Framing Eighteen Coils in Cerebral Aneurysms Trial (FEAT)

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A randomized controlled trial of Eighteen (0.014-0.0155 inch) platinum coils versus standard (<0.014) platinum coils in the endovascular treatment of medium-sized (6 – 14 mm) intracranial aneurysms

Trial Sponsor: Vanderbilt University Medical Center

Financial Sponsor: Stryker (Natick, MA)

Lead Principal Investigator: J Mocco, M.D., M.S. – Mount Sinai

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1. Background

In recent years, the treatment of intracranial aneurysms has shifted from a primarily surgical paradigm to one of endovascular management. The International Subarachnoid Aneurysm Trial (ISAT), published in 2002, demonstrated improved mortality and dependency rates at 1-year in those undergoing endovascular coil embolization to those undergoing clipping[1]. However, follow-up data from the ISAT revealed a higher incidence of late re-bleeding and recurrence among aneurysms treated via embolization compared to clipping[2]. The difficulties with recurrence have been relatively consistent in the literature, with an estimated angiographic recurrence rate of approximately 10-20% (although as high as 33% in one study); fortunately, however, the re-bleed rate has consistently been very low[3-8]. In light of these factors, many institutions have shifted towards endovascular management, and close follow-up to detect recurrence, with surgical clipping as a secondary option for specific patients or those who fail endovascular means.

Larger aneurysms have demonstrated higher hemorrhage rates when observed in longitudinal studies[9, 10]. Similarly, larger aneurysms are more difficult to treat successfully via coil embolization; initial and long-term occlusion is inversely related to aneurysm size[11-13]. Smaller aneurysms are generally easier to obtain satisfactory packing density and occlusion while giant aneurysms are much more challenging and plagued by high recanalization rates. For this reason, studies of small aneurysms usually demonstrate uniformly excellent results while studies of large or giant aneurysms usually demonstrate poor long-term results. Therefore, mid-sized aneurysms (6-14 mm) likely represents the optimal study group for evaluating true differences between coiling treatments.

A major focus of clinical research has been improving aneurysm occlusion and recurrence rates through modification of techniques, devices and embolic materials. Until recently, bare platinum detachable coils, which are biologically inert, had been the mainstay for neuro-interventionists. The first bioactive coil approved by the U.S. Food and Drug Administration, the Matrix coil (Stryker), has only modest evidence supporting its use[14-17]. More recent bioactive and non-bioactive coils, including hydrogel and Cerecyte coils, have more robust evidence supporting their use[18-28]. Both types of coil have recently completed evaluation in large, prospective randomized trials[28, 29]. Promisingly, the unpublished data suggests excellent aneurysm occlusion rates; however, the primary endpoints of both studies were not statistically different compared to bare platinum coils[30-32]. Although it is apparent that occlusion rates have improved since the initial ISAT data, new coil designs have yet to demonstrate superiority over bare platinum coils in a randomized controlled trial.

Considerable emphasis has been placed on the volumetric filling of aneurysms, or 'packing density', which has been related to long-term outcome[33-35]. Packing density of 20-30% has been suggested as being the desired packing to ensure stable occlusion[33, 34], however achievement of densities exceeding 25% can be difficult in aneurysms larger than 5mm. The use of framing coils, or large-diameter coils initially placed into the aneurysm to serve as a foundation for the placement of smaller-diameter "filling" coils, has demonstrated efficacy in

case series[36]. Framing platinum coils of larger diameter are resistant to deformation regardless of flow rate in a flow-model, unlike smaller-diameter framing coils which became unstable as flow rate increases[37]. These studies suggest that larger diameter platinum coils may be more stable during and after endovascular aneurysm coil embolization, and that smaller-diameter framing coils may have a higher propensity towards recanalization. It should be noted that, contrary to the name, current "Eighteen" platinum coils produced by Stryker (Natick, MA) are actually 0.014-0.0155 inches in size. These coils are larger than standard coils, which are usually sized 0.010 or 0.012".

2. Purpose and Hypothesis

2.1 Purpose: To compare angiographic outcomes in patients receiving 0.014-0.0155" platinum framing and filling coils followed by further aneurysm filling and finishing with less than 0.014" bare platinum coils (as deemed appropriate by the treating physician), versus those treated solely with coils less than 0.014".

2.2 Hypothesis: Angiographic occlusion on follow-up imaging will be more frequent in patients receiving 0.014-0.0155" platinum coils during embolization compared to those receiving smaller-diameter coils.

3. Objectives

3.1 Primary Outcome

Occlusion rate: Angiographic occlusion, improvement or no change in the post-coiling appearance of the aneurysm as judged by an independent core lab on follow-up angiography at 12-18 months after endovascular embolization.

3.2 Secondary Outcomes

1. Treatment related morbidity and mortality, as measured by the NIH Stroke Scale

2. Packing density as measured by volumetric filling of the aneurysm

3. Clinical outcome at 3-6 and 12-18 months post-coiling, as measured by the modified Rankin Scale

4. Re-hemorrhage and re-treatment rates

4. Trial Design

FEAT will be a prospective, randomized trial comparing the utilization of 0.014-0.0155" coils versus smaller diameter coils in mid-sized aneurysm treatment. The 0.014-0.0155" bare platinum coils (Stryker, Natick, MA) are FDA-approved and in common use at institutions in this country and across the world. Patients will be enrolled who meet the inclusion criteria and consent to participate. Patients will be randomly assigned by a central web-based system in a 1:1 manner to either the framing coil treatment or the non-framing coil treatment. Data on each patient will be collected at the time of enrollment and treatment, and at first and second follow-up visits.

4.1 Inclusion Criteria

1. Patient presenting with ruptured or unruptured cerebral aneurysm appropriate for endovascular treatment as determined by the neurovascular treating team (neurointerventionist and/or neurosurgeon).

2. The neurointerventionist feels that the aneurysm can be safely treated with either using, or not using, a 0.014-0.0155" platinum coil.

3. Patient is 18-80 years of age (inclusive).

4. Patient is Hunt and Hess grade 0 to 3.

5. Patient has given fully informed consent to endovascular coiling procedure. If the patient cannot provide self-consent, appropriate written consent has been sought from their authorized surrogate or appropriate power of attorney.

6. Aneurysm is 6-14 mm in maximum diameter.

7. Patient is willing and able to return for clinical evaluation and follow-up imaging evaluation (angiography or MRA) at 3-6 months and 12-18 months after endovascular treatment.

8. The patient has not been previously randomized into this trial or another conflicting/confounding trial.

9. The aneurysm has not been previously treated by coiling or clipping.

4.2 Exclusion Criteria

1. Patient has more than one aneurysm requiring treatment in the current treatment session, and only one of those to-be treated aneurysms fits the FEAT inclusion criteria (i.e., - if either (1) a patient has multiple aneurysms, but only one will be treated at enrollment; or (2) if two or more aneurysms are treated during the current treatment session and BOTH are able to be enrolled, then they remain eligible for the trial. Non-treated additional aneurysms may be treated at a later date with any coil type that the operator chooses).

