A Randomized Multicenter Clinical Trial of Unruptured Brain AVMs (ARUBA)

Clinical Protocol

Sponsors	National Institute of Neurological Disorders and Stroke National Institutes of Health
Number of Patients	800
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Design	Randomized Multicenter Clinical Trial of Unruptured Brain AVMs
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PRÉCIS

Study Title

A Randomized Multicenter Clinical Trial of Unruptured Brain AVMs (ARUBA)

Objectives

Primary: To determine whether medical management improves long-term outcomes of patients with unruptured BAVMs compared to interventional therapy (with endovascular procedures, neurosurgery, or radiotherapy, alone or in combination). The trial has been designed to test whether medical management or interventional therapy will reduce the risk of death or stroke (due to hemorrhage or infarction) by at least 40% (an absolute magnitude of about 7.5% over 5 years). It will require 800 patients to detect the hypothesized 40% reduction in event rate, analyzed using the intention-to-treat principal. This sample size will support a test of non-inferiority if the medical management is not superior to interventional therapy.

Secondary: To compare the impact of medical management to interventional therapy with respect to adverse events, quality of life and cost.

Design and Outcomes

The study design is a prospective, multi-center, parallel design, randomized, controlled trial. Treatment assignment will not be masked; however, clinical coordinating center personnel and outcome events committees will be blinded to treatment assignment. Interim study results will be kept confidential by the DCC. The primary outcome is the composite event of death from any cause or stroke (hemorrhage or infarction revealed by imaging). Functional outcome status will be measured by the Rankin Scale, a widely-used outcome measure for stroke. The secondary measures of outcome include adverse events, quality of life and cost.

Interventions and Duration

The interventional therapy arm of the trial involves prophylactic efforts with a plan for eradication of the observed BAVM utilizing endovascular procedures, microsurgery, or radiosurgery, alone or in combination with pharmacological therapy for existing risk factors and coexisting medical conditions. The medical management arm will involve pharmacological therapy as deemed appropriate for medical symptoms as determined by the treating investigator. Should patients in the medical management arm develop hemorrhage or infarction related to their BAVM, they would then be candidates for any single or combination of interventional therapy using endovascular procedures, microsurgery and radiosurgery. Patients will be followed for a minimum of 5 years and a maximum of 7.5 years (mean 6.25 years) from randomization.

Sample Size and Population

All patients with an unruptured BAVM diagnosed at a participating clinical center without prior interventional therapy to attempt eradication and with no contraindications to interventional therapy, will be candidates for this trial. A total of 800 patients will be enrolled in the ARUBA trial. Patients may be referred for enrollment by their clinical neurologist, neurosurgeon, or interventional radiologist.

1. SPECIFIC AIMS

Current interventional therapy for brain arteriovenous malformations (BAVMs) is varied and includes endovascular procedures, neurosurgery, and radiotherapy alone and in combination, largely dependent on the decisions of the local clinical team. All of these interventional therapies are administered on the assumption that they will decrease the risk of initial or subsequent hemorrhage and lead to better long-term outcomes. Despite these laudable goals, the literature contains almost no reference to the outcome for medical management before or after hemorrhage, or for intervention outcome for unruptured BAVMs. Published reports of interventional therapy outcome typically have blended the bled and non-bled cohorts together as if their risk for lesion-related morbidity and the response to intervention is expected to be the same.

Although no clinical trial data exist on the effect of interventional therapy even after BAVM hemorrhage, the most contentious issue at present is whether interventional therapy should be considered for those increasingly being discovered incidentally by brain imaging, with lesions that have not bled. Recent data from our institution on BAVM patients who presented without bleeding raises the possibility that interventional therapy may be detrimental compared with medical management. Among possible reasons may be that interventional therapy destabilizes the lesion toward hemorrhage. Furthermore, there is disappointing evidence that contradicts prior assumptions that hemorrhage associated with BAVM treatment lie in functionally-inert tissues, and, therefore, are less disabling. It appears that the disabilities associated with such events are equivalent to and possibly worse clinically than that seen with spontaneous BAVM hemorrhages, which still have a relatively low likelihood of occurring in the foreseeable future.

1.1 Primary Aims

The ***primary hypothesis*** of this randomized clinical trial is that medical management improves long-term outcomes of patients with unruptured BAVMs compared to interventional therapy (with endovascular procedures, neurosurgery, or radiotherapy, alone or in combination). The primary outcome is the composite event of death from any cause or stroke (hemorrhage or infarction confirmed by imaging). Functional outcome status will be measured by the Rankin Scale, a widely-used outcome measure for stroke. There are three specific aims associated with the primary hypothesis:

Specific Aim 1.1a To determine whether medical management is *superior* to interventional therapy for preventing the composite outcome of death from any cause or stroke (hemorrhage or infarction confirmed by imaging) in the treatment of unruptured BAVMs.

