
De Kuekeleire (2011)	20	Onyx	17 (85%)	Radiosurgery - 1 (5%)
Li (2016)	46	Onyx	24 (52%)	Coils - 2 (4%) Radiosurgery - 7 (15%)
Maimon (2011)	17	Onyx	15 (88%)	Surgery - 1 (6%)
Nogueira (2008)	12	Onyx	8 (67%)	Radiosurgery - 3 (12%)

1.2.5.1 CONSERVATIVE MONITORING

Type I fistulas are usually conservatively monitored until the symptoms become disabling to the patient. Treatment may only include symptom management.

1.2.5.2 ENDOVASCULAR THERAPY

Endovascular management has become a first-line treatment for dAVFs.[18] The treatment is aimed at complete elimination of the arteriovenous shunt. Incomplete treatment may allow recruitment of collateral vessels and persistent risk of hemorrhage.[19] The endovascular treatment options are particulates, coils and liquid embolics (N-Butyl-Cyanoacrylate (nBCA), Onyx, PHIL).

1.2.5.2.1 PARTICULATE EMBOLIZATION

The particulates are small and irregular flakes of Polyvinyl Alcohol (PVA) used for permanent occlusion within a blood vessel. The PVA particles are easy to handle but are no longer favored because complete dAVF obliteration is almost impossible.[9] It is also associated with higher rates of recanalization from collateral recruitment.[20]

1.2.5.2.2 COIL EMBOLIZATION

In transvenous embolization of dAVFs, coils are deposited at the site of arteriovenous shunting. This almost always allows a complete cure of the fistula.[21, 22, 23, 24, 25] When possible, it can result in cure without having to involve the myriad of feeding arteries.[20] However, venous anatomy may prohibit access to the affected fistula.

1.2.5.2.3 LIQUID EMBOLIC AGENTS

N-Butyl-Cyanoacrylate (n-BCA), Onyx, and PHIL are types of liquid embolic agents used to embolize dAVFs.

N-BCA has been extensively used during the past three decades. It is injected in liquid form and solidifies on contact with ionic solutions such as blood, resulting in occlusion of the desired vascular bed. The use of n-BCA has been used to treat dAVF with variable success. Complete and lasting fistula obliteration can be achieved, particularly when the embolic material reaches the fistulous connection.[9] The major disadvantage of this technique is the somewhat unpredictable nature of n-BCA polymerization, often leading to inadequate penetration into the fistula.[26] Another potential disadvantage is the fact that n-BCA is an adhesive agent and risks permanent retention of the microcatheter.[26] Because of this adhesive effect, the injection duration for n-BCA must be short, and an experienced operator is essential. As a result, multiple procedures are often necessary, and more than one (1) treatment approach may be required for complex lesions.[9]

Onyx is a non-adhesive embolic agent which consists of ethylene-vinyl alcohol co-polymer dissolved in various concentrations of DMSO (dimethyl sulfoxide) with micronized tantalum powder for radiopacity. On contact with blood, DMSO rapidly diffuses from the mixture, causing in situ precipitation of the polymer without adhesion to the vascular wall. The polymer initially precipitates within the peripheral area of the blood vessel, with secondary occlusion of the central vessel. This allows a longer more controlled injection with better penetration of the vascular bed compared with n-BCA. The operator also has the option of stopping the injection if Onyx begins to track toward another arterial pedicle, venous outflow vessel, or suspected dangerous anastomoses. The injection can then be resumed after several seconds because Onyx will track toward the low-pressure environment of the residual fistula. Another technical advantage of Onyx is the possibility of obtaining control angiograms during the embolization. This allows assessment of the remaining fistula flow and the changing hemodynamic pattern of a complex lesion. A major advantage of Onyx is the ability to cure complex multifeeder fistulas via a single pedicle. [27]

The use of Onyx is associated with some disadvantages as well. Since micronized tantalum powder is added to Onyx for radiopacity, it must be shaken for at least 20 minutes to achieve homogenous radiopacity. This increases the procedure time. The long and multiple waiting times between each injection due to the precipitation process with Onyx, also increases fluoroscopy times and consequently increases radiation doses. [28] The increased radiation doses can result in alopecia and radiation burns. The delayed health risks of the prolonged exposure to radiation are unclear and difficult to assess. Despite its cohesive property, Onyx can adhere to the microcatheter and cause breakage. [10] In high flow lesions, Onyx can pass through the shunt, resulting in distal embolism. [29] Other reported events including angiotoxicity from DMSO, and cranial nerve injury. [9]

PHIL is a non-adhesive liquid embolic agent comprised of a Triiodophenol-(lactide-co-glycolide) acrylate and hydroxyethyl methacrylate (HEMA) co-polymer dissolved in DMSO. An iodine component is chemically bonded to the co-polymer to provide a radiopacifier element during fluoroscopic visualization. Refer to Section 1.4 for additional information on the PHIL device.

There are several publications presenting data using glue and the non-adhesive agents, Onyx and PHIL (Table 4); the majority of these represent clinical experience outside the United States as there is no approved liquid embolic agent for treatment of dAVF. Publications with data on less than 10 patients were excluded. Use of glue is associated with lower rates of complete embolization at the completion of the procedure (33% to 66%) [30 , 32, 33] when compared to non-adhesive agents. Complete embolization rates at the completion of the procedure for non-adhesive agents range from 42% to 94% for Onyx [10, 26, 27 , 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45] and 77% for PHIL [1].

TABLE 4 COMPLETE EMBOLIZATION RESULTS AFTER INTRACRANIAL DAVF TREATMENT

Author	N	Agent	Complete embolization at procedure	Complete embolization at 3 months
Abud (2011)	42	Onyx	81%	--
Baltsavias (2014)	170	nBCA	66%	--
Chew (2009)	12	Onyx	75%	--
Cognard (2008)	30	Onyx	66%	76%
De Kuekeleire (2011)	20	Onyx	86%	--
Elhammady (2010)	12	Onyx	42%	--
Hu (2011)	50	Onyx	82%	--
Huang (2009)	14	Onyx	86%	--
Kirsch (2009)	150	PVA / nBCA / coils	54%	
Lamin (2016)	26	PHIL / PHIL+Onyx / PHIL+coils	77%	--
Li (2016)	46	Onyx	67%	--
Long (2011)	21	Onyx	85.7%	--
Lv (2009)	40	Onyx	63%	--
Maimon (2011)	17	Onyx	94%	--
Natarajan (2010)	32	Onyx	81%	
Nogueira (2008)	12	Onyx	83%	--
Rabinov (2013)	35	Onyx	83%	77%
Rabinov (2013)	21	nBCA	33%	--
Stiefel (2009)	28	Onyx	74%	--
Wenderoth (2016)	32	Onyx / PHIL	100%	--

From the publications presenting data on embolization outcomes (Table 4), a low number of procedural complications and/or neurological events (Table 5) were reported.

TABLE 5 OBSERVED MORBID EVENTS AFTER INTRACRANIAL DAVF TREATMENT

Author	N	Procedural complications	Neurological events
Abud (2011)	42	• Venous thrombus (2)	• Facial nerve paresis (2) • Neuropathic pain (2)
Baltsavias (2014)	170	• nBCA migration / embolization to unintended location (2) • Vessel spasm (1) • Venous thrombus (1)	• Permanent neurologic deficit (4)
Chew (2009)	12	• microcatheter ruptured; fragment remained in occipital artery (1)	
Cognard (2008)	30		• Third and fourth cranial nerve palsies and fifth cranial nerve territory pain (1) • Acute cerebellar syndrome (1)
De Kuekeleire (2011)	20	• Entrapped microcatheter broke upon removal (4)	• Facial nerve palsy (1) • Hemithermoanesthesia (1) • Protracted nuchal rigidity (1)
Elhammady (2010)	12		• Complete CN VII palsy (1) • Horner syndrome; partial CN VI palsy (1) • complete CN III; partial CN V palsy (1)
Ghobrial (2013)	12	• Femoral dissection (1)	• Stroke (1) • Postembolization associated hemorrhage (1)
Hu (2011)	50	• Onyx migration to unintended location (1) • Microcatheter broke; migrated into artery (1)	• Stroke (1) • Cranial nerve palsies with diplopia and dysphagia (1)
Huang (2009)	14	• Vessel perforation (1) • Onyx reflux / catheter retention (1)	
Kirsch (2009)	150	• Groin hematoma (2) • Venous perforation (1)	• Intracranial hemorrhage without permanent neurological deficit (3) • Cerebral hemorrhage resulting in death (1) • SSS thrombosis (1)
Lamin (2016)	26	• Worsening ataxia due to draining vein thrombosis (1)	
Li (2014)	46	• Broken microcatheter (1) • Onyx migration (1) • Bradycardia (1)	• Facial nerve paresis (2) • Oculomotor nerve paresis (1)
Long (2011)	21	• Onyx reflux into normal vasculature (2)	• VI cranial nerve palsy (1)
Lv (2009)	40	• Microcatheter gluing (1)	• Permanent neurological deficit (2) • Hemifacial hypesthesia (3) • Hemifacial palsy (2)
Maimon (2011)	17	• Emboli (1)	• Transient fourth nerve palsy (1)
Natarajan (2010)	32	• Microcatheter gluing (2)	• Cranial nerves V and VII palsies (1)
Rabinov (2013)	35		• Major neurological events (3)
Rabinov (2013)	21		• Major neurological events (2)

1.2.5.3 SURGERY

An increasing number of intracranial dural arteriovenous fistulae (DAVFs) are amenable to endovascular treatment. However, a subset of patients with high-risk lesions requires surgical intervention for complete obliteration. Due to

the efficacy of endovascular treatment, surgery is currently indicated in cases in which endovascular approaches have failed or are not feasible. Certain anatomic locations of dAVFs are more amenable to surgery. These include the floor of the anterior cranial fossa and the superior sagittal sinus, where arterial access is difficult and/or sacrifice of the sinus is undesirable. [9] However, surgery can be technically demanding. It places adjacent brain parenchyma at risk, and carries risks common to all craniotomies. [13]

There is consensus that intracranial dural arteriovenous fistulae (dAVF) with direct (non-sinus-type) or indirect (sinus-type) retrograde filling of a leptomeningeal vein should be treated due to the high risk of neurological deficits and hemorrhage. No consensus exists on treatment modality (surgery and/or embolization) and, if surgery is performed, on the best surgical strategy. Wachter et al reported a transient and permanent surgical morbidity rates of 11.9% and 7.1%, respectively in a series of 42 patients who underwent microsurgery for dAVFs. [46]

1.2.5.4 STEREOTACTIC RADIOSURGERY (SRS)

Stereotactic Radiosurgery primarily involves low-risk lesions or those that are not amenable to endovascular or surgical approaches. Lesions are irradiated with 20 –30 Gy, which causes vessel thrombosis and fistula closure during a latency period ranging from several months to a year. Until completion of vessel thrombosis, the hemorrhage risk remains elevated, so radiosurgery is inappropriate as the primary treatment in dAVFs with cortical venous drainage. Early results have been encouraging, with obliteration rates as high as 93% when combined endovascular embolization but have also demonstrated rates as low as 50% when SRS is used as a sole therapy. [9]

1.2.5.5 RADIOSURGERY

Radiosurgery is rarely proposed in the treatment strategy of dAVFs. Soderman et al. reviewed more than 1600 intracranial arteriovenous shunts treated from 1978 to 2003 (25 years) in which 58 cases were dAVFs. [47] In 41 cases with follow up angiography at 2 years, 28 cases (68%) were obliterated, ten had significant flow reduction (24%) and three were unchanged. Two patients had rebleeding with parenchymal hematoma at 2 and 6 months. One patient had a radiation induced complication 10 years after radiosurgery. The authors concluded that the major disadvantage of radiosurgery is the time elapsed before obliteration and the risk of persisting shunts.