2. Target aneurysm has had previous coil treatment or has been surgically clipped.

3. Hunt and Hess score is 4 or 5 after subarachnoid hemorrhage.

4. Inability to obtain informed consent.

5. Medical or surgical co-morbidity such that the patient's life expectancy is less than 2 years.

Death or procedural/disease-related morbidity may result in some subjects not having follow-up angiography. For the primary outcome of angiographic recurrence, the analysis will be conducted 2 ways: (1) among only those patients with angiographic assessment at 12-18 months, and (2) among patients with angiographic assessment, plus those with death or procedural/disease-related morbidity that precluded angiography, with such patients counted as incident events. Similarly, for the secondary outcome of treatment-related morbidity and mortality, patients without angiographic evaluation due to death or procedural/disease-related morbidity will be counted as incident events in the analysis.

Use of coil-assist devices (stent, balloon, etc.) will be allowed. Intention to use such a device will be recorded pre-procedure, along with dome to neck ratio and rupture status.

Additional critical components of the study design include the large number of patients required to demonstrate a statistically significant difference, and the subsequent significant length of time required to allow enrollment. Therefore, we propose a three phase study design to address the following concerns:

1) A 6-year time window renders any conclusions irrelevant due to progress in technology. Typically the conclusions of long-term studies in the endovascular space are called into question because they do not include technology that is considered modern by the time the study is completed. Stryker has multiple coil iterations planned over the next 5 years. To not involve these new technologies would make the study non-viable to

Stryker and irrelevant to current practice by the time it was completed. However, any incorporation of iterative technology needs be done in a regimented manner to ensure it does not affect the fundamental study question.

2) There is an onus on the medical and device industry community to provide quality timely short/mid-term data on new technologic advances.

3) All parties would like to complete the study with a concrete scientific conclusion that has legitimate and credible conclusions that move forward our understanding of this complex disease process and its methods of treatment. Unfortunately, a series of multiple underpowered studies obviates this process.

These concerns create an overarching need to perform a scientifically valid study that develops our knowledge base in a statistically valid way, while simultaneously generating much needed early data on new product benefit and to provide useful medium-term knowledge to guide physician practice and industry product development.

To address these concerns the investigative design will be one contiguous study completed in three phases. The theme across all phases will remain true to the fundamental study design question, "Does use of larger diameter framing coils improve treatment durability?" However, the phases will be introduced to allow controlled involvement of developing technologies and, as a result, an avoidance of the above noted concerns. Stryker products will be used in both arms of the trial (18 plus non-18 versus non-18 only) to minimize potential differences from other coil design variables. To ensure progressive relevance and to generate critical short-term technology evaluations the study will be divided into three phases:

- Phase 1: GDC 18 as deemed appropriate plus current Stryker 10 coils (including Target) versus current Stryker 10 coils (including Target);
- Phase II: Target XL as deemed appropriate plus all Target versus all Target;
- Phase III: Future generation of Target coils as deemed appropriate plus all Target versus all Target.

This study design will allow a number of important improvements over typical long term endovascular studies:

1) A valid statistical analysis of the benefit of large diameter coil size in aneurysm treatment, with other variables removed as only Stryker coils will be used in both cohorts and there will be a consistent number of newly developing Stryker technologies on both sides of the treatment/control arm equation. Upon completion of the trial a legitimate scientific question can be answered with statistical validity.

2) Short/mid-term technology evaluations will be generated on iterative advances in coil technology. At the completion of each phase, the non-18 arm descriptive statistics will be analyzed and reviewed so as to provide short-term critical feedback about the developing technology. This will only be performed for the non-18 arm in order to avoid any potential statistical penalties in the analysis of the primary hypothesis.

3) Data will have relevance to current practice upon completion as it will reflect inclusion of evolving technology.

4) Long-term comparisons of progress over time will be able to be made across phases.

5. Treatment Protocol

5.1 Methods

5.1.1 Clinical methods

1. Patients randomized to the framing treatment arm will have an initial 0.014-0.0155" framing coil placed. Following this coil, additional 0.014-0.0155" framing coils may be placed, in a "Russian doll technique", and as recommended, until the treating physicians deem, in their best clinical judgment, that a transition to smaller, 0.010" or 0.012" bare platinum coils, is appropriate. Following placement of the primary framing coil (per the randomization assignment), further coil placement is at the treating physician's clinical discretion, until satisfactory aneurysm occlusion is obtained. However, treating physicians are encouraged to use as many 0.014-0.0155" framing coils as they determine are safe and clinically appropriate. Patients randomized to the control arm will have bare platinum coils less than 0.014" placed into the aneurysm only, under the operator's discretion, until satisfactory aneurysm occlusion is obtained.

2. Coiling of aneurysms will be performed according to the standard of care at each institution. Choice of catheters, guide wires and other devices will not be dictated. However, non-bare-platinum coils, such as bioactive or hydrogel coils, may NOT be used in this protocol.

3. For ruptured aneurysms, the use of heparin and anti-platelet agents and the timing of their use will be according to treating physician preference.

4. For unruptured aneurysms, use of and choice of anti-platelet agents will be according to treating physician preference and local standard of care.

5. If, during the course of the procedure, the operator determines that it would be safer to use other coils or devices, such as bioactive or hydrogel coils, patient safety should take precedence over the randomly assigned treatment protocol. Reasons for protocol deviations, which are anticipated to be infrequent, will be recorded in the eCRF.

5.1.2 Research methods

1. Investigators should only randomize patients if they believe they can actually treat the patient equally safely and effectively regardless of the presence or absence of a 0.014-0.0155" platinum coil(s).

2. As far as possible, the intention is to exclusively use 0.014-0.0155" bare platinum coils for the initial coil in the Eighteen coil treatment arm and for as many subsequent coils as safe and appropriate, as determined by the treating physician. However, if for any reason a treating physician needs to forego placement of a 0.014-0.0155" coil or use a different coil for this purpose, the patient will remain in the study according to the intention to treat principle. Conversely, in patients assigned to the non-Eighteen coil treatment arm, no 0.014-0.0155" platinum coil is to be placed. However, if for any reason the treating physician determines he/she needs to place a 0.014-0.0155" bare platinum coil, the patient will remain in the study according to the intention to treat principle.

3. JPG's of de-identified images will be uploaded for independent evaluation and stored in the study's electronic database. These images will be reviewed by an independent, blinded core lab.

4. An electronic case report form (eCRF) will be completed at the end of the procedure. The procedural details collected for the eCRF will include findings of angiographic anatomy, size, location, neck size and dome-to-neck ratio .

5. At time of discharge, any adverse events will be recorded on the eCRF.

6. Data on any further aneurysm treatment or re-treatment of the study treated aneurysm will be collected during the study period.

5.1.3 Follow-up

1. The following assessments will be performed at each standard care follow-up visit (3-6 months and 12-18 months post-coiling): (1) clinical outcome; (2) follow-up angiography/MRA; (3) modified Rankin Score; (4) NIH Stroke Scale.

