PHIL evaluation in the endovascular treatment of intracranial cerebral ArterioVenous Malformation (cAVM)

European multi-center Study, observational, prospective, single arm and open label.
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### SUMMARY

**Study title:** PHIL<sup>®</sup> evaluation in endovascular treatment (EVT) of cerebral arteriovenous malformations (cAVM)

**Study design:** European observational, prospective, multicenter, non-randomized, single-arm and open label study.

**Device:** PHIL<sup>®</sup> = Precipitating Hydrophobic Injectable Liquid (PHIL<sup>®</sup> 25%, PHIL<sup>®</sup> 30%, PHIL<sup>®</sup> 35%)

PHIL<sup>®</sup> is a non-adhesive liquid embolic agent CE marked for endovascular treatment of cAVM.

**Main objectives:**
1. Assess efficacy and safety of PHIL<sup>®</sup> liquid embolic agent in endovascular embolization of cerebral arteriovenous malformations.
<table>
<thead>
<tr>
<th>Primary endpoints:</th>
<th>1. Efficacy:</th>
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<tbody>
<tr>
<td></td>
<td>Cure rate* of cAVM with PHIL® immediately after last embolization in all patients</td>
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<td></td>
<td>Cure rate* at 3-6 months in patients treated with EVT alone.</td>
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<tr>
<td>* cure rate:</td>
<td>- the overall cure rate.</td>
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<td></td>
<td>- the cure rate with regard to the aim of the endovascular treatment.</td>
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<td></td>
<td>- calculated volume reduction as a percentage of the initial, pretreatment cAVM volume on DSA /flat panel CT</td>
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<td>2. Safety:</td>
<td>Clinical outcome compared to baseline by mRS at discharge, 1 month after each procedure and at 3-6 months after the final embolization in all patients performed by an independent neurologist.</td>
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<td></td>
<td>For patients who have had NS or RT within 1-2 months after the last embolization it is recommended that the clinical follow up is performed as close as possible to 6 months.</td>
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<td></td>
<td>A new clinical evaluation (mRS) will be performed before this intervention (i.e. the day before surgery or at the time of stereotactic imaging) and at the scheduled evaluation three to six months after embolization.</td>
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</tbody>
</table>
| Secondary endpoints: | 1. Adverse events related to the PHIL® procedure and/or to the techniques used during each embolization as well as events evolving shortly after or in between the EVT procedures and up to the last follow up.  

2. Technical performance of PHIL® with regard to:  
   - Total volume of injected PHIL®  
   - Volume/superselective injection (pedicle)  
   - Length of reflux of PHIL® (along micro-catheter)  
   - Amount of pedicles catheterized  
   - Overall injection time  
   - Overall radiation dose given to the patient during EVT |
| Study population: | All patients with a cAVM, ruptured or unruptured, eligible for endovascular treatment with a liquid embolic agent, PHIL®, based on multidisciplinary consensus. |
| Number of subjects: | 108 patients  
With 98 patients enrolled in the cohort, we will be able to estimate the principal outcomes with a 95% confidence interval size of ±5.0% considering the frequency of 6.8% found in a previous study (poor clinical outcome rate observed in Elsenousi and all).  
In addition, even with 10% lost to follow-up patients, this sample size (N=108) ensures an accuracy of at least ±10% for observed parameters. |
| Number of sites: | Up to 18 investigational sites |
| Registry duration: | The duration of the study is estimated to be about 39 months; enrollment period will be 18 months and follow up period will be 21 months to cover all enrolled patients. |
| Inclusion criteria: | 1. All patients with a ruptured or unruptured and previously endovascularly* untreated cAVM that are eligible for endovascular treatment with PHIL® alone or in conjunction with N-Butyl cyanocrylate glue (NBCA) and/or coils (e.g. if “pressure cooking” technique is needed or used).**

2. All patients with a previously endovascularly treated cAVM in which NBCA and/or coils (but not another non-adhesive liquid embolic agent) have been used may be included.**

3. All patients with a remaining cAVM, ruptured or unruptured, that has previously been treated with NS and/or RT may be included.**

*Patients with a saccular or flow-related aneurysm previously treated with NBCA and/or coils may be included.

**All enrollment must be based on a multidisciplinary agreement.

4. Patient or patient’s legally authorized representative has received information about data collection and has signed and dated an Informed Consent Form. (Based on the country’s regulation). |
| Exclusion criteria: | 1. cAVM not eligible for endovascular treatment |
| | 2. cAVM previously treated with a non-adhesive liquid embolic agent other than PHIL® |
| | 3. Treatment requiring the use of any other non-adhesive embolic liquid |
| | 4. Patient is allergic to iodine |
| | 5. Premature and newborn infant |
| | 6. Patient with renal failure or significant liver impairment |
| | 7. Patient is participating in another study evaluating other medical devices, other procedures or medications. |
| | 8. Any other condition that might prevent patient participation in the study or follow up |
| | 9. Patient does not want to and/or refuses to give consent to the collection and processing of data required for centralized monitoring |
### Study limitations:

Since this is an observational study there are limitations in the study protocol. Different sites have different protocols for early complementary cAVM treatments, clinical and imaging follow up. Consequently we have to accept that there will be a variation in efficacy and safety evaluation with regards to time point.

### Follow up:

- Usual site practice will be followed
- DSA before and after each procedure for all patients and at 3-6 months after the final embolization for patients treated with EVT alone. MRI included (see above study limitation)
- Flat panel CT at baseline, after the last embolization and as well as 3-6 months of follow up
- Any other MRI/ CE-MRA as well as CT/CTA done within the study duration period will be collected and evaluated for enrolled patients
Independent central review: Two independent committees—an imaging core lab and a CEC—will review the results and clinical events respectively:

1. Imaging core lab will evaluate:
   - The overall cure rate
   - The result with regard to aim of treatment
   - Performance of PHIL® used

2. Clinical events committee (CEC):
   - Will review and adjudicate all reported adverse events throughout the study period and their relationship to the device and/or procedure including post procedure care.

All collected DSA/Flat panel CT and MRI/ CE-MRA as well as CT/CTA performed during the study period will be provided in order to facilitate the above assessments.

Imaging core lab member will perform two separated analysis of the cAVM volume assessment. The First one using the formula:

\[ V = \frac{1}{6} \pi (L \times W \times H) \]

in the three orthogonal directions, the second one using the Element* software from brain lab in order to obtain a more standardized volume and feeders occlusion assessment. Sites will perform their measurement based on their current practice.

*Element software which one module SMARTBRUSH ANGIO is fully dedicated to AVM nidus delimitation and feeders vessels identification dedicated mainly to Neurosurgeons and/or stereotactic radiosurgery.
Statistical method:

All patients included and treated with PHIL® during the study will be analyzed (ITT).

Categorical variables will be described by their frequency distribution and ranges bilateral 95% confidence. Continuous variables will be described by their average, minimum standard deviation, maximum, median and quartiles.

Variables (3-6 months cured (yes / no) or improvement of mRS at 1 month (yes / no)) will be described by their distribution frequencies and intervals bilateral associated 95% confidence.