1.2.6 RATIONALE

Intracranial dAVFs may produce a wide variety of symptoms. Individual risk is evaluated by a precise analysis of the venous drainage. The decision to treat is based on this analysis. Treatment strategy is decided by a multidisciplinary neurovascular team and must consider the individual risk of each dAVF. Embolization is, in most cases, proposed as the first treatment option and often succeeds to obtain a complete and definitive cure of the dAVF. Surgery may be required in some locations or in the case of embolization failure. Radiosurgery is rarely indicated because it is not always efficient and because of the time required for shunt obliteration and the risk of bleeding in this period.

Liquid embolics have distinct characteristics that make them a principle treatment option in the obliteration of dAVFs. They can flow through complex vascular structures so that the surgeon does not need to target the catheter to every single vessel. 10 There is little choice available in the US market for the liquid embolic treatment of dAVF. Currently, nBCA (TRUFILL n-Butyl Cyanoacrylate, Cordis) and Onyx (Medtronic) are the only liquid embolic agents available. Both are approved by FDA for presurgical embolization of cerebral arteriovenous malformations. However, they have been used off-label for dAVFs. This use demonstrates the unmet medical need for the patients suffering with dAVFs.

The aim of this study is to evaluate the use of PHIL in the management of intracranial dural AVFs.

1.3 RISK/BENEFIT REVIEW

1.3.1 POTENTIAL BENEFITS

The PHIL system, when used as directed, is expected to be safe and beneficial when used to treat intracranial dural arteriovenous fistulas. The intent is to stabilize the clinical course of the subject evaluated by clinical assessment and potentially improve the disability score as measured by modified Rankin Scale (mRS).

1.3.2 KNOWN POTENTIAL RISKS

Potential risks associated with the PHIL system can be associated with device use, general anesthesia, catheterization and diagnostic imaging for subjects with dAVF. The components of the PHIL device, Triiodophenol-(lactide-co-glycolide) acrylate and hydroxyethyl methacrylate (HEMA) co-polymer dissolved in DMSO (dimethyl sulfoxide), are generally recognized as safe.

The potential risks and discomforts associated specifically with treating dAVF with the PHIL HUD are expected to be similar to the risks associated with the use of other commercially available, standard of care devices. Potential risks/adverse events associated with the PHIL system, general anesthesia, catheterization and diagnostic imaging for subjects with dAVF are outlined below, as reported in the published literature and. Risks/adverse events may be local or systemic in nature and vary from minor reactions to major reactions that may be life-threatening or result in death. Potential risks are stratified into three categories based on the maximum individual rate published in peer-reviewed literature: possible (<25%), less likely (<10%), and rare (<1%).

Risks associated with PHIL

Possible (<25%)	Cranial nerve palsy Death Entrapped catheter or damage Hemorrhage Incomplete embolization of the fistula Migration of the device Neurological deficit Draining vein thrombosis Postembolization associated hemorrhage Acute cerebellar syndrome
Less likely (<10%)	Angionecrosis Blocked catheter Blockage of other blood vessels Change in mental status Clinically significant reflux of embolic material Dementia Development of clinical symptoms associated with “mass effect” Device fracture with embolism Fistula perforation, rupture, or dissection Focal deficits Headache Infection/inflammation Intracerebral bleeding Intracranial hypertension Loss of consciousness Loss of motor function Pulsatile tinnitus Myelopathy Ocular symptoms Pain Progressive neurologic symptoms related to dAVF Retreatment required Seizure Stroke, hemorrhagic or ischemic Temporary local pain following vascular occlusion Thromboembolic migration Transient ischemic attack (TIA) Venous infarction Vessel perforation or dissection
Rare (<1%)	Allergic reaction Air embolism Arterial spasm Cerebral edema Normal perfusion pressure breakthrough Perforation or rupture of blood vessel Vasospasm

Risks associated with the endovascular procedure and general anesthesia:

- allergic reaction (Symptoms vary from mild hives and pruritus to circulatory collapse)
- air embolism
- anesthesia reaction
- anxiety
- arterial spasm
- aspiration
- back pain
- bronchospasm
- cardiac and/or respiratory arrest
- cardiac arrhythmias
- cerebral edema
- confusion, coma, or other change in mental status
- contrast reaction
- cranial nerve damage
- damage to access vessels
- death
- development of clinical symptoms associated with 'mass effect'
- dizziness
- facial or laryngeal edema
- fever
- fistula formation
- fistula perforation
- fistula rupture
- generalized seizures
- groin injury, including bleeding, pain, vessel or nerve damage
- headache
- hematoma
- hemorrhage
- hydrocephalus
- hypertension
- hypotension
- infection / inflammation
- injury to normal vessels
- intracerebral bleeding / intracranial hemorrhage
- loss of consciousness
- nausea
- neurological deficits
- parenchymal hemorrhage
- peripheral thromboembolism
- progressive neurologic symptoms related to fistula
- pseudoaneurysms
- pulmonary edema
- pulmonary embolism
- renal failure
- retroperitoneal hematoma
- seizure
- sepsis
- stroke, hemorrhagic or ischemic
- subarachnoid hemorrhage
- thromboembolism
- thrombosis
- transient ischemic attack
- transient ischemic deficits including hemiparesis, dysphasia, sensory changes, or visual disturbances
- unintended vascular occlusion
- upper respiratory congestion
- urticaria
- vasospasm
- ventricular fibrillation
- vessel dissection
- vessel perforation
- vomiting
- wound infection

Risks associated with imaging required for dAVF treatment:

- Radiation induced burns appearing as reddening of the skin, blistering and even ulceration
- Hair loss due to injury of skin where hair grows caused by radiation
- Cataracts caused by radiation
- Developing a radiation-induced cancer later in life
- Renal injury associated with contrast

The probability and degree of these risks increase as the amount of radiation exposure increases during procedures and as a result of the cumulative effect of radiation exposure. Exercise necessary precautions to limit X-radiation doses to patients and operators by using sufficient shielding, reducing fluoroscopy times, and modifying X-ray technical factors where possible.

A potential risk associated with participation in this study is confidentiality of protected health information may be breached due to study-related activities beyond those of routine clinical care.

1.3.3 Measures to minimize subject risk

Several safeguards are incorporated into the study to minimize subject risk. All preclinical device testing for the PHIL system was performed in accordance with regulations and recognized standards. All test results have passed the required specifications supporting reasonable safety for this clinical product.

At each investigational site, the study will be conducted under the direction of a qualified physician experienced with endovascular procedures including dAVF treatment with liquid embolics. All participating investigators have experience conducting clinical research and have adequate personnel to assure compliance to the study protocol.

The Investigator will be responsible for monitoring the safety of subjects who enter this study and for alerting the sponsor/designee of any study-related events that seem unusual and/or unanticipated for his/her site. The Investigator will be responsible for the appropriate medical care of the subjects during the study in connection with protocol procedures for his/her site. The Investigator will remain responsible for providing any appropriate health care options after a subject's completion or discontinuation from the study due to adverse events.

Information that may personally identify a subject will not be collected on electronic Case Report Forms (eCRFs) or other study-related documentation to be provided to the Sponsor.

All study data will be monitored by individual site and across all sites. Clinical outcomes of all study subjects will be routinely monitored by the Sponsor during the study. Safety outcomes-related events will be reviewed by the Sponsor's Medical Monitor. In the event of unforeseen or increased risks to subjects encountered during the study, the study may be suspended or terminated.

1.3.4 Justification

Independent publications with the PHIL device provide clinical data to support the reasonable safety of the device. Therefore, the Sponsor considers the benefits of using the PHIL device to outweigh the risks in the defined subject population.

1.4 Compliance

This study will be conducted in full conformity with:

- 21 CFR Part 50 – Protection of Human Subjects
- 21 CFR Part 54 – Financial Disclosure by Clinical Investigators
- 21 CFR Part 56 – Institutional Review Boards
- 21 CFR Part 812 – Investigational Device Exemptions

1.5 Study population

Subjects enrolled in this study will be those presenting with intracranial dural arteriovenous fistulas.

Refer to Section 4 for the selection criteria.

Medicare eligible patients may be enrolled in the PHIL dAVF study. These Medicare patients are not expected to respond differently to treatment compared to other patients enrolled in the study. Therefore, the results of this trial are likely to be highly generalizable to the Medicare population.

2 STUDY OBJECTIVES

The study objective is to evaluate the safety and probable benefits of PHIL® device for the treatment of intracranial dural arteriovenous fistulas (dAVF).

3 STUDY DESIGN

3.1 PRIMARY MEASURED OUTCOMES

The following outcomes will be measured:

- Safety: The proportion of subjects with neurological death or ipsilateral stroke within the first 30 days following completion the first PHIL of treatment procedure.
- Probable benefit: Angiographic occlusion of the pre-specified target vessel intended for treatment at procedure following completion of the first PHIL treatment procedure.