Specific Aim 1.1b If medical management is not superior to interventional therapy, to determine whether medical management is *not inferior* to interventional therapy for preventing the composite outcome of death from any cause or stroke (hemorrhage or infarction confirmed by imaging) in the treatment of unruptured BAVMs.

Specific Aim 1.2 To determine whether treatment of unruptured BAVMs by medical management decreases the risk of death or clinical impairment (Rankin Score ≥ 2) at 5 years post-randomization compared to interventional therapy.

1.2 Secondary Aims

A number of Secondary Aims are planned in support of the primary hypothesis to answer the following questions:

1) Is there a difference in quality of life between interventional therapy and medical management?

2) Is there a difference in mortality between interventional therapy and medical management?

3) Is there a difference in quality-adjusted survival between medical management and interventional therapy?

4) Is there a difference in the incidence of adverse events, such as cerebral hemorrhage and infarction, between interventional therapy and medical management?

5) What are the costs associated with each treatment (medical management and interventional therapy); and if medical treatment is not superior, but also not inferior to interventional therapy what are the cost-effectiveness implication of choosing one therapy over another?

6) Does any benefit of medical management or interventional therapy depend on BAVM size?

7) Does any benefit of medical management or interventional therapy depend on BAVM location?

8) Does any benefit of medical management or interventional therapy depend on venous drainage pattern?

9) Does any benefit of medical management or interventional therapy depend on age at randomization?

10) Does any benefit of medical management or interventional therapy depend upon the length of time the AVM was known?

11) Is there a difference in the risk of the composite event of death from any cause or stroke between prophylactic treatment modalities (i.e. endovascular procedures, neurosurgery, and radiotherapy)?

12) Among patients treated by interventional therapy, is there a relationship between the completeness of eradication of the BAVM and the composite event of death from any cause or stroke?

13) Among patients treated by interventional therapy, is there a relationship between the Spetzler-Martin grading scale and the composite event of death from any cause or stroke?

The *primary null hypothesis* is that there is no difference between medical management and interventional therapy in the time to stroke or death from any cause. The null hypothesis will be tested against the alternative hypothesis that there is a difference between treatments with a two-sided 0.05 level log-rank test. With a plan to enroll 800 patients, the test will have 87.5% power to detect a risk reduction of 40% (hazard ratio of 0.60), and 80% power to detect a risk reduction of 36.5% (hazard ratio of 0.635). These hazard ratios correspond to an absolute decrease in 5-year event rates of 7.5% and 6.7% respectively for medical management, from an assumed 5-year event rate of 20% for interventional therapy.

If the null hypothesis is not rejected, a test of non-inferiority of medical management compared to interventional therapy will be performed. The null hypothesis for the test of non-inferiority is that the hazard ratio for the composite event of death from any cause or stroke for interventional therapy compared to medical management is less than 0.89 (an 11% reduction in risk for interventional therapy). Thus, the null hypothesis that medical management is inferior will be rejected, and non-inferiority claimed, if the reduced risk of interventional therapy compared to medical management is less than the non-inferiority margin of 11% (hazard ratio ≥ 0.89) based on a one-tailed 0.05 level test. An 11% reduction in risk corresponds to an absolute difference in 5-year event rates of 2%.

The *secondary hypothesis* to be tested is that early intervention decreases the risk of death or clinical impairment at 5 years post-randomization. Death in this young, and otherwise healthy, population is a rare event. The primary hypothesis has been constructed to be inclusive of all strokes that occur during the course of the trial (thereby averting judgment about severity), while the secondary hypothesis concentrates only on those events associated with impairment.