Relevant group comparisons will be performed using an adequate test for the variable type:

- Person's chi-square (or Fisher's exact test if the expected frequency in a group is smaller than five) for qualitative variables
- Variance analyses for quantitative variables
- Variance analyses based on ranks for ordinal variables

Statistical test will be performed with a type I error risk of 5%.

The rate of events for which a date of onset has been collected will be described survival curve according to Kaplan-Meier method and the associated Kaplan Meier estimators will be calculated.
| Regulatory: | Before inclusion of patients and in order to obtain opinions and authorizations, this observational study will be submitted to any relevant institutions for review in accordance with the regulations in force in each participating country.

Regarding patient information, an Informed Consent Form shall be given to the patient (or his/her legal representative), and a signed and dated acceptance to participate in the study shall be obtained prior to inclusion in the study.

Information on the data collected as well as on their right to object or withdraw from the collection and transmission of data should be included. |
| --- | --- |
| Data collection, recording and study management: | Data will be collected by the participating investigators through an electronic CRF developed for the study. The access is secured and limited to authorized persons.

Microvention Europe is responsible for monitoring the data collection. To ensure data quality, a plan for monitoring visits will be implemented.

The study data will be stored in a European or international public database. |
## ACRONYMS

<table>
<thead>
<tr>
<th>Abbreviations</th>
<th>Definitions</th>
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<tr>
<td>AE/SAE</td>
<td>Adverse Event/Serious Adverse Event</td>
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<tr>
<td>ACA</td>
<td>Anterior Cerebral Artery</td>
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<tr>
<td>AICA</td>
<td>Anterior Inferior Cerebellar Artery</td>
</tr>
<tr>
<td>BA</td>
<td>Basilar Artery</td>
</tr>
<tr>
<td>CA</td>
<td>Competent Authority</td>
</tr>
<tr>
<td>cAVM</td>
<td>cerebral ArterioVenous Malformation</td>
</tr>
<tr>
<td>CEC</td>
<td>Clinical Event Committee</td>
</tr>
<tr>
<td>CE</td>
<td>Conformité Européenne (European Conformity)</td>
</tr>
<tr>
<td>CRA</td>
<td>Clinical Research Associate</td>
</tr>
<tr>
<td>CT/CTA</td>
<td>Computed Tomography/ - Angiography</td>
</tr>
<tr>
<td>dAVF</td>
<td>dural ArterioVenous Fistula</td>
</tr>
<tr>
<td>DSA</td>
<td>Digital Subtractional Angiography</td>
</tr>
<tr>
<td>DMSO</td>
<td>Dimethyl Sulfoxide</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Description</td>
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<tr>
<td>EC</td>
<td>Ethics Committee</td>
</tr>
<tr>
<td>eCRF</td>
<td>Electronical Case Report Form</td>
</tr>
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<td>EoS</td>
<td>End of Study</td>
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<tr>
<td>EVT</td>
<td>Endovascular Treatment</td>
</tr>
<tr>
<td>ICA</td>
<td>Internal Carotid Artery</td>
</tr>
<tr>
<td>ICF</td>
<td>Informed Consent Form</td>
</tr>
<tr>
<td>ICH</td>
<td>Intracerebral Hemorrhage</td>
</tr>
<tr>
<td>IVH</td>
<td>Intraventricular Hemorrhage</td>
</tr>
<tr>
<td>LOCF</td>
<td>Last Observation Carried Forward</td>
</tr>
<tr>
<td>MCA</td>
<td>Middle Cerebral Artery</td>
</tr>
<tr>
<td>MRI/CE-MRA</td>
<td>Magnetic Resonance Imaging/ Contrast Enhanced Magnetic Resonance Angiography (Time Of Flight)</td>
</tr>
<tr>
<td>mRS</td>
<td>modified Rankin Scale</td>
</tr>
<tr>
<td>NBCA</td>
<td>N-Butyl CyanoAcrylate (Histoacryl)</td>
</tr>
<tr>
<td>NS</td>
<td>Neurosurgery</td>
</tr>
<tr>
<td>PICA</td>
<td>Posterior Inferior Cerebellar Artery</td>
</tr>
</tbody>
</table>
A. Introduction

A cerebral arteriovenous malformation (cAVM) is a vascular disease characterized by a complex network of small abnormal vessels (i.e. a nidus) through which there is an early and rapid arteriovenous shunt (AV-shunt). cAVM is a rather rare disease with an incidence and prevalence of ~1 per 100 000 and < 18 per 100 000, respectively. Its clinical presentation occurs most commonly in younger adults (20-40 years of age). Approximately 85% of all cAVMs are located supratentorial and 15% infratentorial. A cAVM lacks a normal capillary bed. Its nidus may vary in size and is in general fed by one or more enlarged arteries and drained by one or more enlarged veins. There are a variety of cAVM types but they may roughly be divided into three; plexiform, fistulous or combined plexiform-fistulous. Those containing intra-nidal fistulaes generally have an increased degree of high-flow shunting. Due to the increased flow, lack of normal autoregulation and shear stresses to the vascular bed, the main risk associated with a cAVM is an intracranial (ICH) and predominately an intracerebral hemorrhage. The risk evolution to a high extent depends on its angioarchitecture, its location and its clinical presentation. As mentioned,
the most common presentation of a cAVM is an ICH (parenchymal, intraventricular or subarachnoid) which occurs in about 50-60% of cases. The risk of an ICH related to a cAVM is estimated to be 2-3% per year and about 30% in the following 10 years. However, the risk of having an early rebleed is higher if the cAVM presents with an ICH, risk of recurrent hemorrhage is around 15-18% within the first year after the initial ICH and 25% after a second bleed. Seizure is another common presentation (20-50%) as is headache (10-50%) of which approximately 15% are asymptomatic and incidental findings. Progressive or transient neurological symptoms are relatively rare but may occur and are often explained by mass effect, hemodynamic alterations or venous hypertension. cAVMs are responsible for 1-2% of all cerebrovascular strokes but, are more common sources of stroke in the younger population. cAVM is a complex vascular disease which is potentially dangerous and sometimes hazardous to treat and cure. The natural history of a cAVM is still not fully known, although the recently published ARUBA³ study indicates that the risk of an ICH from an unruptured cAVM is not as high as previously understood. Although the conclusion of the ARUBA study is still controversial, its results must be taken into account whenever we determine our treatment strategy, not least for cAVMs that have not bled. Despite the relative low risk of rupture and the relatively high chances (50-86%) of a good neurological outcome (mRS 0-2, i.e. functional independent) the mortality and morbidity rate from a ruptured cAVM cannot be neglected and might be as high as 16-35%. The objective of this observational study is not to compare the different treatment modalities but rather to evaluate a new liquid embolic agent for endovascular use, PHIL®, and to correlate its results with reports from other similar liquid embolic agents.