Neurologic death is subject death reported as having resulted from a neurologic cause. Stroke is defined as a new focal neurological deficit in a defined vascular distribution of abrupt onset with symptoms persisting for >24 hours AND a neuro-imaging study or other quantitative study that does not indicate a different etiology. This includes ischemic and hemorrhagic strokes. It is expected that fewer than approximately 15% of subjects will experience neurologic death or a stroke within the first 30 days following completion of the first PHIL procedure treatment.

Angiographic occlusion of the pre-specified target vessel is defined as cessation of flow at the point of embolic agent administration at the target vessel. It is expected that approximately 60% of the subjects will achieve cessation of flow of the pre-specified target vessel when treated with PHIL.

3.2 SECONDARY MEASURED OUTCOMES

The following outcomes will be measured:

- The proportion of subjects with neurological death or ipsilateral stroke within the first 30 days following completion of all PHIL treatments
- Angiographic occlusion of the pre-specified target vessel intended for treatment at procedure following completion of all PHIL treatments
- New-onset or worsening of permanent morbidity at 6 month follow-up
- New-onset intracranial hemorrhage at 6 month follow-up
- New-onset of cranial nerve palsy at 6 month follow-up
- Clinically significant technical events during the PHIL embolization procedure(s) including but not limited to reflux of embolic material, migration of the embolic material, catheter entrapment or damage, and vessel dissection.
- Device-related adverse events at procedure and 30 days
- Device-related mortality at procedure and 30 days
- Procedure related adverse events including complications of arterial puncture, contrast-induced nephropathy, radiation-induced injuries, renal and anesthesia-related complications.

New-onset of device- or procedure-related neurological deficit or adverse event, or worsening of a previous neurological complaint, disorder, deficit, or adverse event that is unresolved at 6 month follow-up even if not associated with a change in mRS.Permanent morbidity is defined as a worsening of mRS score at 6 month follow-up compared to the baseline mRS score of:

- ≥1 point in subjects experiencing a stroke
- ≥2 points in subjects experiencing neurological adverse events.

Note, worsening mRS scores associated with non-neurological causes, resulting in limitations to the subject's ability to walk or require assistance to attend to own bodily needs, will not be considered permanent morbidity. This includes medical events such as, bone fractures, muscle, ligament and tendon injuries, and other physical injuries.

3.3 ADDITIONAL MEASURED OUTCOMES

The following outcomes will be measured:

- Improvement of neurological symptoms
- Number of procedures required to treat the fistula at 6 months follow-up
- Procedure time (defined as first to last fluoroscopic or digital subtraction angiographic acquisitions)
- Radiation exposure (dosage and time)
- Injected volume of PHIL
- Modified Rankin Scale (mRS) at 3 and 6 months
- Self-reported QOL questionnaire, EQ-5D at 6 months
- Unplanned adjunctive treatments

3.4 TYPE / DESIGN OF THE STUDY

The proposed study is a prospective, multicenter, single-arm, open label clinical study to assess the safety and probable benefits of PHIL® device for the treatment of intracranial dural arteriovenous fistulas (dAVF). The design is depicted in Figure 2.

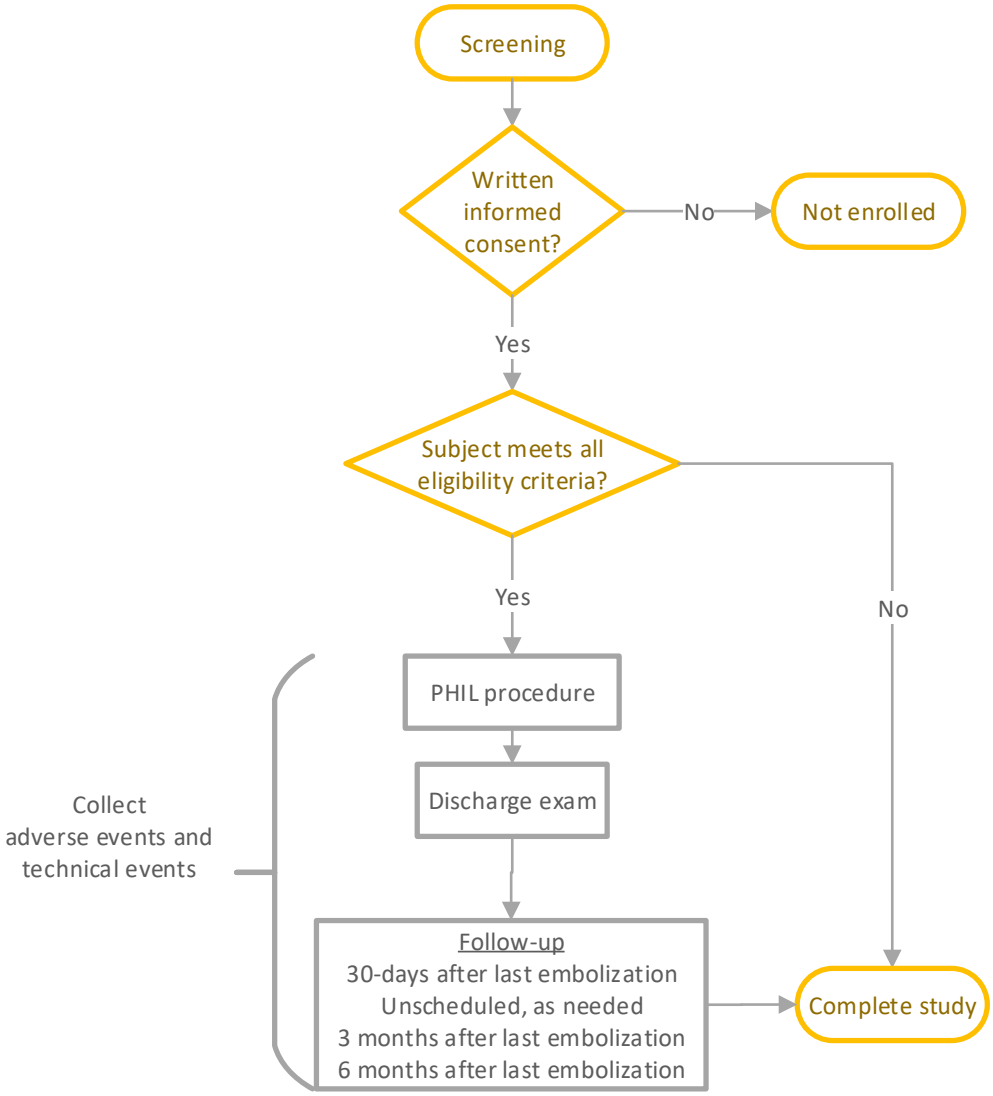

FIGURE 2 SCHEMATIC DIAGRAM OF TRIAL DESIGN

3.5 MEASURES TO MINIMIZE BIAS

A screening log serves as a method for the Sponsor to ensure that there is no selection bias in the trial.

3.6 MEDICAL DEVICE INFORMATION

The PHIL Liquid Embolic Material agent is indicated in the treatment of intracranial dural arteriovenous fistulas.

The PHIL® device is a non-adhesive liquid embolic agent comprised of a Triiodophenol-(lactide-co-glycolide) acrylate and hydroxyethyl methacrylate (HEMA) co-polymer dissolved in DMSO (dimethyl sulfoxide). An iodine component is chemically bonded to the co-polymer to provide a radio pacifier element during fluoroscopic visualization. The PHIL® Liquid Embolic System consists of a sterile, pre-filled, 1.0 mL syringe of PHIL® liquid embolic, a sterile, pre-filled 1.0 mL syringe of DMSO, and microcatheter hub adaptors. A DMSO compatible delivery microcatheter that is indicated for use in the neurovascular or peripheral vasculature is used to access the embolization target site. The PHIL® Liquid Embolic System is available in several product formulations: PHIL® 25%, PHIL® 30%, and PHIL® 35%. PHIL® 25% liquid embolic will travel more distally and penetrate deeper into the nidus due to its lower viscosity

compared to PHIL® 30% or 35% liquid embolic. Final solidification occurs within three minutes for all product formulations.

The PHIL® device is delivered by slow, controlled injection through a microcatheter into the vascular malformation under fluoroscopic control. The DMSO solvent dissipates into the blood, causing the co-polymer to precipitate in situ into a coherent embolus. The PHIL® device immediately forms a skin as the polymeric embolus solidifies from the outside to the inside, while traveling more distally in the vascular lesion.

3.6.1 Device labeling

The PHIL device is considered investigational in this study and is required to be used per the protocol and as specified in the Investigational Device Exemption (IDE) Instructions for Use (IFU) document. The IDE IFU is provided separately to each investigator.

3.6.2 Device accountability procedures

U.S. Federal law requires that all investigational medical devices be strictly controlled. All study devices must be kept in a secured area at the clinical sites in compliance with all applicable FDA regulations.

The Principal Investigator or designated study site personnel must verify the receipt of the study devices. Device disposition must be documented.

For applicable sites, at the end of enrollment in the study, all test devices and device accessories provided by the Sponsor will be returned to the Sponsor. Problematic devices and products, including all components, should be returned to the Sponsor or its designee for investigation.

3.6.3 Devices and equipment

In addition to the PHIL device, devices that may be required for the study procedure include (but are not limited to) those listed below.

- Access devices: Guiding catheter and sheath
- Delivery catheters: Microcatheters
- Non-ionic contrast
- Guidewires
- Any other adjunctive, approved/cleared device for dAVF treatment

The placement procedure is described in detail in the Instructions For Use (IFU) document. The Investigator should review and understand the complete IDE IFU prior to performing any PHIL device placement in this clinical study.

It is recommended that DMSO-compatible microcatheters be used during the study procedure. At present, the following MicroVention microcatheters are DMSO-compatible: Headway® DUO, Headway® 17 and Scepter Occlusion Balloon microcatheter.

Should additional DMSO-compatible microcatheters become available during the course of this study, they may also be used for the study procedure.

3.7 Expected subject duration

Study participation includes initial screening, consent, index procedure, post-procedure, hospital discharge, any supplemental embolization procedures and return for follow-up visits at 30 days post-procedure (following

completion of treatment of dAVF embolization with PHIL) and at 6 months post-procedure (following completion of treatment of dAVF embolization with PHIL).

The total subject duration is expected to be approximately 9 months.