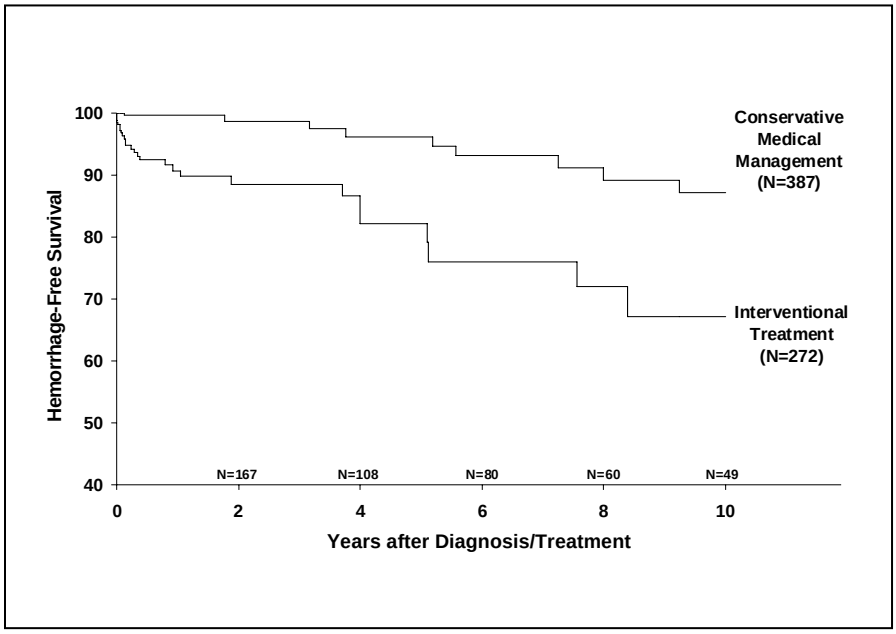
2. BACKGROUND

2.1 Rationale

With the emergence of new non-invasive imaging techniques, there has been a substantial increase in the incidental detection of non-ruptured BAVMs. These BAVMs are being treated in a variety of ways, including medical management, endovascular procedures, neurosurgery, or radiotherapy. The widespread diffusion of these various treatment approaches is partially driven by the existence of variations in the perception about the risks of rupture and how devastating such events would be. The increased treatment rate of non-ruptured BAVMs consumes a considerable amount of health resources. With an annual incidence in the US of nearly 3000 cases, and treatment costs in the range of $50,000 to $100,000 per patient, widespread utilization of early intervention would amount to an expenditure of between $150 million and $300 million per year. Thus, the choice between early interventional therapy and medical management involves making a critical trade-off between avoiding the upfront risks and cost of an early intervention and possibly mitigating the long-term risks and costs associated with medical management. These trade-offs have not been adequately addressed in the clinical literature.

2.2 Supporting Data

There have not been any randomized trials comparing any of the forms of interventional therapy for BAVMs among themselves or with medical management. This is the case despite the enormous resources committed to the treatment of patients with BAVMs. Some data indicate that interventional therapy is superior to medical management for BAVMs, but many of these studies do not distinguish between AVMs that have previously bled and those that have not. Other data suggests that there is a spectrum of risk for medical management of BAVMs and those that are unruptured have a much lower risk for future hemorrhage than those that have previously bled. The currently available published data on both medical management and treatment-related morbidity and mortality do not separate outcomes by pre-treatment status (bled or unbled), and show little consistency for mode and number of treatments or for clinical severity.



An important source of data that we have relied upon in planning this study is the Columbia AVM Databank project, which has prospectively enrolled 622 consecutive AVM patients clinically encountered at Columbia University Medical Center since 1989. The mean age of these patients is 34 years with a standard deviation of 15 years. Three hundred and twenty-two of the patients, or 53%, are female. Of the 622 study subjects, 282 (45%) presented with hemorrhage and 340 (55%) had unruptured AVMs.

A recent analysis of these data favors early treatment intervention in patients who have bled, showing little additional clinical injury for the extirpation of the lesion, particularly in those harboring additional morphological risk factors. Of concern, however, is the low risk of spontaneous rupture in as yet unbled AVMs and the mild clinical syndrome from such rupture. As shown in the figure, interventional treatment was associated with an increased risk of hemorrhage ($p < 0.0001$; hazard ratio (HR) = 5.53, 95% CI 2.91 to 10.49). In this figure the value on the abscissa for the subgroup that underwent interventional treatment was defined as time-since- treatment-was-initiated in order to mimic the result that would be obtained in a clinical trial. The actual analysis utilized time-dependent covariates that classify treatment status at each time point of follow-up on the basis of its relationship to the time at which treatment began. Interventional treatment was also associated with an increased risk of clinical impairment as assessed by a Rankin score ≥ 2 (HR = 11.04, 95% CI 7.21 to 16.90, $p < 0.0001$). These observational data suggest that for AVM patients who have not yet bled, treatment may increase the risk of both hemorrhage and an acute, disabling persisting clinical syndrome.

