"HEAT"

New Generation **H**ydrogel **E**ndovascular **A**neurysm treatment **T**rial

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A randomized controlled trial of new generation Hydrogel coils versus bare platinum coils in the endovascular treatment of intracranial aneurysms

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1 Protocol Synopsis

FULL STUDY TITLE	New Generation **H**ydrogel **E**ndovascular **A**neurysm Treatment **T**rial
STUDY OBJECTIVES	Comparing initial complete occlusion, recanalization, retreatment and adverse event rates of the HydroCoil® Embolic System to those of bare platinum coils.
STUDY DESIGN	International, randomized, prospective, controlled, multicenter trial
DEVICES	Second generation hydrogel coils from the HydroCoil® Embolic System™ (including the HydroSoft®, HydroFill® and HydroFrame® and future FDA and HPB approved Hydrogel coils) ("Hydrogel Group") and Platinum coils ("Platinum Group")
TREATMENT POPULATION	Subjects with intracranial aneurysms between the ages of 18 and 75 years inclusive
ESTIMATED TRIAL SIZE	600 randomized subjects
NUMBER OF SITES	Approximately 50 sites inside and outside of the U.S.
PRIMARY ENDPOINT	Aneurysm recurrence at any point during follow-up defined as any progression on the Raymond aneurysm occlusion scale.
SECONDARY ENDPOINTS	• Packing density as measured by volumetric filling of the aneurysm • Clinical outcome at 18 to 24 months (mRS) • Peri-procedural and post-procedural adverse events related to the procedure and/or the device. • Mortality rate • Initial complete occlusion • Aneurysm retreatment • Hemorrhage from target aneurysm during follow-up • Aneurysm occlusion stability • Major vs. minor recurrence
VISIT SCHEDULE	Baseline, Procedure, 1 day post-procedure, 3 days to 28 days, 3 months to 12 months, 18 months to 24 months
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Introduction and Background on endovascular treatment of Intracranial Aneurysms

Over the last two decades, the endovascular treatment of intracranial aneurysms has seen significant advances. The first landmark came with the advent of the Guglielmi Detachable Coils (GDC) in the early nineties.[1] Almost a decade later, the publication of the ISAT trial validated the use of endovascular coils and, in general, the endovascular approach to treating select intracranial aneurysms.[2]

One major limitation of the endovascular approach, however, is the durability of treatment. Aneurysm recurrences have been shown to be more frequent with coiling than with an open microsurgical approach.[2,3] Major recurrences occur in 15%[4,5] to 19%[6] of cases by 3-6 months and rises to 33% at a mean of 18 months of follow-up.[5,7,8] Major recurrences following endovascular treatment are associated with retreatment rates as high as 58.8%.[5] Although rare, the risk of re-bleeding is also increased with endovascular treatment when compared to open surgical clipping.[2,3] Byrne et al. assessed the risk of aneurysmal rebleeding and found that the risk is significantly increased from 0.4% in stable aneurysms to 7.9% in recurrent aneurysms.[4] A number of approaches have been pursued over the past five years to enhance results. Because recanalization has been associated with poor packing density in aneurysms, one approach has been to enhance packing density which has resulted in the development of a hydrogel coated coil. The hydrogel expands over time and enhances packing density.

3 HydroCoil® Embolic System

3.1 Hydrogel characteristics and the Hydrocoil Embolic System

The Hydrocoil Embolic System, developed and manufactured by MicroVention, Inc. (referred to in this Protocol as “MicroVention” or “Funder”), consists of porous hydrogel that either surrounds the platinum coil (as in the first generation of the HydroCoil Embolic System), or is surrounded by the platinum coil (as in the second generation of the HydroCoil Embolic System). Hydrogel consists of cross-linked hydrophilic copolymers. This material has been widely used in other medical applications (e.g. contact lenses and wound dressings). Hydrogel swells once exposed to the biological pH.

3.2 First Generation of the HydroCoil Embolic System: HydroCoil®

The first generation of the HydroCoil Embolic System is constructed using a core platinum coil surrounded by a sleeve of expandable hydrogel and an outer wire with gaps which allow expansion to occur. As such, the Hydrogel device is relatively stiff because of its dehydrated state, especially when compared to soft, platinum coils. The Hydrogel undergoes substantial swelling over time, markedly increasing its outer diameter and surface area over approximately 20 minutes. The increase in volume of the coil varies among the different HydroCoils. The HydroCoil 10 swells up to 0.022”, 5 times the volume of a platinum 10 coil; the HydroCoil 14 and HydroCoil 18 swell to 3 and 6 times the volume of Platinum 18 coils, respectively. The HydroCoil 14 and 18 coils swell up to 0.027” and 0.034”, respectively. Although substantial swelling is advantageous for aneurysm filling volume, there are limits associated with deployment time and size of the coils. Difficulty in deployment may lead to the need for multiple repositionings and potential untoward early swelling of the device which limits delivery through certain microcatheter systems. The HydroCoil is generally used as filling coils.

3.3 Second Generation of the HydroCoil Embolic System: HydroSoft®, HydroFrame®, HydroFill® and Future Hydrogel Products

In an attempt to offer a hydrogel coil as a soft finishing coil to allow ease in placing gel coils at the neck of the aneurysm, MicroVention developed the HydroSoft® line of embolic coils. These coils which are constructed with a filament of expandable hydrogel within the platinum coil are essentially as soft as platinum coils based on benchtop experiments and thus have handling properties similar to traditional platinum coils. Furthermore, since the hydrogel does not expand excessively, repositioning time is markedly prolonged to 30 minutes per the Instructions for Use (IFU). When fully hydrated, the HydroSoft swells up to approximately

0.013" to fill the gaps between the spirals of the platinum coil.[7,9] The HydroSoft coils are primarily used as finishing or filling coils.

The next coil introduced by MicroVention, Inc., was HydroFrame®, a framing coil with hydrogel on the inside of the coil that is available in both 10 and 18 systems. MicroVention then developed HydroFill® which is used primarily as a filling coil, has a longer working time than HydroCoil (10 minutes in a .0165 microcatheter or 30 minutes in a .021 microcatheter), and swells to .018". The HydroFrame®, HydroSoft® and HydroFill® do *not* require steaming or prepping of the coil.

3.4 Studying the New Generation of the HydroCoil Embolic System

Studies to date on hydrogel coils have necessitated mixing hydrogel coils with platinum coils. With the introduction of the HydroFrame embolic coils, it is now possible to initiate a prospective randomized, multicenter trial to evaluate the effectiveness of packing an aneurysm *exclusively* with all Hydrogel coils compared to that exclusively with bare platinum coils. The question that remains unanswered is whether the new hydrogel technology improves results over traditional platinum coils.

For the purpose of this Protocol, subsequent references to the "HydroCoil Embolic System" refer specifically to the second generation of the HydroCoil Embolic System being utilized in this study and includes the HydroFrame®, HydroSoft®, HydroFill® and future FDA and HPB approved hydrogel products.