The available treatment modalities

There are several options for cAVM treatment including:

• neurosurgery (NS)
• stereotactic radiosurgery (SRS) = (RT)
• endovascular embolization
• a combination of the above three modalities
• partial and targeted embolization
• a more conservative approach (i.e., symptomatic medical treatment without other intervention)
Regardless of the strategy used, the choice of treatment must be based on a multi-disciplinary agreement and there are many factors that influence the decision of which strategy to select, including patient age, how the cAVM presents, the clinical condition of the patient, the angio-architectures, topographic entities, the volume of the cAVM etc. In addition, one must evaluate the presence of potential risk factors for ICH or a rebleed such as flow related or intra-nidal aneurysm, venous drainage (profound, superficial, venous ectasia and venous outflow impairment (stenosis) etc.

The preliminary aim of treatment is to resect or to obliterate the cAVM nidus, to minimize the risk of future bleedings and to offer the best conditions for intensive care and rehabilitation if the patient has presented with an ICH.

A neurosurgical approach is most appropriate for cAVM with a massive ICH that has to be evacuated, for small and superficial cAVMs, or cAVMs located in a non-eloquent area (Spetzler-Martin grade I-II, see appendix). The idea of NS is to perform a total excision of the cAVM if possible.

Stereotactic radiotherapy\(^2\) is most effective for small cAVMs, not least for those in an eloquent area and/or with a deep location (cure rate of 70-80%). SRS is a single fraction, one procedure treatment. The irradiated cAVM gradually obliterates over time and the main drawback of SRS is that the obliteration is not immediate but rather is obtained within 2-3 years after the given treatment.

Embolization is an endovascular technique that has improved tremendously in recent decades. Through this approach there is a good possibility to reach and treat most cAVMs. New devices and techniques as well as better understanding and imaging modalities have improved treatments and the overall cure rate by embolization alone. Results vary with a cure rate of 10-51% published in the literature.\(^4\) to \(^9\) However, this can, to some extent, be explained by the aim of treatment (cure or volume reduction) which seems to vary from one centre to the other. In other words, the success of embolization is partially defined based on the aim of the treatment:

I. Curative, by a complete occlusion

II. Pre-operative embolization to facilitate a surgical intervention (excision) by reducing the size of the cAVM to \(\leq 3\) cm, occluding the deepest portion of the cAVM or eliminating/reducing risk-factors associated with the cAVM and thereby surgery. This is
not least important in cAVMs of SM grade ≥ 3. Furthermore, to obliterate a portion within an eloquent area and/or to occlude a portion with a deep venous drainage etc.

III. To optimize the condition for radiotherapy by reducing the size of the cAVM and consequently to improve the circumstances for cure by RT.

IV. Partial embolization with no intention to cure the cAVM by embolization or any other modalities. The intention of this strategy might be to improve clinical condition of the patient (response to the given pharmacological therapy, seizures etc.). By reducing the size of the cAVM, the grade of shunting or secondarily induced venous hypertension. In addition, partial embolization may include targeted obliteration of associated risk factors such as pre- and intranidal aneurysms.

V. A last option is to have a conservative attitude

Treatment Description:
The purpose of treating a patient presenting with a cerebral AVM is to prevent or reduce the risk of an intracerebral hemorrhage, a re-hemorrhage and other symptoms associated with an cAVM such as seizures, neurological deficits, headaches, cognitive dysfunctions etc.

The embolic agents available for cAVM treatments consist mainly of two types;

Non – adhesive liquid embolic agents which solidify by precipitation such as ONYX®, Squid® and PHIL®.

Adhesive liquid agents (glue) which solidify by polymerization (based on n-butyl-cyanoacrylate (NBCA)), such as Histoacryl® or Glubran®. ¹

Other embolic materials such as coils, detachable balloons and PVA are rarely used in cAVM treatment. However, balloons and coils can occasionally be used as supplementary treatments to reduce the high-flow shunt, to minimize retrograde reflux of the embolic agent (“pressure cooking” technique) along the micro-catheter and to give better control of the injections of the liquid embolic agent during embolization (to minimize potential distal migration).

Glue has for a long time been the standard embolic agent for cAVMs but during the last decade
non-adhesive liquid embolic agents have to a large extent replaced its use. NBCA is, as mentioned, adhesive. It also polymerizes rather rapidly and is very user and flow dependent. Injection has to be done under flow-control and for a short period of time with a limited degree of nidal penetration before pulling back the micro-catheter to minimize the risk of it attaching to the vessel wall. Consequently, NBCA generally requires multiple micro-catheterizations and injections. Non-adhesive liquid embolic agents can be injected for a longer period of time, with good penetration to the nidal within a single injection. Consequently they offer the possibility to obliterate a larger portion/volume of the cAVM nidal during a single injection with the potential to obtain a total cure in one or more sessions. The occlusion rate is improved and the risk of a microcatheter adhering to the cerebral vessels is reduced with these agents, especially since the introduction of micro-catheters with a detachable tip.

ONYX® and Squid® are two types of liquid embolic agents comprised of EVOH (ethylene vinyl alcohol) copolymer dissolved in DMSO (dimethyl sulfoxide) and suspended in micronized tantalum powder to provide visualization under fluoroscopy.

PHIL® is a new, CE- marked and recently presented non-adhesive liquid embolic agent with some similarities to ONYX® and Squid®. It is a co-polymer dissolved in DMSO but instead of tantalum as a radiopacifier, an iodine component is chemically bonded to the co-polymer as described below. Like the other non-adhesive embolic agents, PHIL® offers good control and prolonged injection of the embolic agent during AVM embolization (8). The effectiveness and safety of PHIL® for cAVM embolization is still not fully established and the aim of this observational study is to evaluate its performance in both of these aspects.

A.1 Medical Device Information

The PHIL® Liquid Embolic System received CE mark in July 2014 and is intended for use in the embolization of lesions in the peripheral and neurovasculature, including arteriovenous malformations and hypervascular tumors.

PHIL® is a non-adhesive liquid embolic agent comprised of a 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 neuro 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%. Depending on the concentration of the copolymer the viscosity as well as the opacification of PHIL® varies- low concentration gives reduced viscosity and less opacification. Consequently, 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. PHIL® 30% and 35% are more appropriate for use in high flow conditions with a significant AV-shunt due to one or more direct nidal fistulas and/or when increased visibility is needed. Final solidification occurs within five minutes for all product formulations.

PHIL® 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 copolymer 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.

**B. Study Plan**

**B.1 Study Design**

An European, observational, prospective, multicenter, non-randomized, single-arm, open label study. Study patients will be followed per standard of care in their respective centers.
## B.2. Study Schedule

<table>
<thead>
<tr>
<th></th>
<th>Baseline&lt;sup&gt;1&lt;/sup&gt;</th>
<th>Procedure 2&lt;sup&gt;2&lt;/sup&gt; (1 to 6)</th>
<th>Discharge</th>
<th>1 month FU (1 to 6)&lt;sup&gt;4&lt;/sup&gt; Optional by phone</th>
<th>3-6 months FU post last embolization</th>
<th>RT or NS procedure (Before the intervention)</th>
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<td>Patient demographic</td>
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<td>Neurological status (mRS, WFNS)</td>
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<tr>
<td>DSA*</td>
<td>X&lt;sup&gt;11&lt;/sup&gt;</td>
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<tr>
<td>Flat panel CT**</td>
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<td>X&lt;sup&gt;10&lt;/sup&gt;</td>
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<td>Irradiation info</td>
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<tr>
<td>Procedure complications</td>
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<tr>
<td>Procedure results</td>
<td>X&lt;sup&gt;3&lt;/sup&gt;</td>
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<td>AE(s)</td>
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<td>X</td>
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<td>DSA control</td>
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<td>X&lt;sup&gt;6&lt;/sup&gt;</td>
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<tr>
<td>MRI/CE-MRA/CTA&lt;sup&gt;5&lt;/sup&gt;</td>
<td>x</td>
<td>X&lt;sup&gt;3&lt;/sup&gt;</td>
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<td>X</td>
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</tbody>
</table>
1 At this stage Site will have to define its treatment strategy based on the AVM characteristics, patient symptoms and physical status.