4 SELECTION AND WITHDRAWAL OF SUBJECTS

Subjects who are enrolled in the study but subsequently do not meet the pre-operative inclusion criteria below will not be treated with the PHIL and will be considered enrolled but not treated. These subjects will be considered screen failures, exited from the study, replaced with other subjects that satisfy enrollment and pre-procedural inclusion criteria and will not be included in the analyzed populations.

Before any subject is treated in the study, the screening / baseline angiogram will be reviewed by at least one of the Study Principal Investigators.

4.1 INCLUSION CRITERIA

To be enrolled in this study subjects must meet ALL of the following criteria:

1) Subject is ≥22 and ≤80 years of age.
2) Subject is willing and capable of complying with all study protocol requirements, including specified follow-up period.
3) Subject or authorized legal representative must sign and date an IRB approved written informed consent prior to initiation of any study procedures.
4) Subject has an intracranial dAVF that can be treated by embolization with PHIL without the need for other liquid embolization products (e.g., Onyx, nBCA).
5) Subject has an intracranial dAVF that is deemed appropriate for embolization with PHIL without significantly increased risk to collateral or adjacent territories.

4.2 GENERAL EXCLUSION CRITERIA

Subjects shall be excluded from the study if ANY of the following conditions exist:

1) Subject has a modified Rankin Scale of >3 or has another neurological deficit not due to stroke that may confound the neurological assessments.
2) Subject having multiple dAVFs to be treated
3) Subject has dAVF requiring pre-planned treatment with adjunctive treatments (i.e. embolic coils, surgical resection, etc).
4) Subject presents with an intracranial mass or is currently undergoing radiation therapy for carcinoma or sarcoma of the head or neck region
5) Subject has known allergies to DMSO *(*dimethyl sulfoxide), iodine or heparin
6) Subject with a history of life threatening allergy to contrast media (unless treatment for allergy is tolerated)
7) Subject is experiencing (or has experienced) an evolving, acute, or recent disabling ischemic stroke, has conditions placing them at high risk for ischemic stroke or has exhibited ischemic symptoms such as transient ischemic attacks, minor strokes, or stroke-in-evolution within the prior 3 months timeframe.
8) Subject has had an acute myocardial infarction within 30 days prior to index procedure
9) Subject has had or plans to have any major surgical procedure (i.e. intra-abdominal or intrathoracic surgery or any surgery/interventional procedure involving cardiac or vascular system) within 30 days of the index procedure

10) Subject is currently participating in another clinical study which may interfere with outcome measurements for this study
11) Female subject is currently pregnant.
12) Subject has an acute or chronic life-threatening illness other than the neurological disease to be treated in this study including but not limited to any malignancy or debilitating autoimmune disease
13) Subject has existing severe or advanced comorbid conditions which significantly increase general anesthesia and/ or surgical risk including but not limited to advanced COPD, uncontrolled hypertension / diabetes, congestive heart failure, chronic or acute kidney disease.
14) Subject has evidence of active infection at the time of treatment
15) Subject has dementia or cognitive or psychiatric problem that prevents the patient from completing required follow-up.
16) Subject has co-morbid conditions that may limit survival to less than 24 months.
17) Subject has a history of bleeding diathesis or coagulopathy, international normalized ratio (INR) greater than 1.5, or will refuse blood transfusions.

4.3 ANGIOGRAPHIC EXCLUSION CRITERION

1) Subject has severe calcification or vascular tortuosity that may preclude the safe introduction of the sheath, guiding catheter, or access to the lesion with the microcatheter.
2) Subject has a contra-indication to DSA, CT scan or MRI/ MRA.
3) Subject has a history of intracranial vasospasm not responsive to medical therapy.
4) Subject has extra-cranial stenosis or parent vessel stenosis > 50% proximal to the target lesion to be treated.

4.4 PARTICIPANT WITHDRAWAL OR STUDY TERMINATION

Subjects may withdraw from the study at any time without penalty or loss of medical care, or they may be withdrawn at any time at the discretion of the PI for safety or administrative reasons. The Sponsor may terminate or suspend the study at any time.

4.4.1 SUBJECT WITHDRAWAL

All enrolled subjects have the right to withdraw their consent at any time during this study. All data collected until the time of subject withdrawal will remain in the study database and will be used for analysis. Whenever possible, the site staff should obtain written documentation from the subject who wishes to withdraw his/her consent for future follow-up visits. If the site staff is unable to obtain written documentation, all information regarding the subject's withdrawal must be recorded in the subject's medical record. In addition, the appropriate eCRFs must be completed for the subject and clear documentation of the subject's withdrawal should be provided to the Sponsor.

4.4.2 SUBJECT DISCONTINUATION BY INVESTIGATOR

An Investigator may discontinue a subject from the study, with or without the subject's consent, for any reason that may, in the Investigator's opinion, negatively affect the well-being of the subject. If a subject is withdrawn from the study, the Investigator will promptly inform the subject and Sponsor.

4.4.3 LOST TO FOLLOW-UP

A subject will be considered lost to follow-up if the subject cannot be reached after three (3) attempts to contact the subject for a follow-up visit. The site must document a minimum of three (3) attempts, and the final documented attempt should be made via registered letter.

4.4.4 TERMINATION OR SUSPENSION OF STUDY

This study may be suspended or terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to the investigator, if by the sponsor or regulatory authorities; or the sponsor if by the investigator or the site's IRB. If the study is prematurely terminated or suspended, the PI will promptly inform the IRB and will provide the reason(s) for the termination or suspension.

5 TREATMENT OF SUBJECTS

In this study, subjects undergo screening / baseline evaluation, the study procedure, supplemental embolization procedures as needed and clinical and angiographic follow-up out to 6 months.

Table 6 Schedule of Study Activities by Visit shows the study's visit schedule, allowed windows, and schedule of assessments, which are described in more detail in Sections 5.4 - 5.16.

5.1 SCHEDULE OF EVENTS TABLE

Data will be collected on electronic case report forms at the pre-procedure, at index procedure and post-procedure visits. A schedule of the study activities by visit is provided in Table 6.

TABLE 6 SCHEDULE OF STUDY ACTIVITIES BY VISIT

Visits		Screening / Baseline	PHIL procedure(s)	Discharge(s)	30-day follow-up[1]	3-month Follow-Up[1]	6-month Follow-Up[1]	Unscheduled
Assessments	Method	Office / clinic	Hospital visit		Office/clinic	Office/clinic	Office/Clinic	Office/clinic/hospital
Informed consent		X						
Assess inclusion / exclusion		X						
Demographics and medical history		X						
dAVF information (classification)		X						
modified Rankin Scale score		X			X	X	X	X
NIH Stroke Scale score		X			X[2]	X[2]	X[2]	X[2]
Hunt and Hess Stroke Scale score[3]		X			X	X	X	X
Physical exam (dAVF symptoms)		X		X[4]	X	X	X	X
Clinical chemistry & hematology		X		X	X	X	X	
QOL (EQ-5D)		X[5]					X	
dAVF and embolized vessel data			X					
Irradiation Information			X					
PHIL procedure			X					
Device usage			X					
Angiography		X[6]	X[7]		X[8]	X[8]	X	X[9]
Adverse event / technical event			X	X	X	X	X	X

1. Follow-up to be scheduled after completion of the last PHIL treatment.
2. Required at any time point if signs of new-onset neurological deficit are present.
3. Required in the case of presenting hemorrhage.
4. This exam should be completed within 2-days post-procedure.
5. To be performed within 7 days in advance of the procedure.
6. DSA preferred but CTA/MRA can performed depending on subject health status.
7. Must include a pre-treatment and post-treatment angiogram.
8. Required if subject presents with symptoms relating to the treated dAVF (DSA, CTA or MRA acceptable).
9. Standard Care imaging (DSA, CTA or MRA acceptable).

5.2 RECRUITMENT

Potential study participants will be recruited through standard means or by referral. Any materials used for study advertising generated by the investigational site will be approved by the local IRB to use.

5.3 SCREENING

Subject eligibility assessment is to be performed based on data available to the investigator at the time of screening. This initial screening phase may include review of existing subject information (previously performed angiography, radiographs, laboratory studies, medical history, physical examination, etc.). Subjects who appear to meet the enrollment criteria should be asked to participate in this study. Subjects asked to participate should be recorded on the study screening log.

5.4 INFORMED CONSENT

Informed consent is a process that is initiated prior to the subject's agreeing to participate in the study and continues throughout the subject's study participation. The process must be documented. A verbal explanation will be provided to the subject (or legally authorized representative) as to the purpose and requirements of this study. Details of the study should include (but are not limited to): the study objectives, alternative treatments, the need to return follow-up visits, participation is voluntary, and there is no penalty for withdrawal, the potential risks/benefits for participation and contact information to ask questions or voice concerns. The participants should have the opportunity to discuss the study with their surrogates or think about it prior to agreeing to participate.

Consent to participate in this study must be obtained in written format in a language understood by the potential subject and using a form approved by the IRB. Each subject shall be given ample time to read the informed consent form (ICF) and ask questions to make an informed decision. All subjects must sign the informed consent form prior to any procedures/tests that go beyond the standard care for assessments for subjects with dAVF and before any study-related assessments are administered and subject-related health information can be entered in the study database.

A copy of the informed consent document will be given to the participants for their records. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study. The participants may withdraw consent at any time throughout the course of the study. For this study, written informed consent does not expire.

5.5 BASELINE EXAMINATION

Following written informed consent, the study investigator or designee will assess potential study candidates against eligibility criteria. The investigator or designee will record reason for failure in any subject actively considered for study participation.

- Review medical history to determine eligibility based on inclusion/exclusion criteria.
- Review medications history to determine eligibility based on inclusion/exclusion criteria.
- Perform medical examinations needed to determine eligibility based on inclusion/exclusion criteria.
- Schedule study visits for participants who are eligible and available for the duration of the study.
- Provide participants with specific instructions needed to prepare for the procedure.

All baseline examinations will be consistent with standard of care. Subjects who are believed by the investigator to potentially qualify will undergo the following baseline assessments:

- Demographic data
- Medical history, including smoking history
- dAVF information (Borden classification)
- Physical exam to assess dAVF symptoms
- Neurologic assessment by Modified Rankin Scale (mRS) and NIH Stroke Scale
- Hemorrhage assessment by Hunt and Hess Stroke Scale score, if applicable

- Angiography

The investigator will document screening and baseline findings in the eCRF. If the subject is found to be ineligible for study participation during the baseline examination, the subject will be notified and exited from the study.