3.5 Previous Clinical Experience and studies of the HydroCoil and the Hydrocoil Embolic System

In early data from the prospective non-randomized HydroCoil for Endovascular Aneurysm occLusion (HEAL) study,[10] the overall recurrence rate at 3 to 6 months was 28.1% (38/135 aneurysms). Further analysis of the data showed that when HydroCoil comprised 75% or more of total coil length the recurrence rate at 3 to 6 months dropped to 0% (0 out of 18 aneurysms). In contrast, when HydroCoil comprised less than 75% of total coil length, the recurrence rate was 23% (16 out of 71 aneurysms). Furthermore, when the last deposited coil was a HydroCoil, the recurrence rate was found to be 11% compared to 29% when the last deposited coil was a platinum coil. The difference was statistically significant. This difference in results, however, reflects one of the major limitations of the HEAL trial which was that no aneurysm was treated exclusively with HydroCoil.

In a prospective study, Gaba et al.[11] compared 50 aneurysms treated primarily with Hydrocoil (mean 71.8% based on coil length) to 57 volume- and shape-matched aneurysms embolized with bare platinum coils. The overall recurrence rate of the Hydrocoil treated aneurysms was 17% and compared favorably to those treated with bare platinum coils (24%) during a mean follow-up period of 12.3 months. These results also compare favorably to those reported by Murayama et al[12] from their 11 year experience with bare platinum coils where the overall recanalization rate was 20.9%. Geyik et al.[13] studied the recurrence rate in 35 bifurcation aneurysms, known for a higher tendency for recurrence, when treated with Hydrocoil and demonstrated an initial complete occlusion rate of 82.9% and at 6 months follow-up the overall recanalization rate was 11.4%.

Several other studies have examined hydrogel coils and the rates of initial complete occlusion have varied between 28% to 75% with recurrence rates between 11% and 28.1%.[14,15] Tables 1 and 2 summarize the most relevant papers and their findings on occlusion rates, recanalization, retreatment, complications, morbidity and mortality rates. As a point of reference, the overall retreatment rate in the International Subarachnoid Aneurysm Trial (ISAT) was 17.4%, with an early retreatment rate of 8.8% and a late retreatment rate of 9.0%.[16] The cut-off point between early and late retreatment was 3 months.[16]

Aneurysms showing the highest degree of occlusion and packing density (PD) are thought to be the best protected against recanalization and potential re-treatment.[7,10,11,17-22] Cloft et al.[9] studied the packing density of 11 aneurysms treated with HydroCoil compared to 11 historical controls that were treated with bare platinum coils. Most of these were small aneurysms (all 3.5-8.5mm) and mean packing density for the HydroCoil was found to be 73% versus 32% for bare platinum coils. Gaba et al.[11] calculated a theoretical volumetric percentage occlusion (VPO) and found that it was significantly higher in Hydrocoil than in inert bare platinum coils for all aneurysm sizes. The HydroCoil Endovascular Aneurysm Occlusion and Packing Study (HELPS) was a prospective, randomized, controlled trial that compared results from the HydroCoil system to results from bare platinum coils. The 500-patient, independently-run, multicenter, multinational 18-month trial was the first comparative study completed since the ISAT was presented in 2002. The angiographic results of the HELPS trial showed that there was a statistically significant decrease (8.6%) in major aneurysm recurrence rates in the HydroCoil system arm as compared to the bare platinum control arm.[7]

In addition to HELPS, one other trial is underway. The trial entitled “Patients Prone to Recurrence after Endovascular Treatment”, or “PRET”, is a large multi-center prospective randomized trial that aims to compare hydrogel coils and platinum coils in the treatment of large aneurysms that have a high-risk of recurrence. PRET intends to recruit 250 patients with large aneurysms (≥10mm) and 250 patients with recurrent aneurysms at 23-40 centers. The clinical impact will be of major significance if substantial differences are found in the outcome of this randomized controlled trial. PRET was initiated prior to the development and introduction of the HydroFrame, however, which necessitated the mixing of hydrogel coils with platinum coils in the hydrogel group. With the development and introduction of the hydrogel framing coil (the HydroFrame) it will be possible to initiate a prospective randomized, multicenter trial to evaluate the effectiveness of packing an aneurysm *exclusively* with the HydroCoil® Embolic System (Hydrogel Group) with comparison to the current gold-standard of endovascular aneurysm treatment using bare platinum coils (Platinum Group).

4 Study Objectives

4.1 Study Hypothesis

The HydroCoil Embolic System allows for a higher packing density, higher initial occlusion, lower recanalization, and lower retreatment rates.

4.2 Primary Endpoint

The primary purpose of the HEAT study is to compare clinical and angiographic outcomes in patients receiving the HydroCoil Embolic System (Hydrogel framing, filling and finishing coils) versus patients receiving Platinum framing and filling coils. The primary outcome is aneurysm recurrence defined as any progression on the Raymond aneurysm occlusion scale anytime during follow-up (for further details, see section 6.4).

4.3 Secondary Outcomes

- Packing density as measured by the volumetric filling of the aneurysm
- Rate of initial complete occlusion
- Procedure and/or device-related morbidity and mortality
- Clinical outcome at 18 to 24 months as assessed using the modified Rankin Scale
- Re-treatment rates
- Hemorrhage from target aneurysm during follow-up
- Aneurysm occlusion stability
- Major versus minor recurrence

4.4 Safety Outcomes

- Peri-aneurysmal edema
- Aseptic meningitis
- Thromboembolic events
- Vasospasm
- Ventricular Enlargement
- Hydrocephalus
- Aneurysm Rupture
- Parent Vessel Occlusion

5 Clinical Study Design

5.1 Study Design

This is a randomized, controlled, multicenter, international post-market clinical trial. All devices used in this study are FDA and HPB (Health Protection Branch) approved. Eligible Subjects with intracranial aneurysms amenable to endovascular treatment and who consent to study participation will be randomly assigned 1:1 to either treatment arm:

- The HydroCoil Embolic System ("Hydrogel Group"), or
- Bare platinum coils ("Platinum Group")

Both arms are standard of care. The patient will receive either Hydrogel or bare platinum coils in each respective arm. No other bioactive coils, including 1st generation coils or liquid embolics, can be utilized. In the Hydrogel arm, up to 10% of total coil length using bare platinum is allowed if deemed necessary by the investigator. Any type of bare platinum coil may be utilized. Assist-devices can be used at the discretion of the investigator.

5.2 Study Duration and Enrollment

The duration of the open enrollment phase will be 24 months or until the required number of patients are enrolled. Each patient will have a post-procedure follow-up of at least 18 months.

The number of Subjects to be enrolled, and randomized, in the study is up to 600. This sample size calculated to provide sufficient statistical power to show the anticipated difference in initial occlusion and recurrence rates between the 2 study arms (see section 9 for detailed statistical analysis). Patients will be recruited from up to 50 national and international centers. Each Investigational Site will be expected to enroll at least 20 Subjects. Each site must meet the eligibility criteria.

A multidisciplinary approach is expected from each qualified study center. The Neurovascular teams should include the appropriate specialties for the proper conduct of the study e.g., neurointerventionalist(s), experienced in intracranial aneurysm coiling, neurosurgeon(s), and study coordinator(s). In addition, the treating physician must meet a minimal level of expertise consisting of at least 5 successful intracranial aneurysm coiling procedures utilizing the HydroCoil Embolic system prior to enrolling patients into the study.

Each site must provide written approval from their reviewing Institutional Review Board (IRB) and all other required regulatory documentation prior to consenting and enrolling the first Subject.