2 Procedure includes data from pre-procedure to procedure (applies to any therapeutic strategy)

3 Based on the post procedural images, procedure results will be assessed and next step will be decided

4 Safety visit at one month post any embolization session including the last embolization before complementary treatment with either neurosurgical resection (NS) or radiotherapy (RT) if suggested.

5 MRI recommended for diagnosis of unruptured cAVM.
MRE including FLAIR, T2W, T1W, DWI
However, any extra MRI/CE-MRA (TOF)/CT(A) performed during the study period will be collected to facilitate the imaging core lab and CEC assessments if performed.

6 Excluding RT and NS treatment strategy

7 mRS will be collected just before NS or RT procedure by an independent neurologist.

8 MRI if performed just after the last embolization

*DSA. According to site practice, frontal and lateral projection pre and post EVT, unsubtracted image with PHIL cast and images illustrating the micro-catheter and potential reflux.

**According to the site practice, Flat panel CT (if not obtained during diagnosis) and post last embolization as well as 3-6 months follow up (Xpert CT, 3D-DSA or Dyna CT or equivalent) in order to have the best possible and complete nidus filling with contrast. We recommend to select your protocol on the following examples:
Flat Panel CT run has to include a native and a contrast run
cAVMs with multiple feeders/territories, Aortic contrast injection for analysis,
cAVM with one or two feeders/territories reach better contrast by transarterial contrast injection via one or two access catheters.
Alternatively also a i.v. contrast bolus can be considered, though keep in mind, that the amount of necessary contrast will be higher
Native, CE and unsubtracted images will have to be obtained from the full skull Flat panel run.

Timing and length of contrast bolus: adjust the contrast bolus in timing and length, so that the contrast filling of the nidus is maintained over the whole length of the acquisition of the flat panel run.

Bolus planning for the individual case:
The injection time of the contrast bolus:
(acquisition time of contrast flat panel CT run) + (contrast peak time -the time the contrast needed to fill the complete nidus in the previous acquired standard DSA run) + 1 extra second as an additional buffer

The X-ray delay; = (contrast peak time)
Contrast volume in ml; (Injection time) * (Injection speed) ml/s

9 Performed by an independent neurologist
10 after last embolization
11 DSA pre, per, post Procedure
B.3. Study Population

All patients with a cAVM, ruptured or unruptured, eligible for endovascular treatment with a liquid embolic agent, PHIL®, based on multidisciplinary consensus.

B.4. Study Duration

Overall study duration is estimated to be around 36 months, including an enrollment period of 15 months and a follow-up period* of around 21 months.

Using EVT a cAVM is usually treated in staged procedures (1-6 sessions) with intervals varying from one EVT center to the other- however in this study a range of one to three months in between each embolization procedure will be highly recommended.

* Since this is an observational study in which all patients will be followed for at least a period of 3-6 months after the final embolization and/or after complementary treatment with NS and RT (safety only) the overall follow-up time might vary. In addition the time in between treatments may, as mentioned, also vary. Altogether this means that the given follow-up time is an average estimation based on 15 months for the duration of treatment (if 6 sessions applied) and 3-6 months after final embolization.

B.5. Study Objectives

Primary endpoints:

1, Efficacy

Cure rate* of cAVM with PHIL® immediately after last embolization in all patients including those who will have complementary treatment with NS or RT.

Cure rate* at 3-6 months in patients treated with EVT alone.

* Cure rate

- The overall cure rate**

- The cure rate with regard to the aim of the endovascular treatment:

  I - Complete occlusion by embolization alone
II - Volume reduction before NS or RT

- IIa \( > 0\text{-}25\% \)
- IIb \( > 25\text{-}50\% \)
- IIc \( > 50\text{-}75\% \)
- IIId \( > 75 < 100\% \)
- IIe =100%

III- Shunt reduction alone to decrease venous hypertension, symptoms (refractory seizure etc.) without an intention for additional therapy or cure.

IV- Targeted embolization alone in an acute setting (aim to occlude a ruptured feeder, intranidal or venous aneurysm (potential bleeding point or fragile structure)) before NS or RT.

- **The cure rate is the calculated volume reduction as a percentage of the initial, pretreatment

  cAVM volume on DSA + Flat panel CT

*Volume calculation of the initial and final cAVM volume nidus is based on the following formula:

Estimated volume spheroid \( V=\frac{1}{6} \pi (L \times W \times H) \) in the three orthogonal directions

\( L= \) Largest length diameter
\( W= \) Largest width diameter
\( H= \) Largest height diameter

Two separated analysis will be performed by the imaging corelab members. A first analysis will be performed and as described above a second analysis will be performed with the help of the element software from brain lab in order to obtain standardize volume occlusion assessment.
Sites will perform their measurement based on their current practice.

2 Safety: Clinical outcome

Clinical outcome compared to baseline evaluated by mRS* at discharge, at 1 month after each procedure and at 3-6 months after the final embolization in all patients by an independent neurologist.
For patients having complementary cAVM treatment (NS) within one month post EVT (NS or RT), a new clinical evaluation will be performed before this intervention (i.e. the day before surgery or at the time of stereotactic imaging) and at the scheduled evaluation three to six months after embolization.

* performed by an independent neurologist at baseline, in association with procedures and 3-6 months post last embolization or just before NS or RT if apply.

Secondary endpoints:

1. Adverse events

   Procedural and post-procedural adverse events related to PHIL®.

   • Adverse events related to the PHIL® procedure and/or to the techniques used during each embolization as well as events evolving shortly after or in between the EVT procedures and up to the last follow up.

2. Technical performance of PHIL® with regard to:

   • The total volume of injected PHIL®
   • Volume/superselective injections in each catheterized and used pedicle
   • Length of reflux along the microcatheter after each superselective injection/embolization
      1. \( \leq 5\)mm
      2. \( > 5\)mm to \( \leq 15\)mm
      3. \( > 15\) to \(< 30\)mm
      4. \( \geq 30\)mm
   • Amount of pedicles catheterized
   • Overall injection time
   • Overall radiation dose given to the patient during EVT

B.6. Assessment Criteria

Primary assessment criteria:
Efficacy

The degree of occlusion of the cAVM will be evaluated by an independent Imaging Core Lab after the last embolization and at 3-6 months.