2. The assessment window allowed for each follow-up visit is as follows: (1) 3-6 month follow-up allowable window is 3-7 months post-coiling; (2) 12-18 month follow-up allowable window is 10-20 months post-coiling.

5.2 Intention to Treat

From the moment of randomization, the patient will be included in the trial irrespective of whether they receive the assigned treatment regimen. Similarly, all enrolled patients will receive clinical follow-up and will be included in the final analysis.

5.3 Patient Numbering

Upon randomization, each patient will be uniquely identified in the study by a five-digit identification number consisting of two parts, the two-digit center number (to be assigned by Vanderbilt University Medical Center) and the three-digit subject number. The investigator will assign patient numbers sequentially within each center (001, 002, 003…). Once assigned to a patient, a subject number will not be re-used and will remain with the patient throughout the study. Subjects meeting all inclusion/exclusion criteria will be randomized to one of the two treatment groups. If the patient has signed the informed consent form and then fails to be randomized for any reason, the reason for not being randomized will be entered on the Screening and Enrollment Log.

If subjects have more than one aneurysm that qualifies for the trial, each aneurysm will be assigned a subject number since each aneurysm will be randomized separately.

5.4 Patient Recruitment

Eligibility will be assessed once the neurovascular team makes a decision on endovascular treatment of an aneurysm. A Screening and Enrollment Log of all screened patients, consented patients, randomized patients, and completed patients will be kept and maintained in the study's electronic data capture system. If a patient meets inclusion and exclusion criteria, a suitable member of the research team will discuss the trial and provide the patient or their acceptable surrogate with written information. This person will allow the patient or acceptable surrogate adequate time to consider inclusion in the trial, and will answer all questions regarding the trial. If a patient/acceptable surrogate agrees to participate in the trial and signs the informed consent document, the patient will be randomized. One copy of the signed informed consent document will be given to the patient, one retained by the local investigators and a copy uploaded into the secure web-based database maintained by the coordinating center.

5.5 Randomization

1. A research team member authorized to randomize will then perform randomization via a web-based randomization process. The randomizer will communicate the result of the randomization to the neurointerventionalist who will coil the aneurysm. Alternatively, the neurointerventionalist can perform the randomization prior to performing the procedure.

2. An algorithm that stratifies the randomization will be used to ensure balance between the two treatment groups on those parameters known to significantly affect the ability to coil and pack densely. The stratification of these variables is as follows:

- Aneurysm status of recently ruptured (within 15 days) versus not recently ruptured;
- Current trial phase
- Dome to neck ratio:
    - Not wide neck – dome to neck ratio ≥ 2, or neck width < 4mm
    - Wide neck – dome to neck ratio < 2, or neck width ≥ 4mm

3. Both treatment arms are anticipated to have approximately equal proportions of acutely ruptured aneurysms. Aneurysm location will be recorded but will not be a basis of stratification due to lack of location as contributing to the recurrence or packing density achieved.

6. Visit schedule and Assessments

6.1 Visit Schedule

	Screening and Enrollment	Embolization Procedure	Discharge	3-6 Month Follow-Up	12-18 Month Follow-Up	Unscheduled Visit(s)
Informed Consent	X					
Inclusion/Exclusion	X					
Randomization	X					
Chart Review	X					
Hunt Hess	X					
Fisher (if applicable)	X					
WFNS (if applicable)	X					
Modified Rankin	X		X	X	X	X
NIHSS			X	X	X	X
Research Data Collection	X	X	X	X	X	X
Clinical Evaluation	X		X	X	X	X
Imaging		X		X	X	X (if indicated)
Embolization		X				
Re-Treat (if applicable)				X	X	X
Evaluate for AEs/SAEs	X	X	X	X	X	X

6.2 Assessments

6.2.1 Angiographic assessment

1. Procedural angiograms (as part of standard of care) will be collected at enrollment and follow-up. Follow-up angiograms should be performed at 3-6 months and again at 12-18 months post-coiling. De-identified JPEG files of the imaging will then be uploaded into the electronic data-capture system and sent to the core lab for evaluation and subsequent analysis. Images should show measurements or a dime should be placed for scale.

2. An independent core lab, not affiliated with Vanderbilt University Medical Center, will review and analyze all uploaded images. The core lab, using standard criteria and being blinded to treatment arm will confirm (1) aneurysm size/volume and dome to neck ratio, and (2) degree of occlusion at the end of treatment and on follow-up imaging. Digital subtraction angiography (DSA) or MRA are required for the 3-6 month and 12-18 months follow-up angiogram.

3. Volumetric filling will be determined by the core lab based on measurements of the aneurysms relative to dimes, and of the coils used provided by participating centers on the procedure case report form.

6.2.2 Clinical outcome assessment

Clinical status at 3-6 months and 12-18 months follow-up will be recorded as a secondary outcome. This will include a NIH Stroke Scale and modified Rankin Scale as administered by a member of the research team at the time of the follow-up angiograms. Members of the treatment team may not administer these questionnaires. This data should be collected by a qualified, independent physician. If a qualified, independent practitioner is not available, a clinical research coordinator or nurse may administer the questionnaire, as long as they are not a member of the treatment team. The modified Rankin Scale and NIH Stroke Scale will be entered into the web-based data entry form.

6.2.3 Safety assessment

The Event eCRF allows for reporting of any adverse events, reporting of unanticipated problems, and reporting of protocol deviations. Local Principal Investigators are responsible for ensuring this form is accurately completed and entered in the web-based data entry system.

6.2.4 Questionnaires and assessments

Research/Clinical assessments: These scales are typically done as a way for the physician or independent evaluator, to measure the aneurysm's effect on the patient. They include Hunt and Hess grade, Fisher scale/WFNS (if applicable), modified Rankin score, and NIH Stroke Scale.

7. Safety Monitoring

7.1 Adverse Events (AEs) Definitions and Reporting Procedures

7.1.1 Definition

An adverse event will be considered any undesirable sign, symptom or medical condition considered related to the intervention. Medical condition/diseases present before starting the intervention will be considered adverse events only if they worsen after starting the study and that worsening is considered related to the study intervention. An adverse event is also any undesirable and unintended effect of research occurring in human subjects as a result of the collection of identifiable private information under the research. AEs will be recorded up to the day of the

final follow-up visit, and if still present, they will be recorded as "ongoing" at the end of the study. The occurrence of AEs should be sought by non-directive questioning of the patient at each visit during the study. AEs also may be detected when they are volunteered by the patient during or between visits.