5.3 Selection and Screening of Subjects

The study population for this clinical trial will be comprised of patients who have been diagnosed with intracranial aneurysms. In addition, these patients must satisfy all study inclusion and exclusion criteria. The trial will prospectively enroll and randomize up to 600 Subjects in a 1:1 ratio within only one stratification factor: participating site. The investigator or an approved member of the research team will review the patient's medical history for study eligibility and will fully inform any potential candidates about the purpose of the study. The difference between both types of coiling systems will be described and the potential risks and benefits will be explained in detail to each study candidate. Patients who voluntarily agree to participate in the trial will be asked to sign and date the Informed Consent Form (ICF). In the event a patient is unfit to provide signed informed consent (e.g. drowsy/confused), his/her Legally Authorized Representative (LAR) can sign the consent form. Once enrolled into the study, each participant will be assigned a study number. Patient names or identifiers will not be used on any study related documents. An electronic case report form (eCRF) will be completed at the end of each procedure and after each study related follow-up. Only the Principal Investigator of the study (Dr. Bendok) and authorized members of the Sponsor including study monitors and auditors will have full access to the eCRF. Information from the eCRF will be entered into a secure, password protected study database. The Funder and its employees will have read-only access to collected eCRF study data, as provided by Northwestern, solely for review and adjudication of information related to any AE, SAE, ADE and UADE (as such terms are defined below) for legal and compliance purposes.

If a subject becomes pregnant while participating in this study, any angiographic follow-up will be done using non-contrast MRA as per standard of care.

5.3.1 Informed Consent

Prior to Subject participation in this study, the study team must obtain written IRB approval for the protocol and the Informed Consent Form (ICF). Once the patient's potential eligibility has been determined, the investigator or an IRB approved member of the research team will discuss the study and ask the patient if they are interested in participating in the study. The study will be explained to the patient in lay terms or at the level of patient understanding. The differences in coiling types will be explained in full detail. The approved ICF must be signed prior to performing study related assessments. The subject will be given a copy of the signed and dated ICF. The informed consent process must be documented and placed in the subject binder. Failure to obtain a signed ICF prior to the procedure constitutes a protocol deviation. It must be clear to subjects that they may withdraw from the study at any time and for any reason without penalty. It will be made clear to study participants that withdrawal from the study will not adversely affect their medical treatment and they will continue to receive therapy as indicated by their physician. Data from subjects obtained prior to withdrawal may be used for statistical analysis but no further data will be obtained.

5.3.2 Inclusion Criteria

Candidates for this study must meet the following criteria to be enrolled in the study (A "NO" answer excludes the subject):

1. Patient is between 18 and 75 years of age (inclusive).
2. Patient has a documented untreated intracranial saccular aneurysm 3-14 mm diameter angiographic lumen, ruptured or unruptured, suitable for embolization with coils.
3. For ruptured aneurysms, patients presenting with a Hunt and Hess Grade 1-3 or improving to such a grade before treatment.

4. Any type of bare platinum coils and HydroCoil Embolic System are treatment options (all shapes allowed).
5. Patient or next of kin or person with appropriate power of attorney has provided written informed consent.
6. Patient is willing and available for study follow-up visits.
7. Patient has not been previously entered into this Study.

5.3.3 Exclusion Criteria

Candidates will be ineligible for enrollment in the study if any of the following conditions apply (A "YES" answer excludes the subject):

1. Inability to obtain informed written consent.
2. Patient is < 18 or > 75 years old.
3. Target aneurysm is not saccular in nature (mycotic, fusiform, dissecting).
4. Target aneurysm is > 14 mm maximum luminal dimension, < 3 mm maximum luminal dimension.
5. Target aneurysm has been previously clipped or coiled.
6. Target aneurysm is in the physician's estimate unlikely to be successfully treated by endovascular techniques.
7. Patient has known hypersensitivity to platinum, nickel, stainless steel or structurally related compounds or hydrogel as found in the HydroCoil Embolic System and/or bare platinum coils.
8. Baseline Hunt and Hess scale 4 or 5 for ruptured aneurysms.
9. Intended use of a flow diverting stent (e.g. pipeline)
10. Subject has concurrent intracranial pathology, e.g.

    - Moyamoya disease
    - Vasculitis documented by biopsy results
    - AVMs
    - AV fistulas
    - Significant atherosclerotic disease (i.e. symptomatic and or >50% narrowing of the parent arteries necessary to traverse in order to coil the target aneurysm)
    - Intracranial Hematoma (unrelated to the target aneurysm)
    - Brain tumors
    - Vascular tortuosity and other conditions preventing access to target aneurysm

11. Subject has serious co-morbidities that could confound the study results:

    - Uncontrolled hypertension
    - Uncorrectable coagulation abnormality
    - Contraindications for heparin, aspirin or clopidogrel
    - Uncontrolled Diabetes Mellitus
    - Organ failure of kidney, liver, heart, or lung

- Myocardial infarction within the past 6 months
- Cancer likely to cause death within 2 years or less.

12. Subject history indicates high risk of non-compliance (e.g., substance abuse, psychosocial issues, etc.)
13. Subject has a known history contraindicating contrast dye or iodine that cannot be pre-medicated prior to coiling procedure (vs. sensitivity which can be safely controlled by antihistamine, steroid, etc.). Medical clearance will be needed for this issue.
14. Patients who are unable to complete scheduled follow up assessments at the enrolling center due to limited life expectancy (<2 years), co-morbidities or geographical considerations
15. Subject is currently breast feeding, pregnant or plans to become pregnant in the next 2 years.
16. Major surgical procedure or trauma within 30 days prior to randomization.
17. The patient is currently enrolled in another clinical study (device or drug).
18. More than one aneurysm needs to be treated at the same time.

6 Subject Enrollment, Procedures, and Follow-Up

6.1 Screening and Consent

Eligibility will be assessed once the neurovascular team makes a decision on endovascular treatment of an aneurysm. A local site log of all eligible patients will be kept and a copy returned to the coordinating site (Northwestern University) when requested by the study monitor.

If a patient fulfills the inclusion and exclusion criteria, an authorized member of the research team will discuss the trial and provide the patient or his/her LAR with the informed consent form. The patient or LAR will be provided adequate time to consider participation in the trial and the research team will answer all questions regarding the trial. A copy of the consent will be retained in the patient's medical record, one will be given to the patient, and the original will be retained by the local site.

All patients who meet the eligibility criteria and give written informed consent are eligible for enrollment into the study which occurs at the time of randomization

Screen failures are defined as a subject consented and screened for enrollment, but not ultimately enrolled on the day of randomization; provided that the failure to enroll was attributable to the subject's failure to meet the inclusion or exclusion criteria listed in the protocol.

Screen failures and subjects who electively withdraw from the study will be dropped from any further follow-up and statistical analysis of this study. The original ICF and any data collected up until the date of withdrawal will be maintained in the clinical site's study files and their number will not be used again in the study.