- For the subgroup of patients having early surgery or RT in between the last embolization and the 3-6 month follow-up, an additional DSA/Flat panel CT or MRI performed before NS or RT may be used for evaluation of cure rate if performed (ex. a stereotactic angiogram). The rate of cure (obliteration) will be determined by measuring the size of the malformation on the DSA/Flat panel CT after last embolization/control (see above) and comparing to the size of the malformation pre-treatment. The result will be classified into 3 categories:

1. Complete occlusion: defined as no remaining nidus combined with no residual early venous return (i.e. no AV shunt) on follow-up DSA/Flat panel CT
2. Subtotal occlusion: defined as a persistent minor AV shunt with a barely or not visible residual nidus on follow-up DSA/Flat panel CT
3. Partial occlusion: defined as a reduced but truly visible remaining nidus with a persistent AV shunt on follow-up DSA/Flat panel CT

The initial experience has shown that Flat panel-CT used mostly in form of 3D-rotational angiograms allows for a much higher accuracy when it comes to defining the rest volume of the cAVM than classical MRI imaging. As 3D-rotational angiogram make part of the routine in cAVM treating Centers selected and a better delineation of PHIL against perfused vessel (in contrast to MRI where the MRI signal of PHIL in some sequences is very close to that of vessels and/or blood) convinced the physician to use this technique to calculate AVM Volume and Volume reduction by PHIL embolization respectively. A first analysis will be performed based on the volume calculation as described in section B5 and a second analyze cAVM based on the Imaging Reconstruction and Volume will be measured with the help of the Elements software from Brainlab company by the imaging core lab members. Both methods will be compared in order to compare technics.

Safety

Clinical outcome evaluated by mRS* score (see appendix M), during and post procedure, at discharge, at 1 month after each single embolization session and at 3-6 months after the last embolization. In addition, for patients having complementary cAVM treatment immediately after (NS) or after discharge but within one month post EVT (NS or RT) a clinical evaluation will be performed at discharge and at three to six months after or just prior to the intervention (RT excluded).
* performed by an independent neurologist at baseline, procedure and 3-6 months last embolization.

Secondary assessment criteria:

- Adverse events (resulting in death or not) during and post procedure, at discharge and at 1 month after each embolization. Adverse events reported throughout the study will be reviewed by the CEC.

- Technical Performance:
  - Volume injected per pedicle and per embolization session
  - Number of embolizations per pedicle and number of sessions conducted
  - Length of reflux of PHIL along the micro-catheter (see secondary endpoint)
  - Overall injection time
  - Overall radiation dose given to the patient during EVT

B.7.  **Data collection**

B.7.1.  **Demography at time of enrollment**

- Age
- Sex
- Handedness: right / left / ambidextrous

Patient clinical presentation:
- ICH, IVH, SAH and/or SDH
- Epileptic Seizure
- Neurological deficits (unspecified)
  - Transient
  - Slowly progressive
- Rapidly progressive (within a week)
  - Focal neurological deficits
    - Motoric (Like Hemiparesis)
    - Sensoric
  - Cranial nerve deficit
  - Dysphasia/Aphasia
  - Blindness or other visual impairment
  - Cognitive dysfunction
  - Headache
  - Incidental finding
  - Other

Medical history (other than cAVM presentation):
- Cardiac failure or atrial fibrillation
- Hypertension
- Diabetes Mellitus
- Renal insufficiency
- Coagulation disorders
- Allergic reactions to iodine
- Known vascular diseases of other origin (HHT etc., but not arteriosclerosis)
  - Baseline clinical status: mRS*, WFNS (if bleeding)

cAVM Ruptured or Unruptured

For ruptured cAVM:
Previously treated (Yes or No)
If yes NS or SRS or Embolization or a combination of these

For ruptured and previously treated AVM:
Treatment:
- Acute (within 48 hours of the rupture time)
- Subacute (> 48h-2 weeks after the rupture time)
- Elective (> 2 weeks from rupture time or diagnosis)

- cAVM location: Right/ left
  - Cerebral
  - Corpus callosum
  - Thalamus
  - Striatum
  - Frontal
  - Parietal
  - Temporal
  - Occipital
  - Frontotemporal
  - Frontoopercular
  - Temporoparietal
  - Temporooccipital
  - Parietooccipital
  - Precentral
  - Central
  - Intra ventricular
  - Cerebellar
  - Hemispheric
  - Vermian
  - Other

- cAVM characteristics:
  - Number of pedicles/feeders
- Compact or diffuse (if yes: arterial: intranidal, flow related feeders, at the circle of willis or venous,)
  - Venous drainage (deep / deep and superficial / superficial)
  - Venous drainage (single / multiple)
  - Presence of an aneurysm (if yes: arterial: intranidal, flow related feeders, at the circle of willis or venous,) if yes how many
  - Presence of one or more direct fistula ((Y or N) if yes (single/multiple and deep /cortical)
  - Presence of meningeal contribution (Y or N)

- cAVM characteristics evaluation:
  Based on the imaging provided by the center (DSA/Flat panel CT, MRI /CE-MRA if needed), the Imaging Core Lab will be responsible for adding the following information related to the treated cAVM:
  - Size (<3 cm / [3-6] cm /> 6cm)
  - Volume
  - Spetzler-Martin grade before (will only be estimated once, i.e. before first embolization, see Appendix L for grading)

*Flat Panel CT can be obtained during pre procedure EVT if not previously performed for diagnostic purpose

- Adverse events

B.7.2. Treatment Strategy

(The aim of the treatment must be provided at baseline)

- I to IV based on the primary endpoint (see B5)

B.7.3. Embolization procedure characteristics

Type of anesthesia  (general /other) if other explain
Procedural medication (yes / no):
- anticoagulants
- antiplatelets (mono or dual)
- spasmolythics
- steroids
- antiepileptia
- others

*(Drug name and total dose will be provided)*

*Activating Clotting time if available (ACT)*

Arterial femoral accesses (sheath/guiding catheter size)
Venous femoral accesses (sheath/guiding catheter size)
Other accesses (sheath/guiding catheter size)

Distal access intermediate catheters used (Y or N)

- No. of catheterized arteries/Veins
- Type of catheter:
  - Headway (Duo or 17)
  - Ultraflow
  - Apollo (1.5F/15mm or 1.5F/30mm or 1.5F/50mm)
  - Marathon
  - Echelon
  - Sonic (1.2F/15mm, 1.2F/25mm, 1.2F/35mm or 1.2F/25mm.190, 1.5F/15mm or 1.5F/25mm, or 1.5F/35mm)
  - Other compatible DMSO microcatheter
  - Scepter (C or XC)
  - Eclipse 2L

- Number of microcatheters used simultaneously (1 or > 1)

- Catheterized Arteries (R/L or both):
- ICA ipsi or contra lateral to the AVM
- Anterior cerebral
- Middle cerebral
- Anterior choroidal
- Lenticulostriate artery/arteries
- Posterior cerebral
- Thalamic perforating artery
- Posterior choroidal
- Superior cerebellar artery
- AICA
- PICA
- External carotid
- Ophtalmic artery
- Unspecified
- Catheterized Veins:
  - Cortical veins (except v Tolard/Labbé)
  - V Trolard
  - V Labbe
  - V Rosenthal
  - V Centralis
  - Septal or thalamic vein
  - Unspecified…