7.1.2 Known risks involved in cerebral angiography with coil embolization are:

1. Bleeding
2. Infection
3. Allergic reaction to contrast or medication
4. Hydrocephalus/inflammation
5. Blood vessel injury or thrombosis
6. Kidney damage or failure
7. Stroke
8. Vessel dissection/rupture
9. Aneurysm perforation
10. Clot formation
11. Device malfunction
12. Disruption of clot from aneurysm
13. Distal emboli resulting in stroke
14. Death
15. Paralysis
16. Cardiac arrest
17. Brain damage

7.1.3 Reporting

All adverse events must be recorded on the Event eCRF with the following information:

1. Whether it was anticipated
2. Its relationship to the procedure, clinical course of the disease, device, or non-procedure
3. Outcome/Patient status
4. Treatment provided
5. Whether an action was taken and a description of said action

All serious adverse events must also be recorded on the Event eCRF with the following additional information:

6. Type of Serious Adverse Event
7. Whether it was reported within 72 hours of becoming aware of the event
8. Whether it happened during the procedure
9. Background Information
10. Whether it will be reported to the local IRB
11. Territory where initial procedure occurred

12. Whether it was serious (not life threatening), serious (life threatening) or lead to death

7.2 Serious Adverse Events (SAEs) Definition and Reporting Procedures

7.2.1 Definition

1. An SAE will be considered any undesirable sign, symptom, or medical condition which is fatal, life-threatening, requires or prolongs inpatient hospitalization, results in persistent or significant disability/incapacity, constitutes a congenital anomaly or birth defect, is medically significant and which the investigator regards as serious based on appropriate medical judgment. An AE that may not result in death, be life-threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in the definitions of SAEs.

2. The Principal Investigator will report unexpected and serious AEs to the DSMB within 15 working days of notification and all others expeditiously. The DSMB will meet on a semi-annual basis or on ad hoc basis if the PI identifies unusual increases in AEs or unexpected events. The following events require expedited reporting: (1) unexpected serious adverse events (must be both serious and unexpected); (2) peri-procedural death within 30 days of procedure (site PIs may be required to provide additional information on such cases); (3) an increase in the rate of expected SAEs occurring in a center.

3. Events NOT considered to be SAE are hospitalizations for: (1) the routine treatment or monitoring of the studied indication not associated with any deterioration in condition; (2) treatment, which was elective or pre-planned, for a pre-existing condition that is unrelated to the indication under study and did not worsen; (3) admission to a hospital or other institution for general care, not associated with any deterioration in condition; (4) treatment on an emergency, outpatient basis for an event not fulfilling any of the definitions of serious given above and not resulting in hospital admission.

7.2.2 Reporting

1. To ensure patient safety, every SAE, regardless of suspected causality, occurring after the patient has provided informed consent and until the final follow-up visit must be reported to Vanderbilt University Medical Center immediately and within 72 hours of learning of its occurrence.

2. An SAE occurring at a different time point or otherwise considered completely unrelated to a previously reported event should be reported separately as a new event.

3. Information about SAEs will be collected and recorded on the Event Form in the study's electronic database. The investigator must assess the relationship to study intervention and complete the form. This must be completed within 72 hours of discovery for review by the Vanderbilt University Medical Center Study Team.

4. Each re-occurrence, complication, or progression of the original event should be reported as a follow-up to that event regardless of when it occurs. The follow-up information should describe whether the event has resolved or continues and if and how it was treated.

7.3 Protocol Deviation

1. A protocol deviation is defined as any change, violation, or departure from the study design or procedures of research project that is NOT approved by the Vanderbilt University Medical Center or the Trial Steering Committee prior to its initiation or implementation, or deviation from standard operating procedures, Good Clinical Practices, or federal, state, or local regulations. Protocol violations may or may not be under the control of the study team or Vanderbilt University Medical Center staff. These protocol violations may be major or minor and will be recorded in the electronic data capture system.

2. Major protocol deviations: All major deviations must be reported to the Vanderbilt University Medical Center study team and the local IRB (according to local regulations) upon discovering them, and no later than seven calendar days from the time the study team receives knowledge of the event. A major violation meets one or more of the following criteria: (1) represents a serious or continuing failure on the part of the study team to comply with the protocol, standard operating procedures, Good Clinical Practices, federal, state or local regulations; (2) impacts subject safety or substantially alters risks to subjects and may or may not result in actual harm (emotional, clinical, social, financial, etc.); (3) significantly damages the completeness, accuracy and/or reliability of the data collected for the study; (4) is under control of the investigator/study team.

3. Examples of major deviations may include, but are not limited to: (1) evidence of willful or knowing misconduct on the part of the investigators or team; (2) failure to obtain informed consent; (3) enrollment of a subject who did not meet all inclusion/exclusion criteria which would affect subject safety or would negatively impact data integrity; (4) performing study procedures not approved by The Vanderbilt University Medical Center study team or IRB; (5) failure to report serious unanticipated problems or AEs to the IRB and Vanderbilt; (6) failure to perform study procedures outlined in the protocol where subject safety or data integrity may be negatively impacted; (6) study visit or procedure conducted outside of required time frame that may negatively affect subject safety.

7.4 Data Safety Monitoring Board (DSMB)

The DSMB will be independent and comprised of neurosurgeons, neuro-interventionalists, or others who are from institutions that are not participating in the trial. The DSMB will meet semi-annually to review any serious unexpected AEs. The DSMB will be supplied with an interim analysis of trial data on mortality/complication rates after the first 70 and 140 patients are randomized. The committee may request data or analyses from the trial or any other relevant information from other sources. In the light of these analyses, the DSMB will advise the Steering Committee if, in its view, the randomized comparisons have provided proof "beyond reasonable doubt" that (1) the use or non-use of Eighteen platinum coils achieves a significantly reduced recurrence rate with no greater risk of AEs, or (2) the use or non-use of Eighteen platinum coils is associated with a substantially poorer clinical outcome. The DSMB will advise the Steering Committee regarding trial continuation or discontinuation, or protocol modification as needed to address patient safety concerns. A third interim analysis will be performed after 380 patients have been randomized (unless the DSMB decides the interim analysis should occur earlier or later). Site PIs and study coordinators will have the name and address of the DSMB chairman, and will be able to communicate confidentially with the chairman to express concerns about patient safety or trial design.

8. Data Management and Entry

8.1 Data Collection

1. Each site will be required to have a local coordinator who will be responsible for entering the study information into the web-based database and uploading the identifiable source documents/medical records associated with the study information. A web-based database housing the electronic case report forms (eCRFs) has been designed for the study, which will improve efficiency, lower cost of the study, and speed up publication of the results. Use of drop-down selection lists, radio buttons, checkboxes, and validation

checks will be incorporated to aid the speed, accuracy and consistency of data entry. The database will be backed up regularly.

2. Data collected will include: (1) enrollment and screening logs; (2) demographic data; (3) admission data (Hunt and Hess grade, Fisher grade, etc.) including the informed consent; (4) procedural data; (5) angiograms or MRA; (6) clinical course data; (7) 3-6 month angiogram or MRA; (8) 3-6 month clinical status; (9) 12-18 month angiogram or MRA; (10) 12-18 month clinical status; and (11) as needed additional follow-up data.

3. All data other than angiograms will be entered and/or uploaded into the web-based data entry forms. In addition, identifiable source documentation verifying all collected study data points will be securely uploaded into the web-based database.