Comparing our own data to those taken from the literature (not stratified by AVM rupture status) offers two extreme cases for comparing the benefits of early interventional treatment versus watchful waiting. Comparing the worst 5-year risk of stroke or death with medical management of 20%, and the best 5-year risk with early intervention of 5%, supports the strategy of early intervention, while the best 5-year natural history outcome of 5% and the worst 5-year early intervention outcome of 19% support medical management. Thus, there is considerable uncertainty in the existing clinical literature, which does not provide conclusive evidence about optimal treatment approaches for this vexing clinical problem. The Columbia database was collected prospectively, but like other clinical series, is not a randomized trial of treatment versus medical management, or of various modes of treatment. The findings in a randomized clinical trial could well be different from that in this one-center clinical cohort.

3. STUDY DESIGN

1. The overall purpose of this multi-center RCT is to evaluate the effectiveness and safety (in terms of survival, clinical impairment, adverse events and quality of life), and costs of medical management compared to interventional therapy of patients with unruptured BAVMs. While the nature of the treatments precludes blinding of patients and their treating clinicians, outcome evaluations should be done by an experienced person who is not directly involved in providing the interventional procedure. Therefore a neurologist at each site who is certified to perform the Rankin assessment will do so for all outcome assessments at that center. A parallel groups design with random assignment of patients to interventional therapy or medical management with equal probability will be performed. A total of 800 patients will be randomized. Patients will be followed for a minimum of 5 years and a maximum of 7.5 years (mean 6.25 years) from randomization.

4. SELECTION AND ENROLLMENT OF SUBJECTS

The patient population for this trial consists of patients with unruptured BAVMs.
All patients who meet eligibility criteria may be included in the study regardless of gender, race, or ethnicity.

4.1 Inclusion Criteria

1. Patient must have unruptured BAVM diagnosed by MRI/MRA, CTA and/or angiogram
2. Patient must be 18 years of age or older
3. Patient must have signed Informed Consent, Release of Medical Information, and Health Insurance Portability and Accountability Act (HIPAA/U.S. only) Forms

4.2 Exclusion Criteria

1. Patient has BAVM presenting with evidence of recent or prior hemorrhage
2. Patient has received prior BAVM therapy (endovascular, surgical, radiotherapy)
3. Patient has BAVM deemed untreatable by local team, or has concomitant vascular or brain disease that interferes with/or contraindicates any interventional therapy type (stenosis/occlusion of neck artery, prior brain surgery/radiation for other reasons)
4. Patient has baseline Rankin ≥ 2
5. Patient has concomitant disease reducing life expectancy to less than 10 years

6. Patient has thrombocytopenia (< 100,000/μL),
7. Patient has uncorrectable coagulopathy (INR>1.5)
8. Patient is pregnant or lactating
9. Patient has known allergy against iodine contrast agents
10. Patient has multiple-foci BAVMs
11. Patient has any form of arteriovenous or spinal fistulas

Previous diagnosis of any of the following:

12. Patient has a diagnosed Vein of Galen type malformation
13. Patient has a diagnosed cavernous malformation
14. Patient has a diagnosed dural arteriovenous fistula
15. Patient has a diagnosed venous malformation
16. Patient has a diagnosed neurocutaneous syndrome such as cerebro-retinal angiomatosis (von Hippel-Lindau), encephalo-trigeminal syndrome (Sturge-Weber), or Wyburn-Mason syndrome
17. Patient has diagnosed BAVMs in context of moya-moya-type changes
18. Patient has diagnosed hereditary hemorrhagic telangiectasia (Rendu-Osler-Weber)

Pregnancy Risks:

This study involves treatments or procedures which could be harmful to a fetus or breastfed baby. Women must not participate if they are pregnant or nursing. If a woman of childbearing potential is enrolled in the study, they will be required to use an effective form of birth control during the entire study. If a study participant suspects that they have become pregnant while participating in the study, they must be instructed to contact the investigator or study team immediately. For women of childbearing age, a serum or urine HCG should be recorded as part of the source documentation.

4.3 Study Recruitment and Enrollment Procedures

There are 104 clinical sites in the U.S. and Europe proposed as participating clinical centers in the ARUBA trial. These centers have extensive clinical and research experience with the management of BAVMs. Combined, these centers have an annual volume between 650 and 1000 patients, who would meet the eligibility criteria for the trial.