- Pressure cooking technique used- Yes or No
- Proximal flow arrest technique used- Yes or No

-PHIL® concentration used: 25/30/35
- PHIL® duration of injection / injection
- Volume of PHIL® injected per artery/vein
- Length of Reflux  (see above: $\leq 5\text{mm}$, $> 5$ to $\leq 15\text{mm}$, $\geq 15$ to $< 30\text{ mm}$, $\geq 30\text{mm}$)

- Other devices used:
  - Histoacryl
  - Glubran
  - Coils (How many?)
  - Protection Balloon
  - Other

- Aneurysm treatment  (Yes or No) if yes location: __________
  Type:  Saccular along Circle of Willis
         Related to Feeder aneurysm
         Intra-nidal
         Venous
  Location
  Device used (stent/FD/coils/Intracascular)

Total dose of radiation: mGy/cm$^2$  (entire DSA procedure/session)

Complication (Y or N)

1. During the diagnostic portion (i.e. positioning of the guiding catheter) Initial DSA (Y or N)
   Embolus
   Dissection

2. During associated saccular or flow related to aneurysm treatment  (Y or N)
   Embolus
   Perforation
   Dissection
   Coil/protrusion/-migration
Device related difficulties (Stent/FD/intrasacular or other)

→ Type of complications related to catheterization or catheter / injection of PHIL®:

- Bonded/stuck/glued microcatheter (Intentionally or not intentionally, Y or no)
- Broken microcatheter
- Occluded microcatheter
- Perforation (micro wire/micro catheter, vessel burst (over injection of PHIL®))
- Arterial or venous migration of the embolic agent
- Occlusion of draining vessels by the embolization agent
- Occlusion of draining veins or dural sinus due to progressive thrombosis
- Hemorrhage (perforation excluded)
  - ICH
  - IVH
  - SAH
  - SDH
- Vessel dissection (intracranial arteries)
- Arterial thromboembolic events
- Hematoma (groin access point)
- Unspecified
  → With or without clinical sequelae due to the device or the procedure (if a complication lead to a clinical event please complete a AE form)

- mRS (12 to 24 hours post procedure), WFNS (if bleeding)
- DSA/Flat panel CT* post-procedure results:

* will apply at last embolization only

  o Cured/Complete occlusion: defined as no remaining nidus combined with no residual early venous return (i.e. no AV shunt) on follow-up DSA /Flat Panel CT
- Subtotal occlusion: defined as a persistent minor AV shunt with a barely or not visible residual nidus

- Partial occlusion: defined as a reduced but truly visible remaining nidus with a persistent AV shunt

Flow situation in the cAVM territory compared to the pre procedure:

- Unchanged
- moderately reduced
- Significantly reduced
- Slow flow
- Partial or complete stop in one or more draining veins

Treatment completed?  (Yes or  No)  *(if yes please complete aim of the treatment and last embolization results)*

Aim of treatment achieved?  (Yes or  No)

- Additional treatment needed and type:
  - New embolization
  - Stereotactic radiotherapy
  - Neurosurgery

Last embolization results:
  - Size (<3 cm / [3-6] cm /> 6cm)
  - Volume of the cAVM treated *(volume reduction)*

**B.7.4.  Post-Embolization patient clinical Status (at Discharge)**

- mRS, WFNS (if bleeding)
- Adverse events
- Changes in symptoms compared to baseline:
  Asymptomatic
  Symptomatic: Stable / improved / deteriorated

Type of clinical deterioration
   Epileptic Seizure

- Neurological deficits (unspecified)
  o Transient
  o Slowly progressive
  o Rapidly progressive (within a week)

- Focal neurological deficits
  o Motoric (Like Hemiparesis)
  o Sensorialc

- Cranial nerve

- Dyphasia/Aphasia

- Blindness or other visual impairment

- Cognitive dysfunction

- Headache

- Other

B.7.5. 1 month post embolization visit follow up (optional by phone)

(can be done just before the N+1 embolization if occur)

- mRS, WFNS (if bleeding)

- Adverse events

- Changes in symptoms compared to baseline:
  Asymptomatic
  Symptomatic: Stable / improved / deteriorated

Type of clinical deterioration
   - Epileptic Seizure
- Neurological deficits (unspecified)
  o Transient
  o Slowly progressive
  o Rapidly progressive (within a week)
- Focal neurological deficits
  o Motoric (Like Hemiparesis)
  o Sensoric
- Cranial nerve
- Dysphasia/Aphasia
- Blindness or other visual impairment
- Cognitive dysfunction
- Headache
- Other

- Additional, unscheduled DSA/Flat panel CT/CTA/MRI/CE-MRA (TOF) availability

**B.7.6.  NS or RT Procedure**

Yes or No

- DSA/Flat panel CT/CTA/MRI/CE-MRA (TOF) availability (before procedure)
- mRS* (just before procedure)
- WFNS (if bleeding)
- AEs

**B.7.7.  3-6 months post last embolization control**

- Imaging: DSA/Flat panel CT/MRI/ CE-MRA (TOF)/CTA
- Results:
  - Completed endovascular treatment (complete occlusion and/or goal of treatment achieved)
- New embolization required (Yes or No)
- Additional treatment required (stereotactic radiotherapy or neurosurgery)
- Treatment abandon (no further treatment intended)

Flow situation in the AVM Territory compared to the pre procedure:

- Unchanged
- moderately reduced
- Significantly reduced
- Slow flow
- Partial or complete stop in one or more draining veins

Angiographic follow up:

- DSA/Flat panel CT/MRI assessment at 3 to 6 months after last embolization

Assessment after the last embolization if additional treatment (other than an embolization) is required for NS and RT are excluded

*Based on the final DSA/Flat panel CT/MRI imaging follow-up provided by the center, the Imaging Core Lab will be responsible for evaluating the cAVM for the following performance criteria:

- Size (<3 cm / [3-6] cm /> 6cm)
- Volume
- Cure rate

Aim of treatment achieved (Yes or No)

If no: less than intended or more than intended

- mRS*, WFNS (if bleeding)
- AEs
- Changes in the symptoms compared to baseline:
  
  Asymptomatic

  Symptomatic: Stable / improved / deteriorated

Type of clinical deterioration

- Epileptic Seizure
- Neurological deficits (unspecified)
  
  o Transient
  
  o Slowly progressive
  
  o Rapidly progressive (within a week)
- Focal neurological deficits
  
  o Motoric (Like Hemiparesis)
  
  o Sensoric
- Cranial nerve
- Blindness or other visual impairment
- Cognitive dysfunction
- Headache
- Other

**B.8. Statistical Analysis plan**

**B.8.1. Statistical analysis**

All patients included and treated with PHIL® during the study will be analyzed (ITT).