8.2 Schedule of Data Entry

1. Within 48 hrs of randomization: Demographic and admission data

2. Within 72 hrs of discharge: Procedural data, imaging data, clinical course data, and discharge data

3. Within 72 hrs of follow-up imaging (angiogram or MRA): 3-6 month angiogram or MRA and 3-6 month clinical status

4. Within 72 hrs of follow-up angiogram or MRA: 12-18 month follow-up angiogram, 12-18 month clinical status

5. Notification for serious, unexpected complications (procedural or otherwise) or deaths will be available for review by the DSMB within 15 days of the receipt

8.3 Data Monitoring

Routine data monitoring will occur to ensure data validity. For the first two subjects at each site, source documentation and target data points will be reviewed for accuracy and at least 20% of the source documentation and target data points will be monitored thereafter. Study data monitoring will be conducted remotely through the uploading of identifiable data via a secure web-based electronic data capture system. Monitoring may also occur in person, or by telephone, on an as needed basis. All monitoring activities will be tracked and stored in the web-based data capture system overseen by Vanderbilt University Medical Center.

9. Statistical Methods

9.1 Sample Size Estimate and Power of the Study

Based upon a presumed absolute improvement in recanalization rate (defined as an increase in Raymond Scale from immediate to 12-18 month follow-up, as determined by the core laboratory analysis) of 9% (73% recanalization rate for non-Eighteen versus 82% for Eighteen) with an Alpha 0.05 and Power = 80, 325 patients would be required for each arm (at least 650 total patients).

10. Committees and Centers

10.1 Trial Steering Committee (TSC)

The TSC will meet as needed but no less than semi-annually. Its main function will be to monitor and supervise the progress of the randomized trial. It will consider recommendations of the DSMB and relevant ethics committees. At regular intervals it will review relevant information arising from other sources and make decisions regarding trial presentation/publication of interim and final results.

10.2 Trial Coordinating Center

The Trial Coordinating Center will be responsible for the daily running of the trial and will be located at the Vanderbilt University Medical Center. Duties include: facilitating site start-up, protocol and eDC training, facilitating timely completion of project milestones, oversight of regulatory affairs and compliance, data management, ensuring data integrity, site monitoring management, and safety oversight.

10.3 Center and Investigator Requirements

1. Neurosurgical care centers with case volume of aneurysm treatment greater than 60 cases per year.

2. Experienced endovascular treatment centers and operators.

3. High quality digital subtraction angiography equipment, preferably with 3D and biplane capability.

4. Willing to adhere to protocol and only use the required coils in enrolled patients and not polymer-enhanced, bioactive or other coils in same patient.

5. Local ethics approval and multi-center ethics approval in process by coordinating center.

11. Publication Policy

The TSC will be responsible for organizing a writing committee once trial recruitment is completed. That committee will formulate timelines for presentation/publication of results on behalf of the TSC and advise on appropriate journals for submission.

12. Financial and Insurance Matters

As Eighteen platinum coils are FDA-approved and used at many institutions and no randomized data exists regarding the use of framing coils in aneurysm embolization, both the use or non-use of these coils in aneurysm embolization are considered Standard of Care and shall be covered by the patient (whether insurance or self-pay).

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Statistical Analysis Plan

Framing Eighteen coils in cerebral Aneurysms Trial (FEAT)

A randomized controlled trial of Eighteen (0.014-0.0155 inch) platinum coils versus standard (<0.014) platinum coils in the endovascular treatment of medium-sized (6 – 14 mm) intracranial aneurysms

Trial Sponsor: Vanderbilt University Medical Center

Financial Sponsor: Stryker (Natick, MA)

Lead Principal Investigator: J Mocco, M.D., M.S. – Mount Sinai

Version: 1.0
Version Date: 3/27/2024

MODIFCATION HISTORY

Version Number	Date of Document Version	Significant Changes from Previous Authorized Version
1.0	3/27/2024	Not applicable – first version

TABLE OF CONTENTS

ABBREVIATIONS AND DEFINITIONS

ACT	Activated Clotting Time
AE	Adverse event
CI	Confidence Interval
DSMB	Data and Safety Monitoring Board
FEAT	Framing Eighteen coils in cerebral Aneurysms Trial
ISAT	International Subarachnoid Aneurysm Trial
ITT	Intent-to-treat
ICH	Intracerebral hemorrhage
IVH	Intraventricular hemorrhage
mRS	Modified Rankin Scale
NIHSS	National Institutes of Health Stroke Scale
SAE	Serious adverse event
SAP	Statistical Analytical Plan
WFNS	World Federation of Neurosurgical Societies

PURPOSE OF STATISTICAL ANALYTICAL PLAN (SAP)

The purpose of this SAP is to outline the planned analyses to be completed for the FEAT trial. The analyses identified in this SAP will be included in abstracts and manuscripts reporting the results of the trial. Exploratory analyses not necessarily identified in this SAP may also be performed. Any post hoc, or unplanned, analyses not explicitly identified in this SAP will be clearly identified as such in any published papers from this study. This SAP may be updated in response to additional developments, either within or outside the trial. All revisions will be made prior to the data lock and the primary analysis.

1. INTRODUCTION

Since the results of the International Subarachnoid Aneurysm Trial (ISAT) were published in 2002, the treatment of intracranial aneurysms has increasingly shifted from surgical to endovascular management. ISAT demonstrated improved mortality and dependency rates at 1-year in patients that underwent endovascular coil embolization compared to patients that underwent clipping (Molyneux 2002). However, longer-term follow-up revealed a higher incidence of late re-bleeding and recurrence among aneurysms treated via embolization compared to clipping (Molyneux 2005). The incidence of recurrence has been consistent in the literature, with an estimated angiographic recurrence rate of approximately 10-20% (although as high as 33% in one study); however, the re-bleed rate has consistently been low (Byrne 1999, Hayakawa 2000, Cognard 1999, Ng 2002, Thornton 2002, Raymond 2003). As such, many institutions have shifted towards endovascular management with follow-up to detect recurrence.

A major focus over the past decade has been improving aneurysm occlusion and recurrence rates through modification of techniques, devices, and embolic materials. Studies suggest that larger diameter platinum coils may be more stable during and after endovascular aneurysm coil embolization, and that smaller diameter framing coils may have a higher propensity towards recanalization. As such this study aims to evaluate the safety and effectiveness of larger diameter versus smaller diameter coils in patients undergoing endovascular treatment for a mid-sized aneurysm.

2. STUDY OBJECTIVES

2.1 Primary Objective

The primary objective of this trial is to evaluate the effectiveness and safety of larger diameter (0.014-0.0155 inch) coils compared to smaller diameter (<0.014 inch) coils for the endovascular treatment of mid-size aneurysms.

3. STUDY OVERVIEW

3.1 Study Design

This is a prospective, multi-center, randomized, clinical trial in patients with mid-size aneurysm. Patients will be randomized (1:1) to receive either larger diameter coils or smaller diameter coils.

3.1.1 Study Duration and Time Points

All patients will be followed for 12 to 18 months post-procedure. Endpoints will be measured at discharge from the index procedure, 3 to 6 months post-procedure, and 12 to 18 months post-procedure. The 3 to 6 month visit and 12 to 18 month visit align with standard of care visits.