Mailings will be sent out, with IRB approved flyers prepared for posting announcement of the study. Our recruitment efforts will target the front-line physicians, local neurosurgeons, and neuro-radiologists to make them aware of the trial, so that when they evaluate a patient with an unruptured BAVM, they have the option of referring them to the clinical investigators for consideration of enrollment in the trial. We will conduct ARUBA seminars for the staff of the local neurology practices to inform them of the trial requirements. A set of Power Point ARUBA slides will be prepared by the DCC and made available to the site investigators so that they can meet and present the trial to physicians who practice in local communities. A pocket size laminated eligibility criteria list will be sent to all investigators to be distributed to all referring physicians. The DCC will develop a template ARUBA informational packet directed at referring physicians, which can be adapted by the sites. All such publicity materials targeted to patients will require IRB approval. Through this method they will be able to identify potential candidates, and make appropriate referrals to the ARUBA team.

All patients who are diagnosed with an unruptured BAVM are potential candidates for this trial. There are three main pathways that patients with unruptured BAVMs may be referred for evaluation for the ARUBA trial. They may be referred by their clinical neurologist, neurosurgeon, or interventional radiologist. If the examination and work-up confirms that a patient has met the eligibility criteria, the trial will be presented. When a patient expresses interest, they can be referred to an ARUBA investigator who will evaluate the medical records and initiate the consent process. All referring physicians will be encouraged to present this trial to all their patients, including women and minority patients.

An ARUBA web site has been developed to allow physicians to have access to up-to-date trial information. Once the web site is approved by the IRB it will also be available to patients and their families. The ARUBA web site will be linked to other medical and clinical trial sites, including the NIH, CDC, WebMD, and Center Watch sites. Key words such as brain aneurysm and cerebral aneurysm will be included. Lay terms will be used to make the information accessible to patients, their families and friends.

4.3.1 Minority Recruitment

Recruitment will not discriminate on the basis of age, gender, race, or socioeconomic status. The proposed clinical trials pose no scientific justification to exclude any gender or ethnic group. Given the international nature of this trial, a wide spectrum of ethnic backgrounds is expected. A special effort will be made to ensure that no opportunity for recruitment of eligible women is overlooked and development of the recruitment database in cooperation with the clinical sites will place a special emphasis on effective recruitment of women from the general population.

4.3.2 Informed Consent Procedures

Only adults (those ≥ 18 years) with unruptured BAVMs will be considered for enrollment in the ARUBA trial. The site clinical investigator will discuss the trial with the patient's primary care physician who will ascertain from the prospective enrollee whether or not they wish to be approached by the investigator. The clinical investigator or a designated member of the investigative team will provide a thorough explanation of the objectives, patient responsibilities, risks and benefits of the study, and will fully address all the concerns raised by the patient and/or family. After all issues have been adequately resolved, and the investigator confirms that the patient has fully consented to participate, the patient will be asked to sign the informed consent. All patients will be given a signed copy of the informed consent for future reference. Patients who decline to be in the trial will receive the same quality of care.

4.3.3 Screening Log

Patients who are screened for enrollment in ARUBA who are not enrolled should be recorded on the patient screening log. (see Appendix V).

4.3.4. Procedure for Enrollment.

The site clinical investigator or clinical coordinator will log into the Electronic Data Center and complete the following data collection forms:

A. Demographics (AR01) which includes verification of signed Informed Consent, Release of Medical Information, and Health Insurance Portability and Accountability Act (HIPAA) Clinical Research Authorization (U.S. only) forms
B. Eligibility Evaluation form (AR02)
C. Imaging data (AR03) or (AR03A)

D. Presentation history (AR05)
E. AVM morphology (AR06)
F. Rankin Scale (AR07)
G. NIH stroke scale (AR08)
H. Medical history (AR09)
I. Medications (AR10)
J. Quality of Life: SF-36 (AR11)
K. Quality of Life: EuroQol (AR12).

4.3.5 Procedure for Image Interpretation and Shipment
Relevant image(s) chosen by the local investigator should not be older than one year.
If an image study is older than one year, a waiver must be obtained from the CCC PI who will decide whether that image may be used for enrollment and randomization. The decision will be based upon further conversation with the site clinical investigator. The CCC PI will document reasons for acceptance/rejection of images. On the EDC, a waiver request box will appear when the date of the images exceeds one year from enrollment date.

Each clinical site will have a credentialed radiologist/neuroradiologist who will read the images and attest to the presence of an unruptured BAVM. In the US, the radiologist will be board certified and all non-US radiologists will have the appropriate clinical privileges at the academic institution affiliated with ARUBA. After completing the Image Data form (AR03), the investigator or clinical coordinator can proceed with the randomization process. A de-identified CD of the images will subsequently be sent to the DCC along with a copy of the radiologist/neuroradiologist's written report.

In the event that a credentialed radiologist/neuroradiologist is not available at the local site, the images can be uploaded to the Imaging data form (AR03A) to be reviewed by the coordinating center radiologist within 24 hours.