Categorical variables will be described by their frequency distribution and ranges bilateral 95% confidence. Continuous variables will be described by their average, minimum standard deviation, maximum, median and quartiles.
The event rate for which a date of occurrence has been collected will be described by survival curve according to the Kaplan-Meier method and the estimator of Kaplan-Meier associated will be calculated.

**Sensitivity analysis**

A sensitivity analysis using the multiple imputation procedure will be performed if more than 10% of the data is missing for one of the main criteria.

All analyses will be performed using SAS version 9.3 software (from SAS Institute).

### B.8.2. Population Size

108 patients

With 98 patients enrolled in the cohort, we will be able to estimate the principal outcomes with a 95% confidence interval size of ±5.0% considering the frequency of 6.8% found in a previous study (poor clinical outcome rate observed in [Elsenousi and all](#))

In addition, even with 10% loss to follow-up patients, this sample size (N=108) ensures an accuracy of at least ±10% for observed parameters.

### B.8.3. Invalid, Unused and missing Data

Missing data will be treated in the following three ways:

- The LOCF method will be used, with the last observation seen used as a reference value for a missing value at the end of follow-up
- The basic method to exclude patients with missing data will be used
- The missing data will be charged through multiple imputation procedure

### B.9. Number of sites

Up to 18 sites in Europe will participate in the study. Site selection will be based on the number of cAVMs treated per year by the site, experience with other liquid embolic agents, flat CT panel availability and participation in PHIL® workshops and test cases.

### B.10 Study duration

The majority of cAVMs are treated in one or more sessions- in this study we have estimated an upper limit of 6 sessions. A period of at least one month and no more than three months between 2 embolization procedures is highly recommended. As this is an observational study in which all patients will be treated with PHIL® and followed 3-6 months after the last embolization as part of a therapeutic path in which the number of embolizations and the time between sessions may vary, the below are only estimates:

- Enrollment period for 108 patients: 18 months
- Patient follow up period:
  - Individual patient monitoring period: 21 months max treatment duration (if 6 sessions) plus 3 to 6 months after the last embolization for follow up
- Patient overall study duration: Up to 39 months

C. Patient selection

C.1. Patient population to be screened

All patients with a cAVM, ruptured or unruptured, eligible for endovascular treatment having been treated previously or not in the past, based on multidisciplinary consensus.

C.2. Inclusion criteria

1. Patient or patient’s legally authorized representative has received information about data collection and has signed and dated an Informed Consent Form (based on the country’s regulation).

2. All patients with a ruptured or unruptured and previously endovascularly* untreated cAVM that are eligible for endovascular treatment with PHIL® alone or in conjunction with N-Butyl cyanoacrylate glue (NBCA) and/or coils (e.g. if “pressure cooking” technique is needed or used).

3. All patients with a previously endovascularly treated cAVM in which NBCA and/or coils but not another non-adhesive liquid embolic agent have been used may be included.
4. All patients with a remaining cAVM, ruptured or unruptured, that has previously been treated with NS and/or RT may be included.

*Patients with a saccular or flow-related aneurysm previously treated with NBCA and/or coils may be included.

All enrollment must be based on a multidisciplinary agreement.

C.3. Exclusion criteria

1. cAVM not eligible for endovascular treatment
2. cAVM previously treated with a non-adhesive liquid embolic agent other than PHIL®
3. Treatment requiring the use of any other non adhesive embolic liquid
4. Patient is allergic to iodine
5. Premature and newborn infant
6. Patient with renal failure or significant liver impairment
7. Patient is participating in another study evaluating other medical devices, other procedures or medications.
8. Any other condition that might prevent patient participation in the study or follow up.
9. Patient refuses to give consent to the collection and processing of data required for centralized monitoring

C.4. Study visits

This is an observational study, so no procedure deviating from the standard practice of each center will be required. After inclusion, the patient will be followed up postoperatively, in accordance with the usual practice of each center to collect data a month after the procedure and at DSA/Flat panel CT follow-up 3-6 months after the last embolization in the case of complete treatment or termination of therapy, or after the last embolization if additional treatment (other than an embolization) is required. (Safety only)
D. Data collection

D.1. Screening log

A screening log of patients having a cAVM will be set up at the time of the study. Sex, age and reason for non-inclusion into the registry will be recorded. This screening log will guarantee that all patients having a cAVM to be treated in the selected study centers will have been considered to participate in the registry.

D.2. Case Report Form

Data will be collected at the time of the patient's admission and the implantation procedure as well as throughout the postoperative hospitalization and follow up periods. Any source document (procedural report, radiological examination report, laboratory values, death certificate, etc.) sent to the sponsor must be made anonymous and will be referenced by patient study ID.

*Forms to be completed:*

- **1. Preoperative period**
  To be completed for each patient to describe medical history and health status at the time of admission.

- **2. Implantation**
  To be completed for each patient to describe the embolization procedure.

- **3. Postoperative period**
  To be completed for each patient to describe the period between intervention and hospital discharge.

- **4. Follow up**
  To be completed for each follow-up visit conducted as part of usual care.
- 5. End of Study  To be completed for each patient at the end of the study to document the normal study termination and the end of data collection or to document any premature termination (patient lost to follow up, patient death, patient withdrawal from the study)

- 6. Additional Procedure  To be completed to describe any additional vascular procedure

- 7. Complication/AEs  To be completed upon the occurrence of a reportable complication according to the Clinical Investigation Plan.

D.3. Adverse event

Any adverse event, whether serious or not, whether symptomatic or not, pre- or post-operative, related or unrelated to the use of the device, will be identified. Problems associated with the use of the device will be communicated to the appropriate country’s authority following the procedures in force.

Any device that is believed to have malfunctioned or have a defect must be returned to the manufacturer for analysis.

Serious Adverse Events (SAEs) are adverse events that meet the following criteria:

a) led to a death,

b) led to a serious deterioration in health that either:
   1) resulted in a life-threatening illness or injury, or
   2) resulted in a permanent impairment of a body structure or a body function, or
   3) required in-patient hospitalization or prolongation of existing hospitalization, or
   4) resulted in 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.

In this study, all serious adverse events must be reported to the safety officer. SAEs will also result in a declaration to the appropriate countries’ authorities in accordance with procedures in force. Adverse events are unanticipated when they are not included in the instructions for use of the medical device.

In the case of an unexpected serious adverse event, the safety officer will immediately contact the investigator to prepare an initial report to be forwarded to the competent authorities in the prescribed procedures material-vigilance and Oversight Committee.

List of main risks related to the use of PHIL®:

- Arterial thrombosis
- Ischemic events due to embolic migration such as vasospasm or thrombosis
- Hemorrhagic accidents such as vascular rupture or perforation
- Hemodynamic changes induced by the embolization that may result in hemorrhagic complications
- Hematoma

These ischemic or hemorrhagic complications may result in various functional neurological deficits, stroke, and possibly death.

D.4. Patient end of study

D.4.1. End of study visit

End of patient study participation will occur in the following cases:

- Patient consent withdrawal for any reason (if possible, the patient will be asked to attend his/her EoS visit in order to assess his/her final safety and clinical outcomes before they stop participation in the study)
- Investigator decision to stop patient participation
- Lost to follow up
- Patient death
- Scheduled end of the study

**D.4.2. Patients lost to follow up**

The investigator will be requested to take any necessary action in order to avoid patients being lost to follow up (including calling the patient, contacting the patient’s family doctor, etc.).