3.1.2 Randomization and Masking

Patients will be randomly assigned in a 1:1 allocation to receive either larger or smaller coils. Patient randomization will be stratified by clinical site, aneurysm status (recently ruptured versus not), and dome to neck ratio (wide neck versus not). Randomization will be performed centrally through a web-based data collection system that automates the delivery of the randomization assignments.

Investigators will not be blinded to treatment assignment due to the nature of the treatment intervention. Investigators will, however, be blinded to all data from other clinical sites. Clinical outcome assessments will be completed by certified research staff that are not part of the treatment team. All angiograms will be analyzed by a blinded angiogram core laboratory personnel who will be blinded to clinical outcomes. Trial oversight will be provided by an independent Data and Safety Monitoring Board (DSMB).

4. ANALYSIS POPULATIONS

Three populations will be used for all summaries and analyses.

Screened Population

The screened population will consist of all screened patients. A screened patient is defined as a subject referred to, or identified at, a clinical site for consideration of entry into the study.

Intent-to-Treat (ITT) Population

The ITT population will consist of all randomized subjects grouped by their assignment at randomization regardless of whether or not they actually received the treatment to which they were assigned. This sample will be used for summaries and analyses of the primary endpoint and the secondary clinical endpoints. The ITT population will be used for all effectiveness analyses and descriptions of patient and baseline characteristics.

Safety Population

The safety population will consist of all randomized subjects who initiate endovascular coiling, grouped by their assignment at randomization regardless of whether or not they actually received the coil size to which they were assigned. The safety population will therefore be identical to the ITT population if all randomized patients receive attempted vascular coiling. The safety population will be used to present safety summaries and for the analysis of safety data.

5. STUDY ENDPOINTS

5.1 Primary Endpoint

The primary endpoint is angiographic occlusion at 12 to 18 months post-randomization as measured by a Raymond score of 1 or 2 (adequate occlusion). Patients' angiograms for the 3 to 6 month visit, the 12 to 18 month visit, and any clinically driven angiogram taken prior to 18 months post-randomization or study exit will be considered for angiographic occlusion. If any of these angiograms show inadequate angiographic occlusion (Raymond score >2), the patient will be considered to have inadequate occlusion at the 12 to 18 month visit and be considered a treatment failure.

5.2 Secondary Clinical Endpoints

The following secondary clinical endpoints will be assessed:

5.2.1 Morbidity/Mortality

- Neurologic morbidity measured at 24-hours post-procedure. Morbidity is defined by neurologic worsening measured by a greater than or equal to 4-point change in the NIH Stroke Scale (NIHSS) from pre-surgical baseline.

- Mortality through end of study follow-up (12 to 18 month visit)

5.2.2 Clinical Outcome

- Modified Rankin Scale score at the 3 to 6 month and 12 to 18 month visits. The Modified Rankin Scale ranges from 0 (no symptoms) to 6 (dead) (Broderick 2017)

Scale Score	Clinical Outcome
0	No symptoms
1	No significant disability. Able to carry out all usual activities, despite some symptoms
2	Slight disability. Able to look after own affairs without assistance, but unable to carry out all previous activities
3	Moderate disability. Requires some help, but able to walk unassisted
4	Moderately severe disability. Unable to attend to own bodily needs without assistance, and unable to walk unassisted
5	Severe disability. Requires constant nursing care and attention, bedridden, incontinent.
6	Dead

5.2.3 Re-hemorrhage/Re-treatment

- Incidence of re-hemorrhage through the end of study follow-up at the 12 to 18 month visit.
- Incidence of re-treatment of the aneurysm through the end of study follow-up at the 12 to 18 month visit.

5.2.4 Packing Density

- Volumetric filling of the aneurysm, reported as a percentage and calculated using AngioCalc (www.angiocalc.com).

5.3 Secondary Safety Endpoints

The following secondary safety endpoints will be assessed:

5.3.1 Serious Adverse Events

- Incidence of SAEs through end of study follow-up

6. STATISTICAL METHODOLOGY

6.1 General Principles

Study day will be calculated from the reference start date and will be used to show the study days of assessments and events. Reference start date is defined as the date of randomization unless otherwise specified.

Continuous variables will be summarized using the following descriptive statistics: number of non-missing values, means, standard deviations, medians, interquartile range, maximum, and minimum. Categorical variables will be summarized using number of non-missing values, counts, and percentages.

Rates of events will be calculated as the ratio of the total number of events recorded divided by the total patient-time. Total patient-time will be calculated by summing the time (in study time units, e.g., days or months) that patients were at risk for a specific event from the reference time point until either study exit or the end of the time period of interest. Rates and their 95% confidence intervals will be reported. Time-to-event variables will be summarized using the Kaplan-Meier method or, in the presence of competing risk, by cumulative incidence curves accounting for competing events as appropriate.

In the situation where an event date is partial or missing, study day, and any corresponding durations are to appear partial or missing in listings. If a partial event date is recorded (i.e. the month and year are known but not the day) and is necessary to calculate patient-time at risk or patient-time to the event, the missing event day will be imputed to the 15th day of the known month and year.

For any variable measured at multiple points in time, change from baseline will be calculated as the difference between the value of the variable at a specific point in time (e.g. 1 year) minus the baseline value. Relative change from baseline will be calculated as the value of a parameter at a specific point in time minus the baseline value of the parameter divided by the baseline value of the parameter. Percent change will be calculated as the relative change multiplied by 100.

All hypothesis testing will be conducted at the 0.05 two-sided significance level unless otherwise specified. P-values will be rounded to three decimal places. P-values less than 0.001 will be reported as <0.001 in tables. P-values greater than 0.999 will be reported as >0.999.

Should any of the statistical methods proposed prove unsuitable during data analysis, more appropriate methods will be used. These include data transformation (for example to a logarithmic scale) to satisfy model assumptions such as normally distributed residuals with constant variance, the application of non-parametric techniques, or the use of a different link function or modeling technique. The SAP will be updated with the methods used and the justification for the change prior to data set and database lock.

Additional ad-hoc analyses may be conducted as deemed appropriate.

All analyses will be conducted using SAS V9.4 or higher and R V4.1.1 or higher.

6.2 Missing Data

6.2.1 Missing Baseline Data

Missing baseline values will not be imputed in summaries of baseline characteristics. Summaries will be based on all available data.

6.2.2 Missing Primary Outcome Data

The plan for handling missing primary outcome data is outlined in section *6.5.3* below.

6.2.3 Missing Secondary Outcomes Data

The plans for handling missing secondary outcome data are outlined by outcome in section *6.6* below.

6.3 Crossover and Missed Treatment

Crossovers (patients who after randomization switch from the allocated treatment to the non-allocated

treatment) will be analyzed in the group they were randomized according to the ITT principle in all efficacy analyses. Safety analyses will be conducted according to section 4 above.

6.4 Patient Characteristics

6.4.1 Patient Disposition

Disposition will be summarized in the screened and ITT populations.