4.3.6. Randomization
The randomization process will assign the patient to either medical management or interventional therapy. When the site investigator or clinical coordinator has completed the data collection forms required for enrollment, a randomization button will appear in the top left hand corner of the EDC. After clicking the button, the randomization form (AR04) will be automatically completed with the patient's randomization assignment. The coordinator or investigator will then sign the form electronically.

5. STUDY INTERVENTIONS

5.1 Medical Management (Refer to Manual of Procedures)

Patients participating in the trial will receive the best medical management possible for the disorder being tested in the trial and for any general medical illnesses they are demonstrated to have. One important consideration in the medical management of patients in this trial is stroke risk factor reduction.

An additional consideration for the medical management group is that an angiogram is not required for randomization for those unruptured BAVMs for whom the diagnosis can be made by non-invasive imaging alone. The purpose of this planned limitation of data source is for patient safety. If a patient has a successful diagnosis of BAVM without conventional angiogram and is randomized to the non-intervention arm, there is no management reason for the risks, however small, of a diagnostic angiogram. That risk (and whatever subsequent angiogram or procedure risk exists) will remain in the interventional therapy arm of the study. If an angiogram exists, performed for reasons decided by the local center or its referring clinical team, the data is to be included with the screening data forms.

5.2 Interventional Therapy (Refer to Manual of Procedures)

A patient randomized to interventional therapy is expected to begin interventional therapy within 3 months following randomization**.** Interventional therapy consists of endovascular attempts at occlusion of the nidus and feeding vessels, coiling or microsurgery for feeding artery aneurysms, microsurgery for BAVM itself, and radiosurgery, these alone or in various combinations and timings.

5.2.1. Endovascular treatment

Endovascular treatment may include AVM embolization, coiling of aneurysms in the vascular territories feeding the BAVM (BAVM-related aneurysm), or coiling of aneurysms unrelated to the BAVM. The embolization materials used for those who undergo embolization as part of the treatment plan will be limited to those agents approved by the FDA or by the approval agency applicable to the country in which the patient receives treatment at the time of the procedure. This plan allows for the introduction of new agents during the course of the study. The name of the agent, the amount, and the frequency of use during each treatment will be recorded on the Interventional Therapy form (AR13).

5.2.2. Microsurgery

Microsurgery may include AVM resection, aneurysm clipping related to AVM, and aneurysm clipping unrelated to AVM.

5.2.3 Radiotherapy

Radiotherapy involves the targeting of the BAVM nidus and adjacent vessels intended to induce a reduction, and possible obliteration, of the BAVM. Based on local patterns of practice, variations exist in the exact equipment used, the methods of measurement used to assess the location and size of the BAVM chosen for therapy, the individual doses and numbers of treatments, and whether radiosurgery is used before or after embolization or microsurgery. The modality, energy, number of isocenters, collimator size, Gamma angle, prescription and duration of treatment will be recorded on the Interventional Therapy form (AR13).

5.3 Completeness of Interventional Therapy

The goal of randomization into the interventional therapy arm is to achieve eradication of the BAVM. The eradication plan may include any or a combination of endovascular, surgical, or radiotherapy treatments. Following interventional therapy, using a diagnostically relevant image study, treatment outcome will be documented as: technically complete AVM removal,

technically incomplete AVM removal, technically complete aneurysm treatment, or technically incomplete aneurysm treatment.

5.4 Handling of Study Interventions

Not Applicable.

5.5 Concomitant Interventions

5.5.1 Required Interventions
The local Investigator will make these decisions for the extent of the treatment.

5.5.2. Prohibited Interventions
Medications and materials not approved by the U.S. FDA for American subjects or those not approved by the local country equivalent of the U.S. FDA are prohibited while the subject is on study.

5.6 Adherence Assessment

Compliance of the subjects with the study will be assessed by adherence to the follow-up visit schedule. If a patient is unable to return for follow-up before the closure of a study visit window, the coordinator will make every attempt to contact the patient and complete the Patient Encounter form (AR14). If unable to contact the patient, a Missed Visit form (AR18) will then be submitted.

6. ENDPOINTS

6.1 Primary Endpoint
The *primary outcome* is the composite event of death or stroke. *Stroke* is defined as an event (revealed by a new focal neurological deficit, seizure, or new onset headache) when associated with brain imaging indicating hemorrhage (defined as fresh intracranial blood on head CT and/or MRI or in the cerebrospinal fluid, the primary bleeding location further classified as parenchymatous, subarachnoid, intraventricular, or any combination) or infarction, also defined as a clinically-related new CT (low density) or MRI (DWI, FLAIR, or T2) lesion. The severity of the resulting clinical impairment from stroke will be analyzed. Clinical impairment will be determined by a score of 2 or greater on the Rankin Disability scale. This scale will be measured at baseline, every 6 months to study completion, at every intervention, and at every neurological adverse event.