**D.5. Protocol Deviations**

A study/protocol deviation occurs when the investigator or other study personnel did not conduct the study according to the Clinical Investigation Plan or according to regulations. The investigator will document and inform the sponsor or his mandated representative of any deviations that occur at his site. If needed, he will take any reasonable corrective action in order to avoid deviation repetition.

**E. Minimizing biases strategy**

In this observational study, biases are minimized by the following:

A screening log of patients for which a cAVM that has not been previously treated but is to be treated and is not included in the study will be prepared. The reason for non-inclusion of these patients will be recorded.

An independent committee (CEC) will evaluate any adverse events per procedure and for the overall study duration. It will assess the existence of a relationship between the device or procedure and any Serious Adverse Events.
A centralized review of laboratory tests will be performed by an independent committee (Core Lab), which will evaluate the DSA/Flat panel CT, MRI and CT(A)/CE-MRA (if made) examinations at the following times:

- Before the first session of embolization to assess the anatomy of the cAVM.
- At the end of treatment.
- 3 to 6 months after the last embolization in the case of complete treatment or discontinuation of treatment.
- After the last session of embolization in all patients, including those with additional treatment required.

This evaluation will be performed in order to assess:

- The overall cure rate
- The result with regard to aim of treatment
- Performance of PHIIL®

Two separated analysis will be performed by an imaging corelab members. A first analysis will be performed as described above, a second analysis will be performed with the help of the element software from brain lab in order to obtain standardized volume occlusion assessment. Sites will perform their measurement based on their current practice.

F. Quality control

Progress of research in the study centers and support issues will be performed in accordance with ethics and medical recommendations.

Case report form completion.

Data from the study will be recorded by authorized study site staff on an eCRF. The information reported in the medical questionnaire should be a reflection of that in the medical records of the subject.

Data quality entered into the eCRF will be assessed during monitoring visits performed by a CRA. Monitoring visits will be conducted as per standard operating procedure and the monitoring plan of the company as mandated by the sponsor.
Data management quality check will be implemented in order to enhance data quality and consistency as per standard operating procedure and the monitoring plan of the company as mandated by the sponsor.

Quality assurance at any step of the study will be performed on a regular basis as per standard operating procedure and the monitoring plan of the company as mandated by the sponsor.

**G. Ethics and regulation**

**G.1. Regulation**

Before inclusion of patients, this non-interventional evaluation will be submitted to any relevant institutions in accordance with the regulations in force in each participating country in order to obtain opinions and authorizations. The final version of the Investigational Plan with the Patient Information document and Consent Form will be submitted to an appropriately constituted EC or relevant country Competent Authority (CA) by the Investigator/sponsor prior to commencement of the Study. A copy of the EC or CA opinion/approval letter along with, for the EC document, the list of EC voting members will be provided to the Sponsor prior to initiating the Study at any center.

The Investigator/sponsor will submit the appropriate documentation if any extension, renewal or amendment of the EC or CA approval must be obtained. In particular Investigational Plan amendments, Informed Consent Form changes or other written information provided to the patient and/or Study procedures directly affecting the patient must be approved by the EC or CA in writing. Each Investigator must sign the Investigational Plan Amendment before implementing the change at his/her Site.

The Investigator/sponsor will report to the EC any new information that may affect patient safety or the conduct of the Study. Written summaries of the Study status shall be sent by the Investigator to the EC according to local requirements, and at least once annually.

Upon completion of the Study, the Investigator shall provide the EC with a brief report of the outcome of the Study as required by the local EC.

**G.2. Patient data collection consent form**
The patient (or the patient’s legal representative) must sign and date an Informed Consent Form prior to inclusion in the study accepting participation in the study after having been provided information on the data collected as well as their right to object, if desired, to the collection and transmission of data. In accordance with the regulation in force, an information note will be given to the patient or his legal representative. Patient identification will be performed with code number allowing patient anonymization (Site number and patient chronological enrollment number)

(Appendix.1).

H. Study documentation and data retention

Research-related documentation must be filed by each site for the appropriate period of time based on their country’s regulation. The sponsor will file these documents based on the longest period of time required by the regulation of any participating country.

The database used for statistical analysis will be archived by the entity performing the analysis.

I. Data analysis and reports

I.1. Access to the data and source documentation

Confidentiality of data shall be observed by all parties involved at all times throughout the clinical investigation. All data shall be secured against unauthorized access.

The privacy of each subject and confidentiality of his/her information shall be preserved in reports and when publishing any data.

The principal investigator or institution shall provide direct access to source data during and after the clinical investigation for monitoring, audits, EC review and regulatory authority inspections.

I.2. Publication rules

Microvention Europe Company owns all of the data, analysis and results for PHIL® resulting from this study and no use or transmission to a third party can be made without prior consent.
However, each individual center is free to use and develop independently the data from the medical records of its own patients.

I.3. Final study report
A final study report will be written under the sponsor’s supervision. This report will be sent to any investigator and EC/CA as per regulation in force in the participating countries.

J. Expected risks and benefits

J.1. Risks
This is an observational study with no change required to standard of care. So there will be no additional risk for the patient participating to that study.

J.2. Benefits
All patients will be managed in the same way as they would have been managed if they had refused to participate to the study. There is no individual benefit to participating in this study.

K. Appendix

K.1. Patient data collection form
See attached CRF
L. Spetzler-Martin grade classification

Spetzler-Martin grading system
The Spetzler-Martin grading system is used to predict the risk of surgery. Three variables are considered:

• Size
  o Small: <3 cm (1 point)
  o Medium: 3 to 6 cm (2 points)
  o Large: >6 cm (3 points)

• Pattern of venous drainage
  o Deep (1 point)
  o Superficial (0 points)

• Neurological eloquence of the brain at the AVM location
  o Eloquent (1 point): areas of the brain that control speech, motor function, and senses, that if injured, result in disabling neurological deficits
  o Non-eloquent (0 points)

The grade is the cumulative total of points allocated for each variable.

M. Modified Ranking Scale

Score Description

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
**N. WFNS**

World Federation of Neurological Surgeons Grading System for Subarachnoid Hemorrhage (WFNS) scale

**Overview:**
The clinical grading system proposed by the World Federation of Neurological Surgeons is intended to be a simple, reliable and clinically valid way to grade a patient with subarachnoid hemorrhage. This system offers less interobserver variability than some of the earlier classification systems.

- Grade 1: GCS score of 15 without focal deficit
- Grade 2: GCS score of 13 or 14 without focal deficit
- Grade 3: GCS score of 13 or 14 with focal deficit
- Grade 4: GCS score of 7-12
- Grade 5: GCS score of 3-6

GCS (Glasgow coma score)

**O. Publications-references**


8van Roij WJ, Sluzewski M, Beute GN. Brain AVM embolization with Onyx. AJNR Am J Neuroradiol 2007:28:17277