6.2 Baseline Assessments (up to 30 days prior to procedure)

The following information will be assessed and documentation will be maintained as source records at the study site:

- Neurological assessment of the subject and evaluation of symptoms will be performed by an experienced neurosurgeon, neurointerventionalist or authorized designee. In the case of a ruptured aneurysm, the severity of symptoms is to be administered and assessed by authorized and certified research staff using both the National Institutes of Health Stroke Scale (NIHSS) and the Hunt and Hess scale (Table 3)..
- The Subject's modified Rankin Scale (mRS) assessment score will also be collected for the eCRF to reflect baseline functional status
- SF-36 questionnaire to assess general quality of life (for ruptured cases when the subject is impaired and unable to complete the SF-36 questionnaire, this can be completed by the subject prior to discharge)
- Medical History
- Current medications history including anti-platelet and anti-coagulation drugs
- Physical Examination
- Laboratory values to include hemoglobin (Hg), platelet count (Plt), prothrombin time (PT), partial thromboplastin time (PTT), international normalized ratio (INR), and creatinine (Cr).A pregnancy test is required if the subject is female with child-bearing potential. Any female of child-bearing potential who has not been diagnosed with menopause or any other clinical condition that would prohibit conception and/or has not undergone any kind of surgery that would prohibit conception (e.g. total hysterectomy or bilateral oophorectomy) should receive a pregnancy test prior to enrollment.
- A CT scan or MRI may be used to evaluate study Subject eligibility. However, this imaging is not required to be recorded on the eCRF nor is the imaging CD required to be sent to the Imaging Core Lab or Sponsor.

Once the consent form has been signed, all subjects should complete the baseline assessments discussed in Section 7.2 and the Schedule of Assessments (Table 4).

6.2.1 Clinical and radiographic evaluation

A pre-treatment clinical assessment will be performed by the treating physician or designee and a mRS score should be obtained. The NIHSS and Hunt and Hess scale scores will be recorded for those patients presenting with ruptured aneurysms and/or SAH. The patient's medical co-morbidities will also be recorded for study analysis. Results of a pre-embolization brain angiography, MRA or CTA may be recorded and submitted to the Imaging Core Lab and Sponsor if imaging was performed within 30 days prior to enrollment (optional). Measurement of the three (3) aneurysm dimensions of interest (height, length, and width), its neck size and maximal diameter will be recorded as well as any additional relevant radiographic features (e.g. partial thrombosis, peri-aneurysmal edema, etc.).

For conventional angiography, two 10 mm silicon-coated spherical ball bearings must be used for each enrolled subject during procedural angiography (immediately pre- and post-coiling) as well as during any subsequent follow-up angiograms to make measurements as standardized as possible. One ball bearing will be placed on the forehead and the second in the periauricular area ipsilateral to the aneurysm. Image intensifiers will be placed as close to the head as possible. A 4-axis orthogonal view of the aneurysm will be obtained.

Imaging data will be recorded on the Imaging eCRF. Imaging CDs will be sent to the Imaging Core Lab and the Sponsor, Northwestern University. In the event ball bearings are not used during procedural angiography, the Sponsor may require submission of baseline imaging including CTA or MRA to enable the Imaging Core Lab to more accurately obtain measurements.

Please see Table 7 which outlines the imaging schedule.

6.3 Randomization

Subjects who meet study inclusion and exclusion criteria and who have signed an informed consent form will be randomized through the study's Electronic Data Capture (EDC).Randomization will be performed through the EDC on the day of the coiling procedure. This must be completed once pre-coiling imaging has been reviewed and immediately before endovascular coiling begins. At this time, the Subject will be given a unique study identification number generated by the EDC. This number should be used on all study documents so that data is reported anonymously to protect subject confidentiality and patient health information (PHI). Patients will be randomized 1:1 to one of two study arms: 1) The HydroCoil® Embolic System ("Hydrogel Group") or 2) bare platinum coils ("Platinum Group").

Patient safety is a priority. In the event the treating investigator deems it clinically necessary to switch a subject randomized to the Hydrogel arm to the platinum coils arm for safety reasons, the crossover should be documented as a protocol deviation in the eCRF. However, the subject will continue to be followed and will receive all study-related procedures as per protocol. Similarly, if the investigator switches a subject, randomized to the bare platinum arm to the Hydrogel arm or uses more than 10% platinum coils (based on length) in a subject randomized to the Hydrogel arm, the same procedures will be followed. The reason(s) for the preference of one type of coils over the other will be documented in the eCRF.

If during the course of the treatment the investigator decides to perform staged coiling or to use a flow-diverting stent (e.g. pipeline), a protocol deviation should be documented in the eCRF and the subject should continue to be followed as per protocol.

If during the course of the treatment the investigator decides to switch to open surgery or decides not to treat the aneurysm at all, a protocol deviation should be documented and subjects should continue to be followed according to standard of care (i.e. as per site management protocol). The reason for the preference of surgery or no treatment over coiling will be documented on the eCRF.

6.4 Angiographic occlusion evaluation

Angiographic aneurysm occlusion rate will be assessed using 2 scales. The first is based on the new reporting standards described by Meyers et al. (grades 0 to 5).[23] This reporting system will be used by the Imaging Core Lab only for study and validation purposes. It is comprised of 6 grades: (Figure 1)

- Grade 0: complete and total aneurysm occlusion
- Grade 1: ≥ 90% volumetric aneurysm occlusion
- Grade 2: 70% to 89% volumetric aneurysm occlusion
- Grade 3: 50% to 69% volumetric aneurysm occlusion
- Grade 4: 25% to 49% volumetric aneurysm occlusion
- Grade 5: < 25% volumetric aneurysm occlusion

The second scale will be the Raymond scale[24] (complete, residual neck and residual aneurysm) (figure 2). This scale will be used by the Imaging Core Lab and the investigator at each participating site to report aneurysmal occlusion rates.

In the event of recanalization*, the treating physician will be asked to grade the recurrence by answering the following questions:

1- Can the aneurysm be retreated? YES or NO

2- Should the aneurysm be retreated? YES or NO

3- If answers to both questions are YES, the treating physician will be asked to indicate the most appropriate subsequent treatment option (i.e. recoiling, clipping, stent-coil, flow diverter stent, or parent artery occlusion).

*As part of the Imaging Core Lab's evaluation of the submitted imaging, they will also perform the above assessments for study purposes, but will do so while being blinded to the treating physician's grading and assessment. The Imaging Core Lab will be unblinded to the rupture/unruptured status of the aneurysm as this may affect their decision making process in case retreatment is warranted.

6.5 Packing density measures

The packing density calculations will be based on total coil length, coil volume, and aneurysm volume. The following equation will be used to calculate the packing density per coiling procedure:

$$\textbf{Packing density} = \frac{\text{Total Coil Volume}}{\text{Aneurysm Volume}} \times 100$$

The coil volume calculation assumes a cylindrical shape of the coil:

$$\textbf{Coil Volume} = \frac{\pi \times Dc^2 \times L}{4}$$

Dc: Coil outer diameter
L: Coil length

The aneurysm volume will be calculated using the following equation:

Aneurysm Volume = 4/3 pi(a/2)(b/2)(c/2)

a, b, and c are the aneurysmal height, length and width in millimeters.

In order to keep measurements as uniform as possible, the Imaging Core Lab will provide the aneurysm volume and the treating physician will provide the total coil volume as the Imaging Core Lab will be blinded to the type of coils used.