6.2 Secondary Endpoints
6.2.1 Quality of Life and Patient Preferences
This clinical trial will employ a combined approach to assessing the health-related quality of life of participants by using two broad types of measurements: those that capture health status through the description of functional capabilities, symptoms, and general health perceptions and those that generate global utility measures, which reflect both the health status and value placed on the health status by the individual. Patient utility measures will be used as quality adjustment factors to derive quality adjusted life years for the cost-effectiveness study.

The SF-36 is a 36 item generic self-report QoL instrument which provides measures on 8 dimensions of quality of life: physical functioning, role limitations due to physical factors, mental health, general health, role limitations due to emotional factors, social functioning, bodily pain and vitality. The analysis of quality of life as a secondary endpoint will include both the physical and mental composite scores of the SF-36.

We will use the EuroQoL questionnaire to derive patient preferences. This instrument examines five quality of life dimensions (mobility, self-care, usual activities (work, study, housework, family, or leisure), pain/discomfort and anxiety/depression). In addition, respondents record their perception of their overall health on a visual analog scale (0, worst, 100, best). The visual analog scale score directly reflects the respondents' view of their own health status. A societal view of the health states can be derived from population-based valuations of the 243 unique states of health described by the 5 quality of life dimensions.

6.2.2 Adverse Events

The incidence of all protocol defined adverse events will be evaluated, regardless of whether they are anticipated. Serious adverse events are defined as those that cause death or permanent disability, are life threatening or require a hospitalization, or prolong an existing hospitalization.

Protocol-defined events will include:

I. Neurological Adverse Events:

1. *Stroke* is defined as a clinically symptomatic event (revealed by a new focal neurological deficit, seizure, or new onset headache) when associated with brain imaging indicating hemorrhage (defined as fresh intracranial blood on head CT and/or MRI or in the cerebrospinal fluid, the primary bleeding location further classified as parenchymatous, subarachnoid, intraventricular, or any combination) or infarction, also defined as a clinically-related new CT (low density) or MRI (DWI, FLAIR, or T2) lesion.

Stroke presentation will be classified by the following subtypes:

A. *Intracranial hemorrhage*: Revealed by imaging showing subarachnoid, parenchyamtous or intraventricular fresh blood, or by spinal tap.

B. *Brain infarction*: Signs of infarction on brain CT or MR imaging by DWI, T2, or FLAIR imaging.

Stroke symptoms will be classified by:

A. *New focal neurological deficit:* A functional deficit on examination, stratified as to whether the deficit was persistent, progressive or reversible.

B. *New onset headache:* Patient complaint of new onset headache.

C. New onset seizures: Newly observed seizure activity.

2. *Seizure (unrelated to stroke):* Clinically suspected epileptic activity without signs of recent intracranial hemorrhage or cerebral infarction on brain imaging (CT and/or MRI).

3. *Focal neurological deficit (unrelated to stroke):* Focal neurological deficit on clinical exam without signs of recent intracranial hemorrhage or cerebral infarction on brain imaging (CT and/or MRI).

4. *Headache (unrelated to stroke):* Patient complaint of new onset headache without signs of recent intracranial hemorrhage or cerebral infarction on brain imaging (CT and/ or MRI).

5. *Other Neurological Event:* Any new, temporary or permanent, focal or global neurological deficit ascertained by standard neurological exam and appropriate diagnostic tests that is not a stroke, seizure, focal neurological deficit, or headache.

II. Non-Neurological Adverse Events

1. *Acute renal failure:* An episode of acute renal failure requiring peritoneal dialysis, hemodialysis or hemofiltration (excluding hemofiltration for fluid management alone).

2. *Procedure related nephropathy* —a rise in the plasma creatinine concentration of more than 50 percent above baseline or of more than 1 mg/dL (88 μmol/L), whichever is smaller within 7 days following a procedure.

3. *Contrast reaction:* Anaphylactic reaction in the context of intravenous or intra-arterial contrast dye injection.

4. *Infection related to BAVM invasive therapy*: Clinical or paraclinical signs of local or systemic infection related to invasive therapy.

5. *Peri-procedure bleeding (other than intracranial):* Bleeding that results in death or transfusion of packed red blood cells during the 24 hour period following an invasive therapy for an AVM.