5.5.1 Female subjects of childbearing potential

This study involves radiation during dAVF treatment as well as at follow-up visits. The investigator should follow standard medical practices to ensure that a woman of child-bearing age is not pregnant at the time of the study procedure. If a woman is pregnant at a follow-up visit that requires catheter angiogram, alternative methods to visualize the dAVF (e.g., MRA) should be used.

5.5.2 Late screening failures

Study eligibility requires confirmation of anatomical characteristics that, in many cases, can only be confirmed at the time of the study procedure by angiogram. Subjects who initially appear to qualify for the study will be excluded at the time of the study procedure if the anatomical characteristics do not meet eligibility criteria or if access to the index lesion with a microcatheter is not possible or would introduce unnecessary additional risk.

5.5.3 Pre-Procedure Assessment

Routine clinical chemistry and hematology labs will need to be collected from the subject, this may be obtained between baseline and pre-procedure. Within 7 days preceding the index procedure, the subject must complete self-reported QOL questionnaire using EQ-5D.

5.6 PHIL Procedure

Unless medically justified, the initial embolization procedure should be performed within 45 days of completion of the baseline assessment. The study procedure consists of pre-placement imaging, study device placement and post-placement imaging. Subjects require no special preparation for the procedure beyond standard of care for endovascular neuro-interventions. Investigators at their discretion may elect to pre-medicate with antiplatelet agents.

It is expected that the majority of PHIL initial and supplemental embolization procedures are completed under general anesthesia but a minority of procedures may be completed under conscious sedation, depending upon the center's standard of care. Heparin is administered according to standard practices. The PHIL device should be used per the IFU provided in the PHIL packaging. The PHIL procedure will be performed only by the physician investigator(s) trained by the Sponsor or its designee to perform the procedure.

The point of enrollment occurs when the PHIL liquid embolic syringe and adaptor assembly is connected to the microcatheter hub.

The investigator will record key characteristics of the device and procedure in the study's eCRF. The investigator will also record technical events/device malfunctions. Radiation exposure will be recorded as absorbed radiation dose and cumulative fluoroscopy time will be recorded. The investigator will retain and provide to the sponsor all images taken during or immediately after the study procedure (including any not specified above).

5.7 Discharge examination

The subject is discharged from the hospital after standard post-procedure recovery. The subject will have a physical exam to assess dAVF symptoms; this exam should be completed within 2-days post-procedure. The investigator/designee will collect routine post-procedure routine clinical chemistry and hematology labs before

discharge, record discharge status information, including hospital length of stay, and occurrence of any postoperative adverse events in the eCRF.

5.8 SUPPLEMENTAL PHIL PROCEDURE

Complete treatment of the target dAVF may require one or more PHIL procedures. Additional procedure(s) are to be scheduled and performed at the treating physician's discretion. It is estimated that up to seven (7) PHIL procedures may be required to treat the fistula. The physician shall determine the number of treatment procedures based on factors specific to each patient, such as dAVF size, number of feeders, fistulous connections, and location relative to eloquent territory. The treating physician should discontinue PHIL treatment if reflux into an eloquent artery is observed during the procedure.

The supplemental PHIL procedure consists of pre-procedure physical exam to assess dAVF symptoms, collection of routine clinical chemistry and hematology labs pre-procedure, pre-placement imaging, study device placement and post-placement imaging. Subjects require no special preparation for the procedure beyond standard of care for endovascular neuro-interventions. Investigators at their discretion may elect to pre-medicate with antiplatelet agents.

It is expected that the majority of PHIL initial and supplemental embolization procedures are completed under general anesthesia but a minority of procedures may be completed under conscious sedation, depending upon the center's standard of care. Heparin is administered according to standard practices. The PHIL device should be used per the IFU provided in the PHIL packaging. The supplemental PHIL procedure will be performed only by the physician investigator(s) trained by the Sponsor or its designee to perform the procedure.

The investigator will record key characteristics of the device and procedure in the study's eCRF. The investigator will also record technical events/device malfunctions. Radiation exposure will be recorded as absorbed radiation dose and cumulative fluoroscopy time will be recorded. The investigator will retain and provide to the sponsor all images taken during or immediately after the study procedure (including any not specified above).

5.8.1 DISCHARGE EXAMINATION

The subject is discharged from the hospital after standard post-procedure recovery. The subject will have a physical exam to assess dAVF symptoms; this exam should be completed within 2-days post-supplemental procedure. The investigator/designee will collect routine post-procedure clinical chemistry and hematology labs before discharge, record discharge status information, including hospital length of stay, and occurrence of any postoperative adverse events in the eCRF.

5.9 FOLLOW-UP

Subjects will undergo follow-up at a location designated by the research staff at 30 days, 3 months and 6 months following completion of treatment. The investigator will document all findings in the eCRF.

5.9.1 30 DAY (-14 / +14 DAYS)

This visit is to be conducted 30 days following completion of the last PHIL treatment. At this visit, the subject will undergo

- Neurological assessment by Modified Rankin Scale (mRS)
- Neurological assessment by NIH Stroke Scale (if applicable)
- Hemorrhage assessment by Hunt and Hess Stroke Scale (if applicable)
- Assessment dAVF symptoms

- Collection of routine clinical chemistry and hematology labs.
- Record adverse events as reported by participant or observed by investigator.
- Angiographic assessment if the subject presents with symptoms relating to the treated dAVF (DSA, CTA or MRA is acceptable).

5.9.2 3 MONTH VISIT (-2 / + 4 WEEKS)

This visit is to be conducted 3 months following completion of the last PHIL treatment. At this visit, the subject will undergo

- Neurological assessment by Modified Rankin Scale (mRS)
- Neurological assessment by NIH Stroke Scale (if applicable)
- Hemorrhage assessment by Hunt and Hess Stroke Scale (if applicable)
- Assessment dAVF symptoms
- Collection of chemistry and hematology labs
- Record adverse events as reported by participant or observed by investigator.
- Angiographic assessment (if applicable)

5.9.3 6 MONTH VISIT (-3 / + 6 WEEKS)

This visit is to be conducted 6 months following completion of the last PHIL treatment. At this visit the subject will undergo

- Neurological assessment by Modified Rankin Scale (mRS)
- Neurological assessment by NIH Stroke Scale (if applicable)
- Hemorrhage assessment by Hunt and Hess Stroke Scale (if applicable)
- Physical exam to assess dAVF symptoms
- Collection of chemistry and hematology labs
- Subject self-reported QOL questionnaire using EQ-5D
- Record adverse events as reported by participant or observed by investigator.
- Angiographic assessment

5.10 UNSCHEDULED VISIT

Unscheduled visits are those that take place after the study procedure and before the subject completes the study follow-up period (6 months following completion of the last PHIL treatment). Any visit by the subject to the Investigator related to the target dAVF treated or a potentially associated adverse event should include a neurologic examination using mRS, an assessment of dAVF symptoms, and angiography, as per standard of care. The Investigator should document the review of the adverse event status.

5.11 MISSED VISIT

Any study subject who does not attend a scheduled follow-up visit should be contacted by site personnel to determine the reason for the missed appointment(s). If the missed visit was due to an adverse event (AE), an AE electronic Case Report Form (eCRF) must be completed and any reporting requirements met.

5.12 SPECIAL CIRCUMSTANCES

On January 31, 2020, the Department of Health and Human Services (HHS) issued a declaration of a public health emergency related to COVID-19 and mobilized the Operating Divisions of HHS. On March 11, 2020, the World Health Organization declared COVID-19, the coronavirus infection, a pandemic. In addition, on March 13, 2020, the

President of the United States declared a national emergency in response to COVID-19. Local officials have issued recommendations limiting non-essential public gatherings. As a result of quarantines, clinical site closures and/or travel limitation, study patients may not be able to return the clinical study sites to complete follow-up visits.

For the remainder of the COVID-19 pandemic, telephone follow-up visits for safety information may be conducted for the 30 day, 3 month, and 6 month visits for any study patient who cannot return to a clinical study site. A list of visits that deviated from the follow-up schedule in clinical protocol Revision B as related to COVID-19 will be provided. The 6 month follow-up visit window is extended to -3 / + 20 weeks to collect additional follow-up information including blood tests and angiography to assess the continued safety and probable benefit of the PHIL device. It is anticipated that clinical site operations will return to normal operations (pre COVID-19) by approximately August 2020.

This protocol revision may be implemented without prior approval from Food and Drug Administration and/or Institutional Review Boards as noted in the guidance document, *FDA Guidance on Conduct of Clinical Trials of Medical Products during COVID-19 Pandemic*, issued March 2020.

5.13 Study specific procedures

The following procedures and/or assessments that will be completed during the study are considered study specific.

- Quality of life with EQ-5D
- Clinical chemistry and hematology at 30 day and 3 month follow-up

5.14 Standard of care procedures

The following procedures and/or assessments that will be completed during the study are considered standard of clinical care.

- Review medical history
- Fistula classification
- CT angiography / MR angiography
- Embolization to occlude blood vessels
- Neurologic assessment with modified Rankin Scale
- Neurologic assessment with NIH Stroke Scale
- Hunt and Hess Stroke Scale score
- Clinical chemistry and hematology before the procedure, after the procedure and at 6 month follow-up.

5.15 Study exit

Upon completion of the specified study follow-up the subject will be exempt from further data collection. The subject will be seen by the treating physician according to standard care following dAVF treatment.

5.16 Deviations from this protocol

A protocol deviation is defined as an event where the Investigator or study personnel did not conduct the study according to the clinical protocol. The deviation may be either on the part of the participant, the investigator, or the study site staff. Deviations shall be reported to the Sponsor regardless of whether medically justifiable or taken to protect the subject in an emergency.

Except for a change that is intended to eliminate an immediate hazard to a subject, the protocol will be followed as written. Subject specific deviations and non-subject specific deviations, (e.g. unauthorized use of a study device outside the study, unauthorized use of a study device by a physician, etc.) will be reported. Investigators will also adhere to procedures for reporting study deviations to their IRB in accordance with their specific IRB's reporting policies and procedures.

Sites with a high rate of protocol deviations will be closely evaluated and are expected to implement corrective actions to prevent further deviations. If a site demonstrates persistent deviations, as described above, the site may be terminated. The sponsor may terminate investigators and/or investigative sites from the study if the rate of protocol deviations is deemed high or subject safety is in question.