6.6 Treatment protocol

6.6.1 Coiling procedure

Coiling will be performed according to the standards of each institution. The choice of catheters and guide-wires will not be dictated. The investigator will also have the choice to use assist devices (balloon and/or stents). The use of assist devices will be recorded on the Procedure eCRF. No flow diverter stents are to be utilized in this study. Coiling will be done in a one-step procedure. Every attempt should be made to treat with as much of the randomized coil type as possible to achieve optimal occlusion. Use of any bioactive or non-HES 2nd generation coils (e.g. Matrix, EV3 or Cerecyte) and/or use of liquid embolic materials is not allowed. Use of such devices will be considered a protocol deviation but the subject will continue to be followed according to HEAT protocol.

The use of Antiplatelet therapy is left to the discretion of the treating physician. Antiplatelet therapy type and dosing should be recorded on the eCRF. Timing of anticoagulation and ACT during the procedure should be documented on the eCRF.

For the Platinum group, any type of FDA or HPB approved or cleared (as applicable) bare platinum coils can be used. For the Hydrogel group, the investigator will use any type of FDA or HPB approved or cleared (as applicable) second generation HydroCoil Embolic System product (which includes HydroSoft, HydroFrame, HydroFill and future FDA or HPB approved hydrogel products). For subjects randomized to the Platinum arm, treatment should involve exclusive use of bare platinum coils. For subjects randomized to the Hydrogel arm, treatment should involve exclusive use of HES products with up to 10% of total coil length using bare platinum allowed.

After the procedure, digital copies of the pre and post-coiling angiograms with AP and lateral working projections will be sent to the Imaging Core Lab for independent evaluation and analysis. A copy will also be sent to the Sponsor, Northwestern University. The images will be de-identified and the CD/DVD will be labeled with the subject's assigned study identification number, imaging type, and date of imaging.

6.7 Post-procedure follow-up: Day 1 post-coiling

On day 1 post-coiling, clinical and neurological assessment of the subject is performed and documented on the eCRFs. This visit involves a mRS assessment for all subjects and NIHSS and Hunt & Hess scale assessments for subjects presenting with a ruptured aneurysm.

6.8 Immediate follow-up visit: Between 3 to 28 Days post-coiling

The immediate post-coiling follow-up will consist of a clinical assessment and specifically a neurological exam. This visit involves a mRS assessment for all subjects and NIHSS and Hunt & Hess scale assessments for subjects presening with a ruptured aneurysm. The investigator or an authorized member of the research team will assess for any new or unresolved adverse events. The need for cerebral imaging will be assessed and performed according to the standard of care at each institution to evaluate aneurysm occlusion and to study the early recanalization rate. If the length of hospitalization post-procedure equals or exceeds 3 days, then the 3 to 28 day follow-up will also be considered as the discharge follow-up and it will be marked as such on the eCRF. If a 3-28 day visit is not standard of care at a site, the mRS score and review of adverse events can be obtained via phone.

6.9 Early follow-up Visit: Between 3 months to 12 months post-coiling

Clinical and neurological assessments will be performed. The neurological examination will include the mRS. The investigator or an authorized member of the research team will assess for any new or unresolved adverse events. A digital subtraction cerebral angiogram will be performed. MRA can be performed instead of or in addition to the angiogram if considered standard of care at the institution. Quality of life will be assessed with the SF-36 questionnaire. For subjects enrolled with ruptured aneurysms, an NIHSS score will also be obtained.

6.10 Final follow-up Visit: Between 18 to 24 months post-coiling

Clinical and neurological assessments will be performed. The neurological examination will include the mRS. The investigator or an authorized member of the research team will assess for any new or unresolved adverse events. A digital subtraction cerebral angiogram will be performed. MRA can be performed instead of or in addition to the angiogram if considered standard of care at the institution. Quality of life will be assessed with the SF-36 questionnaire. For subjects enrolled with ruptured aneurysms, an NIHSS score will also be obtained.

6.11 Unscheduled Follow-up Visit

Should an unscheduled follow-up visit occur, the reason for the visit should be clearly marked in the eCRF. In the event there is a change in the clinical neurological status due to an adverse event/serious adverse event, the mRS score should be assessed and entered in the eCRF. If the subject presents with a hemorrhage, the NIHSS and Hunt and Hess scores should be assessed and entered in the eCRF. The investigator or an authorized member of the research team should assess and report any unresolved or new adverse events. If imaging is ordered to assess occlusion or recurrence of the aneurysm, the Imaging eCRF must be completed and the imaging CD should be sent to the Imaging Core Lab and the Sponsor, Northwestern University. If imaging is performed for purposes other than to assess occlusion or recurrence, the Imaging eCRF does not need to be completed and no CD is required for submission.

6.11. 1 Re-treated Subjects

For subjects who are retreated, please complete the Unscheduled follow-up visit. If a subject is retreated by coiling or stent-coil, sites will need to send the images to <u>both</u> the **IMAGING CORE LAB** and **Sponsor**.

For subjects who were retreated prior to their 18-24 Month follow-up visit, please follow the above depending on how the subject was treated.

6.12 Schedule of Assessments

A summary of the study related assessments as outlined above is described in Table 4.

6.13 Study Completion

Once a subject completes all study follow-up visits which include the 18 to 24 month visit, the Final Follow-Up eCRF must be completed. During the course of the study, it is possible that subjects will be

withdrawn from the study prior to completing the final 18 to 24 months visit. Factors leading to Subject withdrawal may include, but are not limited to the following:

- **Subject Withdrawal** - A Subject may voluntarily withdraw from the study at any time for any reason, whether disclosed or undisclosed, without affecting their future medical treatment or benefits. In addition, if a patient refuses follow-up examinations and evaluations the investigator may remove her/him from the study after appropriate notice.
- **Subject Lost to Follow-Up** – If the subject does not show up to the planned follow-up visits, attempts should be made to contact her/him. If after at least three (3) attempts the subject remains unreachable, she/he may be withdrawn from the study. The research team must document at least three contact attempts before declaring a subject as lost to follow-up.
- **Subject Death** - When a Subject dies, the ADVERSE EVENT and STUDY EXIT eCRFs must be completed immediately (within 24 hours of the event). If available, documents such as the death summary, the autopsy report and a copy of the death certificate shall be provided to the principal investigator of the site and the Sponsor, Northwestern University, and the funder, MicroVention. Personal identifiers should be removed from any documentation provided. The site's IRB shall also be notified promptly.

If a subject was withdrawn for any of the above mentioned reasons, the Study Exit eCRF form must be completed.

7 Management of Adverse Events

7.1 Definitions

An Adverse Event (AE) is any undesirable clinical event occurring to a subject enrolled in the trial, whether or not it is considered related to the investigational product. This includes a change in a patient's clinical condition including changes in neurological status or laboratory results that has or could have a deleterious effect on the patient's health or well-being.

An Adverse Device Effect (ADE) is any AE related to the deployment of any coil type.

A Serious Adverse Event (SAE) or a Serious Adverse Device Effect (SADE) is an event that:

- Results in death
- Is life threatening
- Is disabling
- Requires initial or prolonged hospitalization (does not include planned hospitalization)
- Requires intervention to prevent permanent impairment / damage

An Unanticipated Adverse Device Effect (UADE) is 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 any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

See Figure 3 for a classification of adverse events.