Disposition summaries of the screened population will include:

- The number of patients screened
- The number and percentage of eligible patients randomized

Disposition in the ITT population will be summarized by randomization group and will include:

- The number of patients randomized
- The number and percentage of patients who received their assigned treatment
- The number and percentage of patients withdrawn or lost to follow-up by the 3 to 6 month visit and the primary reason for withdrawals
- The number and percentage of patients withdrawn or lost to follow-up by the final study visit at 12 to 18 months and the primary reason for withdrawals

6.4.2 Protocol Deviations

Protocol deviations and violations are defined as deviations from the procedures outlined in the protocol. All statistical analyses and summaries will be conducted on an intent-to-treat basis with the exception of safety analyses, which will be conducted on the safety population.

6.4.3 Patient Characteristics

6.4.3.1 Demographic characteristics

Demographics including age, gender, race, and ethnicity will be summarized by randomization assignment using the appropriate descriptive statistics.

6.4.3.2 Baseline characteristics

Baseline characteristics will be summarized by randomization assignment using the appropriate descriptive statistics. The specific baseline variables collected include randomization stratification factors, anthropometrics (weight, height), medical history (prior aneurysms treated, smoking status, pre-existing conditions), presenting symptoms, Modified Rankin Scale score, and rupture characteristics (if ruptured, time since rupture at randomization, Fisher Scale, Hunt and Hess scale, WFNS grade, IVH presence, ICH presence, and presence of infarct prior to embolization).

6.4.3.3 Operative characteristics

Operative data including aneurysm characteristics (height, width, depth, neck size, shape, type, and location), heparin dosing, activated clotting time (ACT), medications, presence of vasospasm, and coil/device log data will be summarized by randomization assignment using the appropriate descriptive statistics.

6.5 Primary Efficacy Analysis

6.5.1 Analysis of the Primary Efficacy Endpoint

A log binomial regression model will be used to estimate and test differences in angiographic occlusion between randomization groups. Similar to the logistic regression model, the log-binomial model is a generalized linear model. The models differ only in the link function used for the "success" probability *p*; logit (log odds) for logistic regression and log (log *p*) for log-binomial. The different links parameterize the model differently, with parameters of the log-binomial model yielding log relative risks rather than the log odds ratios of the logistic model.

The basic form of the log binomial models is:

$$\log P[Y_i = 1|X_{1i}, X_{2i}, X_{3i}] = \beta_0 + \beta_1 X_{1i} + \beta_2 X_{2i} + \beta_3 X_{3i} \ ,$$

where Y_i is a binary indicator of angiographic occlusion for the i^{th} patient, X_{1i} is a binary indicator of randomization assignment for the i^{th} patient, and X_{2i} and X_{3i} are indicators of recently ruptured aneurysm status (X_{2i}) and wide neck (X_{3i}) respectively, factors by which randomization will be stratified. While randomization will also be stratified by randomizing center, the analysis will not adjust for center due to their relatively large number compared to the proposed sample size. The exponentiated estimate of β_1 ($e^{\widehat{\beta}_1}$) in this model is the risk ratio for angiographic occlusion for patients randomized to larger coils compared to patients randomized to smaller coils. The risk ratio and its associated 95% confidence interval will be used to quantify the relative risk of the endpoint. Differences between randomization groups in the risk of angiographic occlusion will be determined by testing the null hypothesis H_0:$\beta_1 = 0$ versus a two-sided alternative (H_1:$\beta_1 \neq 0$) using a 0.05 level intention-to-treat normal approximation test (i.e., the Wald test).

6.5.2 Determination of Sample Size

Sample size calculations were based on the primary endpoint under the following assumptions and operating characteristics: a) 73% angiographic occlusion at the 12-18 month visit in patients receiving smaller coils (control arm); b) a 9% absolute improvement (to 82%) in the incidence of angiographic occlusion in patients receiving larger coils; c) Approximately 80% power on a two-sided proportion test; and d) a significance level of 0.05. A sample size of 650 (325 in each arm) will allow us to detect the specified effect size with adequate power. Sample size was calculated using the power.prop.test function in R (R Core Team 2021).

6.5.3 Missing Primary Endpoint Data

Patients without previous evidence of inadequate angiographic occlusion, either on the 3 to 6 month visit angiogram or on a clinically driven angiogram taken prior to study exit, that miss the 12 to 18 month angiogram, or whose 12 to 18 month angiogram is not readable by the core lab, will be missing the primary endpoint. Patients missing the primary endpoint who die prior to or during the 12 to 18 month visit window (up to 18 months post-randomization) and die with known cause of death related to their aneurysm or unknown cause of death will be considered treatment failures with inadequate occlusion. Patients missing the primary endpoint with a known cause of death unrelated to their aneurysm will be considered missing.

Patients with missing primary endpoint data will have their 12 to 18 month angiographic

occlusion status imputed via multiple imputation assuming that the data are missing at random. The imputation model will be stratified by randomization assignment and include age, sex, randomization strata for aneurysm status, randomization strata for wide neck status, aneurysm size, and angiographic occlusion status at the 3 to 6 month visit. Since this model includes a mixture of variables types (i.e. continuous and binary), a fully conditional specification method will be used (Berglund 2014).

The main feature of the imputation approach is the creation of a set of clinically reasonable imputations for angiographic occlusion for each patient with missing data. This will be accomplished using a set of repeated imputations created by predictive models based on the majority of participants with complete data. The imputation models will reflect uncertainty in the modeling process and inherent variability in patient outcomes, as reflected in the complete data. Thirty datasets will be imputed.

After the imputations are completed, all of the data (complete and imputed) will be combined and the analysis performed for each imputed-and-completed dataset. Rubin's method of multiple (i.e., repeated) imputation will be used to estimate treatment effect (Rubin 1986).

6.5.4 Multicenter Studies

The trial will be conducted in up to 25 clinical centers. Data will be pooled across all clinical centers. A sensitivity analysis of the primary endpoint will be conducted using a mixed effect log-binomial regression model with center as a random effect.

6.5.5 Assessment of Balance of the Randomization

The success of the randomization procedure in balancing important covariates between randomization groups will be assessed. Continuous measures will be compared using t-tests, while chi-square tests will be used to compare categorical variables. Should the treatment groups differ significantly with respect to any covariate at the 0.01 level, we will adjust for those covariates in a secondary analysis of the primary endpoint using multivariable log-binomial regression.

6.5.6 Examination of Subgroups

Subgroup analyses of the primary endpoint will be performed for key clinical subgroups, classified at baseline. Pre-defined subgroups include:

- Aneurysm status (recently ruptured (within 15 days) vs. not recently ruptured)
- Dome to neck ratio (not wide neck vs. wide neck)
- Aneurysm location (anterior vs posterior circulation)
- Age (<65, vs. ≥65)
- Sex (male vs. female)
- Race (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Island, and White)
- Ethnicity (Hispanic vs. non-Hispanic)
- Presence of co-morbidities
    - Diabetes (yes vs. no)
    - Obesity (BMI ≥ 30 vs. BMI <30)
    - Smoking status (current, previous (>6 months), never)
- Aneurysm shape (regular vs. irregular/multilobulated)

With the exception of severity of aneurysm status and wide neck status, for which formal interaction terms will be tested, these analyses will be descriptive and conducted to explore the effect of the treatment within the subgroups. Risk ratios with their respective 95% confidence intervals will be reported within each strata. Strata that contain less than 20% of the sample size and/or in which the number of patients assigned to a specific group is less than 20 will not be considered.