For reporting purposes, protocol deviations may be characterized as major or minor using the definitions below in Table 7.

TABLE 7 PROTOCOL DEVIATION SEVERITY

Deviation Type	Definition
Major deviation:	Any deviation from subject inclusion and exclusion criteria, unauthorized device use, or performing study specific procedures without obtaining written informed consent. Incomplete/inadequate measured outcome data.
Minor deviation:	Deviation from a protocol requirement such as incomplete/inadequate subject testing procedures, follow-ups performed outside specified time windows, etc. Deviations in administrative procedures for documenting informed consent.

Some information collected in this study is not essential to confirming subject eligibility or to the study measured outcomes and will not be considered a deviation if absent.

5.17 MONITORING COMPLIANCE

Study monitoring will be a continuous process conducted in accordance with 21 CFR 812.46 and applicable Sponsor procedures.

Clinical site monitoring is conducted to ensure that the rights and well-being of human subjects are protected, that the reported study data are accurate, complete, and verifiable, and that the conduct of the study is in compliance with the currently approved protocol/amendment(s) and with applicable regulatory requirement(s).

- Monitoring for this study will be performed by qualified clinical research personnel, or designees, of MicroVention, Inc.
- Details of clinical site monitoring are documented in a Clinical Monitoring Plan (CMP). The CMP describes in detail who will conduct the monitoring, at what frequency monitoring will be done, at what level of detail monitoring will be performed, and the distribution of monitoring reports.

5.17.1 INDIVIDUAL SITE MONITORING

5.17.1.1 SITE SELECTION

The Sponsor or representative of the Sponsor will assess each potential site to ensure the principal investigator and his/her staff has the facilities and expertise required for the study. Sites will be selected based upon a site assessment, appropriate facilities, and the qualifications of the investigator(s). Individual investigators will be

evaluated by the Sponsor based on experience with the intended procedure(s) and ability to conduct the study according to the study protocol.

To participate, a site must meet the following requirements:

- A physician trained in the use of liquid embolics and has a history of treating dAVFs.
- Commitment from the participating physician to pursue details of any safety outcomes.
- Commitment from the participating physician to enroll only subjects meeting the study criteria.
- A dedicated study coordinator who can enter data and respond to queries.
- Internet access (for electronic data capture) in the hospital or clinic setting.
- Be willing to perform necessary documentation (e.g., eCRF).
- Agree to sign and adhere to the Investigator Agreement.

5.17.1.2 SITE TRAINING

The Sponsor or representative of the Sponsor will train each investigational site to the investigational plan. Investigator/Site Personnel will be trained before performing any study-related procedures. All training must be documented. The PHIL procedure will be performed only by the physician investigator(s) trained by the Sponsor or its designee to perform the procedure.

Training to the investigational plan will include the following topics:

- The study objectives and requirements of this protocol
- Device overview (for non-investigator research personnel)
- Device handling procedures
- Instructions for Use (IFU)
- Responsibilities of the investigator/staff
- Consenting procedures
- Reporting requirements (adverse events and protocol deviations)
- eCRF completion and correction procedures
- Protection of subject confidentiality
- Regulatory files
- Study supplies
- General guidelines for good clinical practices, to be conducted by Sponsor only if the site does not have a current good clinical practices training course.

Existing study site personnel who have been delegated new tasks and new study site personnel will undergo training to the investigational plan, as appropriate.

5.17.1.3 SITE INITIATION

The Sponsor or a representative of the Sponsor will conduct a training session with site staff to review the protocol, eCRFs, the informed consent process, IRB/EC involvement and guidelines, responsibilities and obligations, reporting requirements, and general guidelines for good clinical practices (if applicable).

Prior to enrolling subjects at an investigational site, the following documentation must be provided to the Sponsor:

- IRB approval for the Investigational Plan
- IRB and Sponsor approved Informed Consent Form for the study
- Signed Confidentiality Agreement (CDA)
- Signed Clinical Study Agreement (CSA) and if applicable, Sub-I Agreement(s)

- Training log documentation to verify the appropriate study staff has been trained on the protocol, eCRFs, and study conduct.
- Financial disclosure(s) for the PI and Sub-I(s)
- Investigator(s') curriculum vitae (CV)

5.17.1.4 ONGOING SITE MONITORING

Periodic site monitoring visits will be performed during the study by a designated study monitor assigned by the Sponsor. The purposes of the visits are to confirm compliance to the protocol, review regulatory documents, ensure accurate and complete records are being maintained and to compare source documents to completed eCRFs for completeness and consistency. Specific assessments during a monitoring visit include:

- Continued site acceptability
- Compliance to the protocol
- IRB approval status
- Use of the approved informed consent
- Adequacy of source documents
- Complete and accurate eCRFs
- Reporting of adverse events
- Protocol deviations
- Site records

If it is determined during a monitoring visit that there are significant non-compliance issues at a site, including adherence to the protocol or applicable regulatory requirements, the issues will be discussed with the investigator and study coordinator and the site will be instructed how to gain compliance. If continued non-compliance is detected on a subsequent monitoring visit, it may be necessary to terminate site participation in the study.

5.17.1.5 SITE CLOSE-OUT

Upon completion of the study and the final report, a close-out visit will be conducted. The purpose of the visit will be to:

- Review the records retention requirements for the study
- Arrange for the return of all study related materials to the Sponsor
- Review the final IRB requirements for the study

5.17.1.6 MONITORING REPORTS

After each monitoring visit, the monitor will send to the principal investigator an e-mail or letter summarizing the monitoring visit. A monitoring report will be sent to the Sponsor. The report will include the date of the monitoring visit, the site name, the name of the monitor, the name of the investigator, the names of other individuals present for the monitoring visit, items reviewed during the visit, findings, and any required follow-up. The principal investigator will be responsible for ensuring that follow-up action items requiring resolution at the site are completed in an accurate and timely manner.

5.17.2 OVERALL DATA MONITORING

The Sponsor/designee will monitor all AE reports to identify and trend all events that would require temporary discontinuation of study enrollment, to fully characterize device safety, to modify the study protocol, or to terminate the study.

6 ASSESSMENT OF PROBABLE BENEFIT

The following outcomes will be measured intra-operatively:

- Angiographic occlusion of the pre-specified target vessel(s) intended for treatment at procedure following completion of the first PHIL for treatment procedure
- Angiographic occlusion of the pre-specified target vessel(s) intended for treatment at procedure following completion of all PHIL treatment procedure

The following additional outcomes will be measured:

- Improvement of neurological symptoms
- Number of procedures required to treat the fistula at 6 months follow-up
- Procedure time (defined as first to last fluoroscopic or digital subtraction angiographic acquisitions)
- Radiation exposure (dosage and time)
- Injected volume of PHIL
- Modified Rankin Scale (mRS) at 3 and 6 months follow-up
- Self-reported QOL questionnaire, EQ-5D at 6 month follow-up
- Unplanned adjunctive treatments

Angiographic occlusion of the pre-specified target vessel is defined as cessation of flow at the point of embolic agent administration at the target vessel. It is expected that approximately 60% of the subjects will achieve cessation of flow of the pre-specified target vessel when treated with PHIL.

7 ASSESSMENT OF SAFETY

The aggressive type of intracranial dural arteriovenous fistulae (dAVF) with either direct (non-sinus-type dAVF) or indirect (sinus-type dAVF) retrograde filling of a leptomeningeal vein has a high propensity of ischemia, intracranial hypertension, and cerebral bleeding. [11, 14] If left untreated, the mortality rate is 10.4%, the annual bleeding and the non-hemorrhagic neurological deficit risks are 8.1% and 6.9%, respectively. This leads to an annual event-rate of 15%. In the series by Wachter et al of 42 patients who underwent surgical treatment of aggressive dAVFs, the transient and permanent surgical morbidity was 11.9% and 7.1%, respectively. [46] Lv et al reported a similar permanent morbidity rate of 7.5% in a series of 40 patients who underwent transarterial dAVF embolization with Onyx. [40]

The following outcomes will be measured:

- The proportion of subjects with neurological death or any ipsilateral stroke within the first 30 days following completion of the first PHIL treatment procedure.
- The proportion of subjects with neurological death or any ipsilateral stroke within the first 30 days following completion of all PHIL treatment procedures.
- New-onset or worsening of permanent morbidity at 6-month follow-up.
- New-onset Intracranial hemorrhage at 6-month follow-up.
- New-onset of cranial nerve palsy at 6 month follow-up
- Clinically significant technical complications during the procedure including but not limited to reflux of embolic material, migration of the embolic material, catheter entrapment or damage, and vessel dissection.
- Device-related adverse events at procedure and 30 days.
- Device-related mortality at procedure and 30 days.
- Procedure related adverse events including complications of arterial puncture, contrast-induced nephropathy, radiation-induced injuries, renal and anesthesia-related complications.

New-onset of device- or procedure-related neurological deficit or adverse event, or worsening of a previous neurological complaint, disorder, deficit, or adverse event that is unresolved at 6 month follow-up even if not associated with a change in mRS.Intracranial hemorrhage (ICH) is defined as hemorrhage within the fixed vault of the cranium (skull).

Neurologic death is subject death reported as having resulted from a neurologic cause.

Stroke is defined as a new focal neurological deficit in a defined vascular distribution of abrupt onset with symptoms persisting for >24 hours AND a neuro-imaging study or other quantitative study that does not indicate a different etiology. This includes ischemic and hemorrhagic strokes.

It is expected that fewer than approximately 15% of subjects will experience neurologic death or a stroke within the first 30 days following completion of the first PHIL procedure treatment.

7.1 PROCEDURE FOR ADVERSE EVENT REPORTING

Any medical condition that is present at the time that the subject is screened will be considered part of the subject's baseline medical history and not reported as an adverse event. However, if the subject's condition deteriorates at any time during the study, it may be recorded as an AE. Adverse events will be collected from the point of enrollment in the study until a subject exits the study.

Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study product (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. AEs will be categorized using the definitions in Section 7.2. All AEs collected during the study must be followed by the Investigator until resolution or until the end of the 6 month follow-up. All applicable AEs occurring while on study must be documented appropriately regardless of the relationship.

A list of potential anticipated adverse events is provided in Section 1.3.2. AE reporting responsibilities are described in Section 7.2.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed.