7.2 Reporting of Adverse Events

For this post-market study, only AE/SAEs that are related to the procedure, device or a change in neurological status should be captured on eCRFs and in the Subject's medical records, for both treatment arms. In case of occurrence of any SAE and/or UADE, the site's principal investigator shall promptly submit a report along with any other required documentation to the Sponsor, Northwestern University and funder, MicroVention, Inc and follow site-specific IRB procedures.

If there is a serious adverse event, the clinical study site will report such to the Sponsor, Northwestern University and the funder, MicroVention, Inc within 24 hours of learning the event.

If there is an unanticipated adverse device effect, the Principal Investigator will submit a report to the Sponsor, Northwestern University and the funder, MicroVention, Inc and to the reviewing IRB as soon as possible, but not later than 10 working days after the investigator learns of the effect.

All other reportable events should be reported no later than 10 working days after the investigator or site first become aware of the adverse event in question.

The adverse event report should at least include the following parameters:

- Date of event and time
- Type of event (E.g., AE, SAE, UADE)
- Narrative
- Duration of adverse event or adverse device effects (start-end)
- Treatment
- Outcome/Resolution Status

The principal investigator and the principal investigator of the site shall present any additional information or documentation (e.g. imaging results) to the DSMB and steering committee if required by these committees.

7.3 Expected Risks

Known risks associated with aneurysm coiling are as follows:

- Aseptic meningitis
- Inflammation
- Thromboembolic events
- Stroke
- Vasospasm
- Hydrocephalus
- Aneurysm Rupture
- Coil protrusion into parent vessel
- Parent Vessel Occlusion
- Premature coil detachment (coil breakage due to technical device malfunction)
- Death

8 Ethics and Regulatory Considerations

8.1 Subject Information and Consent Procedures

The Investigator, study coordinator or any other member of the research team approved by the IRB will obtain written informed consent from the patient or his/her LAR before subjecting her/him to study assessment procedures. The Subject will be clearly informed that the principal investigator, study coordinator and study monitor of the coordinating site (Northwestern University) will have access to personally identifiable information for the purposes of monitoring data against source documentation. However, only de-identified data is entered into the study database.

Each site participating in this study will have their own consent form that must be approved by their IRB. In addition, a study consent form approved by the primary site IRB will be provided to each clinical site. Only the local participating site consent form should be signed prior to enrollment and treatment. The coordinating site must receive and approve each participating site's ICF. Each Investigational site must provide to the Sponsor or Principal Investigator a copy of its IRB approved ICF, renewed approvals and signed patient consents, as appropriate, for the duration of the study.

The original, signed and dated ICF should be retained in the Subject's study records, and a copy provided to the Subject. Documentation of the informed consent process should also be retained in the subject's study records.

8.2 IRB Approval

The Investigator or the study coordinator is responsible for submitting the study protocol and any changes issued by the Sponsor during the course of the study for IRB approval prior to any Subject enrollment and amendments taking effect as well as obtain renewals at periods determined by the IRB for the duration of the study.

9 Statistical Methods

Primary analysis of primary and secondary outcomes will be based on the intent-to-treat (ITT) principle. Secondary analyses will examine differences based on per protocol principles, as well as a detailed analysis of missing data, should there be any (see below).

9.1 Sample Size Estimation

For univariate associations, using a two-sided two-sample test of proportions (Chi-square test), Table 5 shows the effect sizes one would be able to detect for given baseline rates (assuming 1:1 randomization and 5% type I error rate) at 80% power.

Using multiple logistic regression to predict recurrence (baseline rate in Platinum group of 33%), the sample of 600 patients would provide 80% power to detect an odds ratio between 0.60 and 0.47, depending on the r-squared of the other covariates to coils (between 0-0.2; note r-squared of 0 corresponds to hydrogel rate of 22.8% as in the univariate analysis). Likewise, for complete occlusion (baseline rate of .556), a sample of 600 provides 80% power to detect odds ratios between 1.60-1.70, depending on the r-squared of the other covariates to coils (between 0-0.2; note r-squared of 0 corresponds to hydrogel rate of .678 as above). Similarly, for recanalization, one would have 80% power to detect odds ratios between 0.613-0.577 (n=600).

9.2 Statistical Analysis Plan

9.2.1 Primary endpoints:

Chi-square tests (simple logistic regression) will be used to determine if rates of recurrence differ by coil type. Additionally, multiple logistic regression models will be used to examine those rates while adjusting for various covariates, including, but not limited to: site, age, gender, aneurysm size, neck size, packing density and rupture status. Models will be fit to examine potential interactions between covariates and randomization group in predicting outcomes; and final models will be fit depending on statistical and clinical significance of the covariates to the outcome as well as any change in the relationship between the randomization group and outcome. Analyses will be presented both as univariate and adjusted Odds Ratios and corresponding [Wald] 95% Confidence intervals.

While the study has been designed to minimize any missing data due to this being a longitudinal study, the potential for missing data or loss to follow-up is present. Patterns of missing data and dropout will be examined to determine if complete case analysis or available data analyses are appropriate or if imputation methods will need to be incorporated. Should a complete case analysis be appropriate, PROC LOGISTIC will be used to analyze these binary outcomes; otherwise PROC GLIMMIX will be used for an available data analysis. If imputation methods are called for, PROC MI and PROC MIANALYSE will be used and results presented. All analyses will be run at a type I error rate of 5% using SASv9.2, Cary, NC.

9.2.2 Secondary endpoints:

The rates of initial complete occlusion, partial occlusion, recanalization, retreatment, or hemorrhage from the target aneurysm during follow-up (and other binary outcomes) will be analyzed similar to the primary endpoints. Packing density will be analyzed by comparing means or medians (depending on the underlying distribution) between groups. Additionally, this will be compared using linear regression models (PROC REG or PROC MIXED, as above) adjusting for potential confounders including site, age, gender, aneurysm and neck size, and rupture status. Clinical outcomes and quality of life will be compared between groups using models appropriate for repeated measures (generalized linear mixed models). This will take into account changes in these outcomes over time as well as the 18-month evaluation and can accommodate some missing data as it does not require only complete cases be used but rather uses an available data analysis. Again univariate and multivariate results (means and 95% Confidence intervals) will be presented.

9.3 Demographics by race/ethnicity

This is an international study. Since intracranial aneurysms are more prevalent in females than in males, it is anticipated that there will be a higher relative percentage of females represented in the study population.

10 Records and Reports

10.1 Records

Each study site will maintain eCRF and source study records for monitoring and/or audit purposes for the latter of:

- At least five (5) years after study completion; or
- For the period required by the local governing authority and reviewing IRB

These records also include the following:

- Correspondence with the Sponsor, the Funder, the Imaging Core Lab, the DSMB, the steering committee, the various committees and other investigators
- Patient Records, including ICFs and supporting documents in addition to the eCRF
- Most current version of the study protocol with dates and details of reasons for any deviations from the protocol
- Reports of any adverse events, serious adverse event or adverse device effects
- A copy of all approvals related to the clinical investigation
- The approved, blank ICF and blank CRFs
- Certification that the investigational plan has been approved by the IRB from each site
- Signed sub-site agreements with the Sponsor, the site and principal investigator of the site.