6. *Systemic (non-brain) embolization:* Unintended dislocation of embolic material into non-cerebral arteries or veins.

7. *Vascular injury related to BAVM invasive therapy:* Mechanical injury to any arterial or venous structures during the course of the intervention without stroke.

8. *Catheter adherence to embolization material:* Unintended adherence of a catheter delivering embolization material to the BAVM and the inability to remove the catheter without causing damage to the vessel and/or requiring a surgical procedure to correct it.

9. *Other non-neurological Adverse Event:* An event that causes clinically relevant changes in the patient's health or any event that is life-threatening, results in a fatality, results in permanent disability, requires hospitalization, or prolongs an existing hospital stay.

6.2.3. Cost Endpoints

We will employ a health care perspective in this RCT and calculate the costs of all services

associated with care, regardless of who bears the cost. These costs will include the direct costs of medical care, the costs of non-medical care and indirect health care costs. The investigators will identify those costs that are related to the research protocol and are not part of usual care. We will conduct the economic analysis in the cohort of U.S. patients, with an expected sample size of 500 patients.

6.2.3.1 Direct Costs of Medical and Non-Medical Care

We will derive costs by using the clinical dataset to identify the resources that patients use during the course of the trial, and then assign payments/prices for each resource used. There are a multitude of payers in the U.S. that reimburse for services at different rates. We propose to use the Medicare payments as representative rates. For inpatient hospital days, we will use the Medicare reimbursement for the DRG codes assigned on the patient's discharge. We will not include physician time in our costing, as it is a much smaller part of the overall costs and it requires substantial data collection efforts to capture. For those patients who need nursing facilities or long-term institutional care, we will use the National Medicare average allowed daily rate to impute payments. The use of services outside the study hospitals, such as emergency room visits, out of network hospitalizations, nursing home care, and rehabilitative facility care will be determined by a structured questionnaire administered by site coordinators to all enrolled patients.

In seeking medical treatment, patients may also incur significant non-medical care costs. These costs may include the value of unpaid care provided by family members and friends, the costs of uncompensated home health care and the "costs' of time dedicated to care by the patient. We will focus on obtaining the value of unpaid care provided by family and friends with the following question administered at 6 month intervals by site coordinators on the Patient Encounter form (AR14): Has your illness required any members of your family or friends to restrict their work or social activities? If yes, about how many hours per week have friends or family spent in helping with your care? Each hour of care will be valued at an average hourly total compensation rate for civilian workers as reported in the base year by the Bureau of Labor Statistics. The value of home health care will be determined by asking patients directly if they had a home health aid or home nurse and the number of hours per week that they are employed. The hourly wage rate will be determined by the average Medicare reimbursement rate. We will not collect data on travel costs or the amount of time patients must spend seeking treatment (i.e. the opportunity cost of lost leisure time as measured by the wage rate), because of the substantial burden involved in such data collection.

7.1 DATA COLLECTION SCHEDULE

Study Visit (months after randomization) (V)=Visit, (P)=Phone Call	Screening / Baseline	6 (V)	12 (V)	18 (V)	24 (V)	30 (P)	36 (V)	42 (P)	48 (V)	54 (P)	60 Month Visit (V)	66 (P)	72 (V)	78 (P)	84 (V)	End of Study (V or P)		Event Driven
																(V)	(P)	
Window (days)	0	±30	±30	±30	±30	±30	±30	±30	±30	±30	±30	±30	±30	±30	±30	-30		
Informed Consent	X																	
Release of Medical Information	X																	
HIPAA Authorization (US only)	X																	
Demographics	X																	
Eligibility Evaluation	X																	
Randomization	X																	
Image Study	X																	
Presentation History	X																	
AVM Morphology	X																	
Rankin Scale	X[#]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X*
NIH Stroke Scale	X	X	X	X	X		X		X		X		X		X	X		X*
Medical History	X																	
Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Quality of Life: SF-36	X	X	X	X	X		X		X		X		X		X	X		
Quality of Life: Euroqol	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Interventional Therapy																		X
Delayed Treatment																		X
Patient Encounter		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X[&]
Adverse Event																		X
Hospitalization																		X
Mortality																		X
Missed Visit																		X
Voluntary Withdrawal																		X
60 Month Visit											X^							
End of Study																X		
Investigators Statement																X		

* collected following each BAVM interventional therapy, all neurological adverse events and hospitalization
[&] collected following each BAVM interventional therapy
^ window of -6 months for image study
[#] if Rankin scale collected more than 6 months prior to randomization, assessment should be repeated