7.2 REPORTING EVENTS

Safety events must be reported to the Sponsor in a timely manner. The primary method of reporting events will be through the eCRFs. If the database is unavailable, the investigator may send the information to the study team. As soon as the database becomes available, the investigator must complete data entry. The investigator will send all available supporting documentation (blinded/de-identified as to the subjects' identity) to the Sponsor.

As additional information becomes available, copies of that source documentation which contain significant information related to the event such as progress notes, consultations, nurse's notes, operative reports, imaging studies and subject summaries etc. are requested for a complete evaluation of the event.

Regarding subject deaths, it is requested that a copy of the death certificate and a copy of the autopsy report, if applicable, be sent to the Sponsor when available. Any other source documents related to the death should also be provided to the Sponsor. If no source documents are available, the PI is requested to describe the circumstances of the subject's death in a letter, e-mail or other written communication. The Sponsor will report all deaths on an interim basis to FDA, as they are reported by the PI.

UADEs/USADEs have expedited reporting requirements. **The investigator is required to report any UADEs/USADE's to the Sponsor as soon as possible (i.e. within 24 hours) but no later than 10 working days after first learning of the event.** The Sponsor is required to report any event that meets the definition of Unanticipated Adverse Device Effect (Section 7.2) to FDA, all investigators and reviewing IRBs within 10 working days after becoming aware of information that an unanticipated adverse device effect has occurred. The site will notify the reviewing IRB within 10 working days after becoming of aware of the effect.

7.2.1 DEFINITIONS

An **Adverse Event** (AE) is defined as any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the investigational medical device. (ISO 14155:2011 3.2)

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 investigational medical devices.

A **Serious Adverse Event** (SAE) is defined as an adverse event that

a) Led to death,
b) Led to serious deterioration in the health of the subject, that either resulted in
    i. A life-threatening illness or injury, or
    ii. A permanent impairment of a body structure or a body function, or
    iii. In-subject or prolonged hospitalization, or
    iv. 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 (ISO 14155:2011 3.37)

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

An **Unanticipated Adverse Device Effect** (UADE) is defined as any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects. (21 CFR 812.3 (s))

Severity:

- Mild: No limitation of usual activities, no therapy or only symptomatic therapy required to treat the injury or illness.
- Moderate: Some limitation of usual activities or specific therapy is required.
- Severe: Inability to carry out usual activities, hospitalization, emergency treatment, life threatening events, or death.

Relatedness:

- Study Disease-related: Event is clearly attributable to the underlying study disease state with no temporal relationship to the device, treatment, or medication.

- Concomitant disease-related: Event is clearly attributable to the underlying concomitant disease state with no temporal relationship to the device, treatment, or medication.
- Procedure-related: Event has a strong temporal relationship to any PHIL procedure. This includes AEs attributable to any device(s) other than the PHIL™ device used at any PHIL procedure, such as access devices, delivery microcatheters, non-ionic contrast, guidewires, radiation emitting devices or any other adjunctive, approved/cleared device for treatment of intracranial dAVFs.
- Device-related: Event has a strong temporal relationship to the study device, and alternative etiology is less likely. The study device is the PHIL system used at any procedure including the liquid embolic components, adapter and syringe. All events considered "device-related" will be further characterized as either:
    - Anticipated: Previously identified in nature, severity or degree of incidence in the investigational plan. Or
    - Unanticipated: Not previously identified in nature, severity or degree of incidence
- Unknown: Event relationship cannot be attributed to any of the above categories and remains undetermined.

7.2.2 Technical event

A technical event is any malfunction or deficiency of the study device.

All technical events must be reported. If a technical event results in an adverse event for the subject, this adverse event will be considered a reportable adverse event and must be reported as an Adverse Event (AE). The investigator will retain and provide to the sponsor all images taken during or immediately after the study procedure when a malfunction or deficiency is observed.

7.3 Adverse event follow-up

Subjects experiencing an adverse event will be followed as per standard medical care. Data collection will be ongoing for the subject's duration in the clinical study as defined in follow-up period described in Section 5.

7.4 Data Safety and Outcomes Monitoring Committee

The purpose of the Data Safety and Outcomes Monitoring Committee is to evaluate the relative treatment effects for subjects treated in this study. The primary and secondary measured outcomes will be adjudicated and the cumulative rate will be reviewed. Clinical study safety and probable benefit data including but not limited to enrollment, device performance, pre-defined clinical outcomes will be periodically evaluated and recommendations to the Sponsor will be made accordingly. These activities will be conducted by at least three independent physicians knowledgeable in the appropriate disciplines and medical specialties pertinent to the disease state being evaluated in this clinical study.

The independent Data Safety and Outcomes Monitoring Committee processes will be further described in a charter upon approval of the study protocol and shall specify stopping rules and meeting frequency, which may be commensurate with projected enrollment.

8 Statistical considerations

8.1 Sample size

This study will enroll up to seventy five (75) subjects in this study to obtain 6 month follow-up in 60 subjects. This assumes up to fifteen (15) subjects may be lost to follow-up. No statistical justification is established.

8.2 GENERAL APPROACH

Descriptive statistics (mean, standard deviation, frequency charts, etc.) for baseline participant characteristics, subject disposition and other relevant study parameters will be reported. Where applicable, a comparison to rates reported in the scientific literature will be performed.

Tabulations of summary statistics, graphical presentations, and statistical analyses will be performed using SAS software version 9.2 or higher. The statistical analyses will be based on data pooled across sites in aggregate. All subset summary tables and data listings will be sorted by site and subject. The pre-procedure observations will be used as the baseline value for calculating post-procedural changes from baseline.

Continuous demographic parameters, such as the age of the subject at the time of enrollment, will be summarized using descriptive statistics (N, mean, median, standard deviation, minimum and maximum value). Categorical demographic parameters, such as gender, will be summarized as a proportion of the population.

Data obtained during the neurological examination using the Modified Rankin and self-reported EQ-5D will be summarized at each time point using descriptive statistics.

Routine clinical chemistry and hematology will be assessed by the investigator as normal/abnormal and not clinically significant/clinically significant. The incidence of abnormal and clinically significant values will be summarized and reported in frequency tables for each visit at which the data are collected.

Subject counts will be tabulated for all adverse events for the population. Adverse events will also be tabulated for events that occurred at procedure and at 6 month follow-up after last embolization. Tabulated subject counts will be presented as a proportion of the population.

All recorded data will be presented in the individual data listings.

8.3 ANALYSIS POPULATION

The analysis population will be comprised of the results from up to 75 treated subjects. Results will be presented based on one population:

Full Analysis Set (FAS): defined all enrolled subjects in whom the PHIL device was implanted.

9 DIRECT ACCESS TO SOURCE DATA / DOCUMENTS

By participating in this research study, the Investigator agrees to permit monitoring and auditing by the Sponsor and/or its designee(s) and inspection by applicable regulatory authorities. The Investigator also agrees to allow the Sponsors CRAs/monitors/auditors/FDA investigators to have direct access to his/her research-related study records (e.g. medical records, source documentation, and billing information) for review. If an Investigator is notified of a pending investigation by a regulatory agency, IRB/EC, or other similar organization, he/she will inform the Sponsor promptly.

10 QUALITY ASSURANCE AND QUALITY CONTROL

All documents and data shall be produced and maintained in such a way to assure control of documents and data to protect the subject's privacy as far as reasonably practicable. The Sponsor and representatives of the FDA or other regulatory authorities are permitted to inspect the study documents (e.g., study protocol, eCRFs, and original study-relevant medical records/files) as needed. All attempts will be made to preserve subject confidentiality.

All clinical sites are subject to audit by study sponsor personnel or designee for protocol adherence, accuracy of eCRFs and compliance with applicable regulations. Any evident pattern of non-compliance with respect to these standards will be cause for the site to be put on probation until appropriate corrective action is taken.

The study protocol, data-recording procedures, data handling as well as study reports are subject to an independent clinical Quality Assurance audit by the sponsor, its designee, or health authorities. These audits will require access to all study records, including source documents, for inspection and comparison with the eCRFs.

11 ETHICS

11.1 CONFIDENTIALITY

The Investigator shall consider all information, results, discoveries; records accumulated, acquired, or deduced in the course of the study, other than that information to be disclosed by law, as confidential and shall not disclose any such results, discoveries, records to any third party without the Sponsor's prior written consent.

IRB members have the same obligation of confidentiality.

11.2 INSTITUTIONAL REVIEW BOARDS

Institutional Review Board (IRB) approval is required for the study to start at a site and subjects to be enrolled. The investigator is responsible for fulfilling any conditions of approval imposed by the reviewing IRB. The investigator must also obtain renewal of IRB approval as dictated by local requirements during the entire duration of the study. The investigator will provide the study sponsor with copies of such approvals and reports.

Withdrawal of IRB approval must be reported to the study sponsor immediately (not more than 5 working days) following the investigator's knowledge of the withdrawal.

The reviewing IRB must review and approve an informed consent form (ICF) specific to this study. The study center may modify this example ICF to meet specific requirements; however, the ICF must contain all the elements of informed consent as described in 21 CFR 50.25. Each investigational site will provide the sponsor with a copy of the IRB approved ICF and any revised consents as appropriate for the duration of the study.

The written informed consent (and any other written information to be provided to the study subject) should be updated whenever new information becomes available that may impact the subject's consent. Any such revision or update must be approved by the reviewing IRB/EC before being provided to the study subject. Should it be necessary that such information is verbally provided to the study subject (in the case that the information may impact the subject's willingness to continue study participation), communication of the information must be documented.

11.3 ETHICAL CONDUCT OF THE STUDY

The rights, safety and well-being of clinical study subjects shall be protected consistent with the ethical principles laid down in the Declaration of Helsinki. This shall be understood, observed and applied at every step in this clinical study.

It is expected that all parties will share in the responsibility for ethical conduct in accordance with their respective roles in the study. The sponsor and investigators/coordinators will avoid improper influence or inducement of the subject, monitor, the clinical investigator(s) or other parties participating in or contributing to the clinical study.

11.4 PROTECTION OF SUBJECT CONFIDENTIALITY

At all times throughout the clinical study, confidentiality will be observed by all parties involved. All data shall be secured against unauthorized access. Privacy and confidentiality of information about each subject shall be preserved in study reports and in any publication. Each subject participating in this study will be assigned a unique identifier. All data will be tracked, evaluated, and stored using only this unique identifier.

Any source documents copied for monitoring purposes by the Sponsor will be identified by using the assigned subject's unique identifier to protect subject confidentiality; any subject identifying information must be redacted.