The site principal investigator and the study coordinator will be responsible for archiving the data for the periods mentioned above. If the data is to be archived at an off-site, the IRB will be notified and the principal investigator and the study coordinator will be responsible for keeping it confidential. The Sponsor will have full access to this data, and the Funder will have read-only access to this study data, as provided by Northwestern, solely for review and adjudication of information related to any AE, SAE, ADE, SADE and UADE (as defined in section 7.1) for legal and compliance purposes

10.2 Reports

Investigators at participating sites are required to submit reports in conformance with the regulations mentioned throughout this protocol.

10.3 Protocol deviation

Any deviation from the protocol should be reported within 10 days to the Sponsor and clearly documented. Each site will be responsible for reporting any protocol deviation to their IRB according to their institution's standards.

If the investigator finds that the aneurysm characteristics require a deviation from the protocol, he/she must contact the principal investigator of the site as soon as possible and the principal investigator of the site or investigator shall submit a report as to why this decision was made. Any protocol deviation must be clearly documented in the eCRF.

11 Data Management

All required data for this study will be collected on appropriate source medical records and source documents for entry into the EDC within 5 days of the subject visits. A database lock timeline will be created to ensure proper and timely collection of data from all sites (this will be done every 3 months).

12 Monitoring of the study and Quality Control

12.1 Medical Monitoring by DSMB

All SAEs and ADEs will be reported to and evaluated by the DSMB members for a potential relationship to the study device or procedure as set forth in Section 7.2. All AEs will be evaluated by the investigational site and the principal investigator of the site, and they will follow site specific IRB procedure with respect to AEs. The principal investigator of the site will complete the eCRF and notify the Sponsor and Principal Investigator with respect to AEs in accordance with Section 7.

12.2 Data Collection and Monitoring

Each site's study coordinator will collect and document data in hospital and clinic charts. eCRF data will be entered in anonymous form into the secure web-based and password-protected database within 5 days of each subject study visit. Only the investigator, study coordinator and other designated authorized research personnel will have access to the database. Each participating site will have access to only its own data. In addition, the Sponsor, the Principal Investigator, monitor and the study coordinator of the Sponsor's site will have access to the entire database with full rights to act as the administrator of the database.

Data verification occurring during monitoring visits will involve the review of the subject's medical record (for study specific visit dates only) and source documents. These source documents should only be used in instances where the subject's medical record does not contain the data required for study. These forms should be signed and dated by study personnel collecting the data at the time of collection.

Completed eCRFs in final form may be printed and filed in hardcopy for archiving if required by the local governing authority. All data will be exported and stored on appropriate electronic media by the Principal Investigator and to study biostatistician for analyses.

The Principal Investigator of each site is responsible for data integrity at the site and will review and electronically sign all Patient Selection, Adverse Event, Protocol Deviation, Imaging and Study Exit eCRFs.

The clinical site will be monitored routinely by the Sponsor and by a trained study coordinator and/or monitor for adequate enrollment, timeliness of data submission, and compliance with the investigational plan and applicable local and federal regulations. If the site in question fails to show compliance with the above mentioned, the site investigator will be contacted by the principal investigator, and if corrective actions are not taken to resolve the issues, the clinical site may be withdrawn from the study.

12.3 Site Compliance / Deviations

In order to optimize correct and detailed records, all eCRFs should be entered in the web-based database as indicated in Table 6.

In some cases, a site investigator may want to include and randomize a potential Subject who meets all but one Inclusion/Exclusion criterion. The investigator will present the case and report their medical opinion to the Sponsor, Principal Investigator and, if appropriate, the DSMB for consideration. If the prospective deviation is approved then the Subject may be enrolled in the study. This protocol deviation will be documented in the subject's eCRF.

13 Financial and Insurance Matters

As all devices used in this trial are FDA or HPB approved, the coiling procedures are considered Standard of Care and shall be the patient's responsibility (insurance or self-pay). Any follow-up assessments that are protocol driven and not standard of care shall be covered under study agreement.

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Table 1. Major hydrogel coil studies - initial results

Author and year	Type of study	Number of aneurysms treated	Aneurysm size	Ruptured vs. Unruptured	Mean Neck size	Initial Complete Occlusion	Residual Neck	Residual aneurysm	% hydrocoil used
Berenstein et al. 2006	Retrospective Single center	104	S/S: 42 S/W: 27 L: 32 G: 3	48 vs. 56	-	34%	35%	32%	45.5%
Cloft et al. 2006 (HEAL)	Prospective Multicenter Registry	191	Mean: 8 mm	71 vs. 120	4.3mm	48.7%	41.4% (near-complete)	9.9%	Frame: Platinum coil Fill: HydroCoil
Gaba et al. 2006	Prospective	50	S (≤ 5mm): 17 M (6 - 10 mm): 26 L (11 - 20 mm): 5	31 vs. 19	-	58%	36%	6%	71.8%
Deshaies et al. 2007	Prospective	67	S: 30 L: 27 VL: 7 G: 3	35 vs. 32	-	43%	35%	22%	-
Fanning et al. 2007	Prospective observational	100	<7 mm:42 7 -15 mm: 52 16 - 25 mm: 6	64 vs. 36	≥ 4mm: 40	28%	54% (>95% occluded)	18%	42.5%
Kang et al. 2007	Prospective Multicenter	80	S :58 L (≥10 mm): 22	32 vs. 48	-	75%	17.5% (near-complete)	7.5%	46 to 74% of followed-up aneurysms
White et al. 2008 (HELPS)	Randomized Controlled trial	495 (249 randomized to the Hydrogel group)	Mean: 6.5 mm 2 - 4.9 mm: 42 5 - 9.9 mm: 144 10 - 24.9 mm: 63	139 vs. 110	-	47.3%	31.3% (near-complete)	21.4%	-
Gunnarsson et al. 2009	Retrospective	200	S (<10mm): 125 L (10 - 25 mm):75	104 vs. 96	-	53.8%	29.6%	16.6%	58%

Table 2. Major Hydrogel coil studies - follow up results

Author and year	Complications/ Morbidity	Mortality	% followed up	Mean Follow-up (Months)	Recanalization	Retreatment
Berenstein et al. 2006	14 / 5.8% Immediate post- procedure Morbidity	0% (Immediate post-procedure)	51%	10.3	21%	-
Cloft et al. 2007 (HEAL)	10.9% (Immediate post-procedure)	-	135/191 (70.6%)	3-6	28.1%	-
Gaba et al. 2006	4%	2 (4.4 %)	84%	12.3	17%	10%
Deshaies et al. 2007	32.8%	-	90%	12	15%	-
Fanning et al. 2007	12% / 6.4% morbidity	1.1%	63%	7.5	14.3%	4.8%
Kang et al. 2007	16 procedure related-events	0%	68%	≥ 6 mo: 54 aneurysms ≥ 12 mo: 13 aneurysms	11%	-
White et al. 2008 (HELPS)	70 (Procedural Adverse events)	3.6%	-	-	-	-
Gunnarsson et al. 2009	15% complication (6% leading to permanent morbidity or mortality)		60.5%	16.3	21.5%	10.7%

Table 3. Hunt and Hess classification of SAH

Grade	Description
1	Asymptomatic, or mild H/A and slight nuchal rigidity
2	Cr. N. palsy (e.g. III, VI) moderate to severe H/A, nuchal rigidity
3	Mild focal deficit, lethargy, or confusion
4	Stupor, moderate to severe hemiparesis, early decerebrate rigidity
5	Deep coma, decerebrate rigidity, moribund appearance
Add one grade for serious systemic disease (e.g. HTN, DM, severe atherosclerosis, COPD) or severe vasospasm on arteriography.	