6.6 Analyses of Secondary Clinical Endpoints

All secondary clinical endpoints will be analyzed using the ITT population.

6.6.1 Neurologic Morbidity

The number and percentage of patients who experience neurologic morbidity at 24-hours post-operation will be reported by randomization group. The proportion of patients with neurologic morbidity will be compared between groups using a log binomial model and differences between the groups will be summarized using relative risk and the corresponding 95% confidence interval.

Patients that die within 24-hours will be counted as having neurologic morbidity. Survivors missing the 24-hour NIHSS assessment will have their neurologic morbidity outcome imputed via multiple imputation assuming that the data are missing at random. The imputation model will be stratified by randomization assignment and include age, sex, randomization strata for wide neck status, randomization strata for aneurysm status, aneurysm size, and baseline NIHSS. Since this model includes a mixture of variables types (i.e. continuous and binary), a fully conditional specification method will be used (Berglund 2014). Thirty datasets will be imputed and Rubin's methods will be use to combine them and estimate treatment effect (Rubin 1986).

6.6.2 Survival

Survival over the full duration of follow-up will be described using Kaplan-Meier curves and compared between the randomization groups using a log-rank test. The hazard ratio and corresponding 95% confidence interval for death in the larger coil group compared to the smaller coil group will be estimated using a Cox proportional hazards model. Patients who withdraw consent or are lost-to-follow up will be censored at the time of study exit. Time to event will be computed as the date of death (or the date of censoring) – randomization date. In cases where the patient dies or is censored the day they are randomized, the time will be coded as 0.5 days.

Causes of death and relatedness to the procedure will also be described by randomization group. The number and proportion of patients that have a procedure related mortality within 30 days post-procedure will be presented by group and group differences will be summarized as a relative risk with the corresponding 95% confidence interval.

6.6.3 Modified Rankin Scale

The number and percentage of patients in each mRS score category will be reported at the 3 to 6 month and the 12 to 18 month visits by group. For each visit, a Cochran-Mantel-Haenszel "shift" analysis (also known as van Elteren's test, Savitz 2007) will be used to evaluate differences in the mRS distribution between groups. The distribution of mRS

scores is expected to differ by aneurysm status. Analyses will be repeated separately by randomization strata for aneurysm status (recently ruptured vs. not recently ruptured).

Patients with missing mRS data at the 3 to 6 and/or 12 to 18 month visit will have their data imputed via multiple imputation assuming that the data are missing at random. The imputation model will be stratified by randomization assignment and aneurysm status and include age, sex, randomization strata for wide neck status, aneurysm size, and baseline mRS. Since this model includes a mixture of variables types (i.e. continuous, binary and ordinal), a fully conditional specification method will be used (Berglund 2014). Thirty datasets will be imputed and Rubin's methods will be use to combine them and estimate treatment effect (Rubin 1986).

6.6.4 Re-hemorrhage/Re-treatment

The difference in the rates of re-hemorrhage and re-treatment will be compared between randomization groups over the full duration of follow-up. Patients who withdraw consent or are lost-to-follow up will be censored at the time of study exit. Time to event will be computed as the date of the event (or the date of censoring) – randomization date. In cases where the patient has the event or is censored the day they are randomized, the time will be coded as 0.5 days. Re-hemorrhage or re-treatment may not occur because death from any cause precedes the event; thus, it is possible that censoring patients at all-cause mortality will lead to biased estimates when analyzing time to first event. Therefore, competing risks analysis using the methods of Fine and Gray (Fine & Gray 1999) will be used to estimate group differences for each endpoint.

6.6.5 Packing Density

The mean packing density will be compared between groups using a T-test and summarized as the mean difference and corresponding 95% confidence interval. Missing packing density data will not be imputed and analyses will be based on all available data.

6.7 Analyses of Secondary Safety Endpoints

All secondary safety endpoints will be analyzed using the safety population.

6.7.1 Adverse Events Reporting

All adverse events, serious and non-serious, will be summarized in tabular form for reporting to the DSMB. Adverse events will be tabulated by seriousness, severity and relatedness to the investigational agent or the aneurysm.

6.7.2 Serious Adverse Events

Serious adverse event rates will be calculated as the ratio of the total number of events over study follow-up days divided by total patient-time at risk for the specific event. Patient time at risk will be defined as the duration in which the patient is enrolled in the study since their date of randomization, inclusive of the day they were randomized [Time in study = (Study end date – Randomization date)+1]. Poisson models with robust variance estimation will be used to compare serious adverse events between randomization groups.

6.8 Multiplicity Adjustment

Secondary endpoints will provide insights regarding the value of this therapy. The most clinically important secondary endpoints are neurologic morbidity and the mRS scores at the 3 to 6 month visit.

To control type I error across these endpoints we will use a step-wise gate keeping procedure for four hierarchical families of hypotheses, tabled below.

Family	Hypothesis	Description
F1	H1	There is no difference in the risk of angiographic occlusion between randomization groups
F2	H2	There is no difference in the risk of neurologic morbidity between randomization groups
F3	H3	There is no difference in the distribution of mRS at the 3 to 6 month visit
F4	H4	There is no difference in the distribution of mRS at the 3 to 6 month visit within patients with an aneurysm status of recently ruptured
	H5	There is no difference in the distribution of mRS at the 3 to 6 month visit within patients with an aneurysm status of not recently ruptured

The type I error control procedure will be as follows:

1. Test the hypothesis in F1
    a. If the p-value is greater than or equal to 0.05 stop and conclude no treatment effect
    b. If the p-value is less than 0.05 proceed to step 2
2. Test the hypothesis in F2
    a. If the p-value is greater than or equal to 0.05 stop and conclude a treatment effect in F1 only
    b. If the p-value is less than 0.05 proceed to step 3
3. Test the hypothesis in F3
    a. If the p-value is greater than or equal to 0.05 stop and conclude a treatment effect in F1 and F2 only
    b. If the p-value is less than 0.05 proceed to step 4
4. Test the hypotheses in F4 using a 0.05-level Holm-step down procedure. With this procedure, the p-values of both tests are ranked from smallest to largest.
    a. If the smallest p-value is greater than 0.025, stop and conclude a treatment effect in F1, F2, and F3 only
    b. If the smallest p-value is less than 0.025 and the largest p-value is greater than 0.05, stop and conclude a treatment effect in F1, F2, F3 and H4 or H5 (whichever had the smallest p-value) only
    c. If the smallest p-value is less than 0.025 and the largest p-value is less than 0.05, declare a treatment effect across F1, F2, F3 and F4

While other secondary endpoint data will be featured in the publication of the trial, there will be no formal correction of the Type I error rate for multiple testing of statistical hypotheses for any of the other secondary endpoints.

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