11.5 Sponsor responsibilities

The sponsor's responsibilities include but are not limited to:

- Submission of an IDE application to FDA
- Selecting qualified investigators (qualifications will be documented)
- Providing investigators with the information necessary to conduct the study properly
- Providing appropriate training to each study site and all study personnel (monitors), as necessary
- Documenting training where appropriate
- Selecting monitors qualified by training and experience to monitor the investigational study.
- Ensuring that the IRB approval is obtained
- Ensuring that any reviewing IRB or FDA are informed of significant new information
- Providing investigational product to qualified investigators
- Obtaining signed Investigator Agreement for each investigator prior to their participation in the study
- Obtaining sufficient and accurate financial disclosure information (21 CFR Part 54)

11.6 Investigator responsibilities

The Principal Investigator (PI) shall be responsible for the day-to-day conduct of the clinical study and for the safety and well-being of the human subjects involved in the clinical study as described in the Investigator Agreement. If there is a change or addition of Investigator, an amended agreement must be completed promptly.

11.7 Conflict of interest policy

Any investigator who has a financial conflict of interest (e.g., patent ownership, royalties, or financial gain greater than the minimum allowable by their institution, etc.) must 1) inform the study sponsor, and 2) have the conflict reviewed by a properly constituted conflict of interest committee who has reviewed and approved participation prior to initiating participation in this study.

11.8 Study administration

11.8.1 Study leadership

As the study sponsor, MicroVention, Inc. is the manufacturer of the PHIL Liquid Embolization System and has the overall responsibility for the conduct of the study. For this study, MicroVention will have certain direct responsibilities and will delegate other responsibilities to appropriate consultants and contract research organizations (CROs).

11.8.2 Study registration

This study will be registered on ClinicalTrials.gov (www.clinicaltrials.gov) prior to study initiation.

11.8.3 Data ownership

Rights, duties, and obligations regarding ownership of any ideas, concepts, inventions, or results, whether patentable or not, shall be in accordance with the terms and conditions set forth in the Clinical Study Agreement by and between the Institution and Sponsor unless otherwise expressly set forth in the Clinical Study Agreement, the Sponsor retains exclusive ownership of all data, results, reports, findings, discoveries and any other information collected during this study. The Sponsor reserves the right to use the data from the database in the present study.

11.8.4 Study discontinuation by sponsor

The Sponsor may choose to discontinue the study should the Sponsor discover additional information during the study that may cause harm to subject safety.

If the study is terminated prematurely or suspended, the Sponsor will promptly inform all clinical Investigators of the termination or suspension and the reason(s) for this. The IRB/EC will also be informed, either by the Sponsor or Investigator if a local IRB/EC is utilized, promptly and provided with the reasons(s) for the termination. If applicable, regulatory authorities will be informed. Enrolled subjects will be asked to complete all remaining study visits and the subject will then be seen by the treating physician per standard clinical care following dAVF treatment.

12 Data handling and record keeping

12.1 Electronic case report forms

Data will be collected using electronic case report forms (eCRF) and a 21 CFR Part 11 compliant electronic data capture (EDC) system including:

- Overall system validation, accuracy and reliability
- Audit trail
- Long-term retention
- Password protection
- Time-stamped logging of changes to database on an individual user level
- Limitation of system access only to authorized individuals
- Operational system checks to enforce sequencing of steps
- Authority checks to ensure appropriate levels of access
- Edit checks, as required, to enhance data quality
- Written policies that hold individuals accountable for actions initiated under their electronic signatures
- Appropriate controls over system documentation

Additional aspects of EDC include regular and secure off-site storage and backup.

Site personnel may log on the system securely and enter the data remotely. All subjects' data collected in the system will be extensively verified through data validation programs, database integrity rules, and study-specific data entry conventions for data accuracy and logical meaningfulness. Periodic analysis of all subjects' collected data will be performed in order to examine the expected distributions of data and to identify outliers for possible data entry errors.

The investigator is responsible for reviewing all eCRF entries for completion and correctness. Data changes will be made electronically and the system used will keep an audit trail of changes. If necessary, an explanation for the change(s) may be provided. All study staff that will enter data into eCRFs will undergo appropriate training for use of electronic eCRFs. The sites will be trained in use of the EDC system during site initiation.

Modifications to eCRFs, if required, will be tracked by the sponsor.

12.2 STUDY RECORDS

Study documentation during the study and for a period of two (2) years after the latter of the following two dates: The date on which the study is terminated or completed, or the date that the records are no longer required for purposes of supporting a premarket approval application or a notice of completion of a product development protocol. These documents should be retained for a longer period, however, if required by local regulations. No records will be destroyed without the written consent of the sponsor, if applicable. The sponsor will inform the investigator when these documents no longer need to be retained.

The investigator is responsible for maintaining medical and study records for every subject participating in the clinical study (including information maintained electronically such as digital imaging). The investigator will also maintain original source documents from which study-related data are derived, which include, but are not limited to:

- all correspondence including required reports,
- records of receipt, use, or disposition of the investigational device,
- records of each subject's case history and exposure to the device which must include,
    - signed and dated consent forms
    - condition of each subject upon entering the study
    - relevant previous medical history
    - record of the exposure to the investigational device, including the date and time of each use and any other therapy
    - observations of adverse device effects
    - medical records (physician and nurse progress notes, hospital charts, etc.)
    - results of all diagnostic tests
    - case report forms
    - any other supporting data
- the protocol and documentation (date and reason) for each deviation from the protocol.
- any other records that FDA requires to be maintained.

The sponsor should be contacted if the investigator plans to leave the investigational site so that arrangements can be made for the handling or transfer of study records.

13 FINANCING AND INSURANCE

The Sponsor is responsible for obtaining and maintaining appropriate insurance policies for the clinical study.

14 PUBLICATION AND DATA SHARING POLICY

The Sponsor will post results on the clinicaltrials.gov registry as required by the International Committee of Medical Journal Editors (ICMJE) member journals and applicable U.S. laws and regulations. It is intended to publish the results of this multicenter study, regardless of study outcome. Individual investigators are therefore asked to refrain from reporting results from their study participants prior to publication of the main multicenter report. The Sponsor will establish authorship criteria for such publications for the study group, based on the study conduct and compliance, contribution to the study design, management or enrollment, and willingness to accept the rights and responsibilities of an author.

15 DEFINITIONS

Term	*Definition*
Adjunctive treatment	Additional treatments with to continue or complete the treatment of the fistula other than PHIL. This could include but is not limited to other liquid embolic agents, embolic coils, surgery or radiosurgery.
Adverse Event (AE)	Any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the investigational medical device. (ISO 14155:2011 3.2) 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 investigational medical devices.
Completion of treatment	Cessation of blood flow through all the vessels targeted for embolization, as specified by treating physician in eCRF.
Concomitant disease-related adverse event	Event is clearly attributable to the underlying concomitant disease state with no temporal relationship to the device, treatment, or medication.
Device-related adverse event	Event has a strong temporal relationship to the study device, and alternative etiology is less likely.
Enrolled	Subject has provided written informed consent to participate in the study, meets all enrollment criteria, and treatment with the PHIL device is attempted. The point of enrollment occurs when the PHIL liquid embolic syringe and adaptor assembly is connected to the microcatheter hub.
Full Analysis Set Population (FAS)	All enrolled subjects including only those in whom the PHIL™ device was implanted.
NIH Stroke Scale (NIHSS)	Tool to quantify neurological impairment caused by stroke.
Intracranial hemorrhage	Hemorrhage within the fixed vault of the cranium (skull)
Mild (AE severity)	No limitation of usual activities, no therapy or only symptomatic therapy required to treat the injury or illness.
Moderate (AE severity)	Some limitation of usual activities or specific therapy is required.
Modified Rankin Scale (mRS)	Scale for measuring general neurologic function. 0 No symptoms at all 1 No significant disability despite symptoms; able to carry out all usual duties and activities 2 Slight disability; unable to carry out all previous activities, but able to look after own affairs without assistance 3 Moderate disability; requiring some help, but able to walk without assistance 4 Moderately severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance 5 Severe disability; bedridden, incontinent and requiring constant nursing care and attention 6 Dead
Neurologic death	Subject death reported as having resulted from a neurologic cause.
Procedure	The index study procedure involving the placement of the PHIL™ device.
Procedure-related adverse event	Event has a strong temporal relationship to any PHIL procedure. This includes AEs attributable to any device(s) other than the PHIL™ device used at any PHIL procedure, such as access devices, delivery microcatheters, non-ionic contrast,

	guidewires, or any other adjunctive, approved/cleared device for treatment of intracranial dAVFs.
Procedure time	Start: Time of first fluoroscopic or digital subtraction angiographic acquisition End: Time of last fluoroscopic or digital subtraction angiographic acquisition
Screen Failure	Screened patient who did not meet the enrollment criteria and was not enrolled in the study.
Serious Adverse Event (SAE)	An adverse event that: a) Led to death, b) Led to serious deterioration in the health of the subject, that either resulted in a. A life-threatening illness or injury, or b. A permanent impairment of a body structure or a body function, or c. In-subject or prolonged hospitalization, or d. Medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function, Led to fetal distress, fetal death or a congenital abnormality or birth defect (ISO 14155:2011 3.37) NOTE: Planned hospitalization for a pre-existing condition, or a procedure required by this protocol, without serious deterioration in health, is not considered a serious adverse event.
Severe (AE severity)	Inability to carry out usual activities, hospitalization, emergency treatment, life threatening events, or death.
Stroke	Stroke – A new focal neurological deficit in a defined vascular distribution of abrupt onset with symptoms persisting for > 24 hours AND a neuro-imaging study or other quantitative study that does not indicate a different etiology.
Study disease-related adverse event	Event is clearly attributable to the underlying study disease state with no temporal relationship to the device, treatment, or medication.
Supplemental procedure(s)	A supplemental PHIL procedure(s) conducted to continue or complete the treatment of the fistula.
Technical event	Any malfunction or deficiency of the study device.
Transient Ischemic Attack (TIA)	A focal ischemic neurological deficit of abrupt onset and of presumed vascular etiology that resolves completely within 24 hours of onset.
Unanticipated Adverse Device Effect (UADE)	Any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects. (21 CFR 812.3 (s))
Unknown (AE relatedness)	Event relationship cannot be attributed to any of the above categories and remains undetermined.

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