Table 4. Schedule of assessment

HydroCoil Embolic System Clinical Trial	Screening & Baseline	Procedure	Post-procedure Follow-up	Immediate Follow-Up	Early Follow-Up	Final Follow-Up
Schedule of Events	Up to 30 days prior to surgery	Day 0	Day 1	3-28 Days	3-12 Months	18-24 Months
Review Inclusion/Exclusion	X					
Data Entry, Validation, Query Resolution	X	X	X	X	X	X
Obtain Informed Consent	X					
Randomization		X				
Adverse Events		X	X	X	X	X
Demographic Data	X					
Medical History	X					
Hunt & Hess Scale[1]	X	X	X			
Modified Rankin Score	X	X	X	X	X	X
NIH Stroke Scale (NIHSS)[1]	X	X	X		X	X
SF-36	X[3]				X	X
Angiogram	X	X			X	X
MRA	X[2]				X[2]	X[2]
Final Visit Assessment						X

[1] For Subjects enrolled with ruptured aneurysms
[2] According to standard of care of each institution.
[3] For Subjects with ruptured aneurysms who are unable to complete the SF-36 prior to procedure, the SF-36 can be completed prior to subject discharge following procedure.

Table 5. Effect Sizes for outcomes with N=600, with 80% power

Outcome	baseline (platinum) rates	*Hydrocoil rates*	% change
Recurrence	33.0%	22.8%	-30.9%
Complete occlusion	55.6%	66.7%	20%
	47.6%	59.0%	23.9%
Complete or nearly complete occlusion	85.5%	92.6%	8.4%
Retreatment	17.4%	9.6%	-44.8%

Table 6. Electronic Data Entry Timelines

eCRF	Timeline
Adverse Event eCRF	In the event of a serious adverse event, complete the AE CRF on the web-based database and fax report within 24 hours of learning of the event to the Sponsor and Funder. Comply with local reviewing IRB reporting rules. In the event of an unanticipated adverse device effect, complete the AE CRF on the web-based database and fax report as soon as possible, but no later than 10 working days after the investigator first learns of the effect to the Sponsor and Funder. Comply with local reviewing IRB reporting rules.
All other eCRFs	Within 5 business days of subject discharge or follow-up

Table 7: Required Imaging Schedule

HydroCoil Embolic System Clinical Trial	Screening & Baseline	Surgery		Post-Procedure Follow-up	Immediate Follow-up	Early Follow-up	Final Follow-up
Schedule of Events	**Up to 30 days prior to surgery**	**Pre-Coil**	**Post-Coil**	**Day 1**	**3-28 Days**	**3-12 Months**	**18-24 Months**
Angiogram		X	X			X	X
MRA						X[2]	X[2]

[2] According to standard of care at each institution

Please note that if an angiogram, MRA or CTA is performed 30 days before surgery, the Imaging eCRF should be completed and the CD shipped to the core lab and Northwestern University. This imaging is optional and is not required for the study.
Results of MRIs or CTs are not needed

Figure 1. Aneurysm occlusion grading system as reported by Meyers et al.[23]

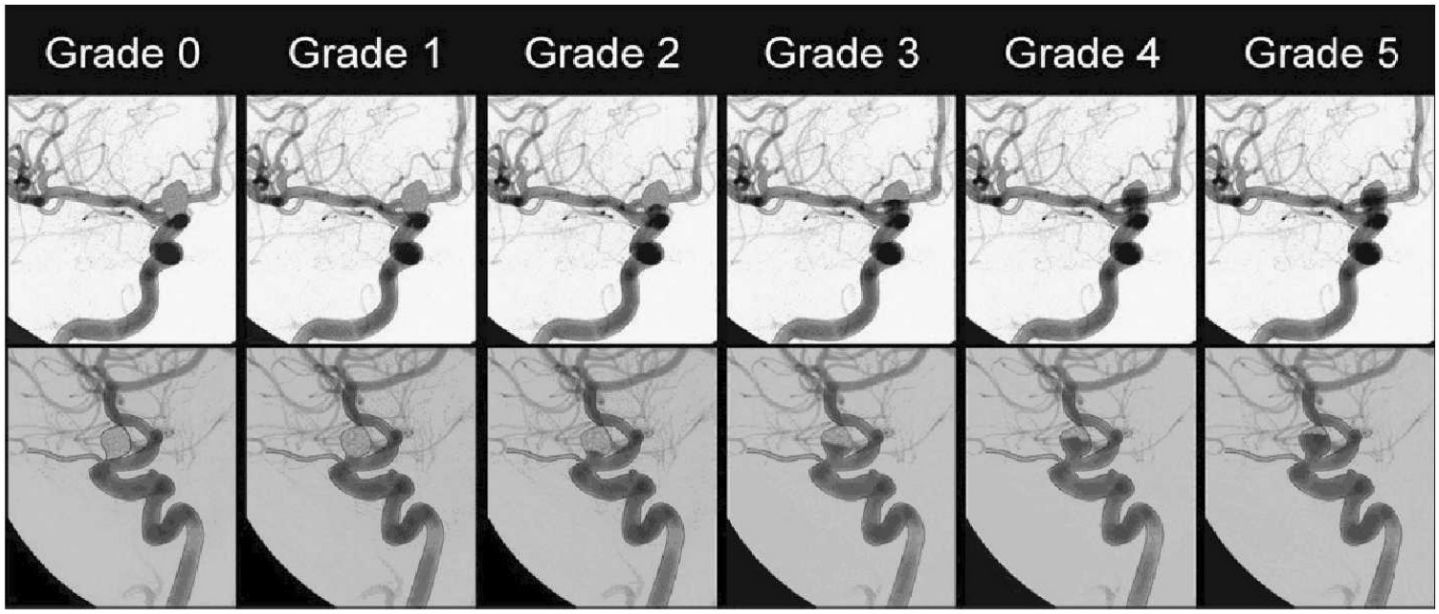

Figure 2. Raymond angiographic classification of residual coiled aneurysm.

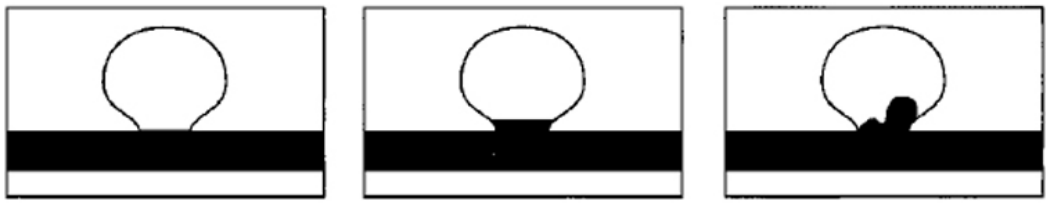

Figure 3: Classification of Adverse Events