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The ARUBA trial: Current Status, Future Hopes

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A Randomized trial of Unruptured Brain Arteriovenous malformations (ARUBA – U01 NS051483) was funded by the National Institute of Neurological Disorders (NINDS) with a pragmatic, simple plan: to determine for those brain arteriovenous malformations (BAVMs) discovered without having bled, whether prophylactic intervention (endovascular, surgical, radiotherapy, alone or in combination) or deferral of intervention unless hemorrhage occurred would prove superior as tested by the outcomes of death, stroke, or functional outcomes status (measured by the modified Rankin Scale) at a minimum of 5 years from randomization.¹ Both groups are treated medically for the common symptoms of headaches, seizures, or co-existing other medical conditions. Eligibility is limited to patients with a brain arteriovenous malformation that has not bled and is deemed suitable for attempted eradication based on the judgment and expertise of the local clinical site investigators. Those randomized to the deferred-intervention arm who experience hemorrhage during follow-up are then eligible for intervention at the discretion of the treating team.

Begun in April 2007, as of Mid-March 2010, ARUBA has randomized 112 patients in a steadily upward slope. Over 900 cases have been screened by a growing multi-continental list of centers (64 approved for randomization and another 23 at various stages of approval and initiation.) With increasing web access, patients are even referring themselves to the trial. The active centers continue to recruit at the expected rate, indicating the accuracy of the pre-trial estimates of availability of cases by center size,^{2, 3} population base,⁴ and bled-unbled frequencies.^{5, 6}

Initially planned for 800 patients to be recruited in a 30-month period, ARUBA experienced the slow accumulation of centers and randomizations common among clinical trials. As a result, the recruitment period was lengthened to 60 months, and the follow-up period will be between 5 and 10 years for all enrolled subjects; this lengthening, plus the continuous addition of new centers, allowed the opportunity for more events during the course of the trial. Based on a sensitivity analysis, these changes permitted a decrease of the trial's sample size from 800 to 400. The changes affected power and the detectable treatment effect: 800 patients provided 87.5% power to detect a 40% reduction in the hazard of stroke or death (the trial's primary endpoint) while 400 patients provides 80% power to detect a 46% reduction. To meet these goals of 400 patients within the 60-month period, even faster recruitment is being sought. (These changes in the study design, which have been endorsed by the DSMB and approved by NINDS, have been made in the web sites describing the trial.)

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Given that BAVMs are embedded in brain, where functionally important tissue may be displaced by or pass through the lesion, intervention for any BAVMs, especially those unbled, is among the most challenging tasks in the clinical neurosciences. It is not a wonder that complications can occur, but that many pass through without major adverse events.⁷ How to achieve the goals with acceptable outcomes? It is possible that treatment-related hemorrhage or ischemic stroke could even be occurring at rates and degrees of clinical severity that exceed what is seen in those whose intervention is deferred.^{8, 9, 10} Interventional outcomes are not notably worsened for those having bled.¹¹ BAVM hemorrhage severity appears less than that from parenchymal hemorrhage of other cause.^{12, 13, 14} The true natural history for BAVMs may have lower risk of hemorrhage than for intervention.⁹ Hence the question, “which is worse, the disease or the cure?”¹⁵ Although its rationale is still unchallenged by the latest literature, ARUBA appears to need some reiteration to address criticisms from those who may not be fully familiar with the study protocol.^{16, 17} First, the trial is limited to those whose lesions have not yet bled. Bleeding being the dominant concern for BAVMs, the strongest predictor for hemorrhage is the occurrence of prior hemorrhage.¹⁸ Once hemorrhage had occurred, there is ample justification for intervention. ARUBA tests the outcomes for those not yet having bled. For them, intracranial pressure (not easily measured),¹⁹ deep lesion location and deep venous drainage are the major angioarchitectural risk factors;²⁰ headaches and seizures are not.^{5, 15}

Second, length of follow-up has been criticized as possibly too short for the natural history hemorrhage rate to exceed the complication rate of procedures. In the application for NIH funding, the trialists several possible scenarios: the most favorable for intervention was based on earlier widely-quoted pre-trial neurosurgical literature estimates of rates of hemorrhage²¹ and complications for interventions.^{22, 23, 24, 25} Applying these values showed a 5-year follow-up would have sufficed to allow demonstration of the superiority of intervention. However, it is now well understood that the earlier literature included the outcomes for the full range of BAVMs, including many having bled and/or many not considered suitable for intervention, using current techniques.²⁶ Hemorrhage risks and event rates for those having bled are of great clinical interest but, as noted, are not the subject of ARUBA. Where published, the natural history hemorrhage rate for ARUBA-eligible BAVM subtypes seems far lower than that for the overall BAVM cohort.²⁷ Given the possibility the this inferred lower rate may take longer than 5 years for the natural history event rates to cross those of intervention, the ARUBA investigators happily reviewed with the DSMB and laid plans for follow-up to at least 10 years, assuming continued NIH funding via competitive renewal.

Third, fears of an imbalance in randomization of BAVM subtypes have not materialized. Many interventionalists were concerned the trial would be confined to those cases that posed major challenges for eradication, thereby biasing the outcomes towards those with higher complication rates, and misrepresenting success for the presumably more easily managed cases of the lower Spetzler-Martin grades.²⁸ To date, participating centers have not refused to randomize Spetzler-Martin I-II grade BAVMs and the trial has a satisfactory balance: There are no grade Vs, and few grade IVs, this despite success by some publications.²⁹ At present, those randomized have a median age 43; 52% are female; and the Spetzler-Martin Grades are 21% S-M I, 26% S-M II, 40% S-M III, 13% S-M IV, 0% S-M Vs.

Finally, the study has been criticized for its lack of a standard plan for therapy. Such lack has been inferred by some to allow too wide a variation in approach for useful analysis. The ARUBA investigators agree that a single treatment comparator might have simplified interpretation of the results. However, there is no single plan for eradication of BAVMs overall or for any individual subtype. Proponents exist for each of the various approaches, including one-stage neurosurgical resection,³⁰ embolization alone,³¹ embolization to reduce

lesion size followed by surgery or radiosurgery; radiosurgery before or after endovascular or surgical efforts, or radiosurgery alone.³² Some case series demonstrate spontaneous occlusion of the lesion,³³ recurrence despite successful surgical resection³⁴ or stereotaxic radiosurgery.³⁵ Much of the literature includes case series where several of the approaches are used in the same institutional cohort. Thus far no widely-accepted plan endorsed by the interventional societies has appeared in the published literature for any Spetzler-Martin grade, size, or even for the prominent hemorrhage risk factors such as deep location, deep venous drainage, or for aneurysms (intranidal, on feeding arteries, or both).^{36,37} This situation exists to varying degrees in other interventional trials, such as stenting or carotid endarterectomy,³⁸ extracranial-intracranial bypass,³⁹ clipping or coiling of aneurysms,⁴⁰ all of which contain variations in the fine details of techniques subject to post-hoc debate, depending on the results of the studies.

The choice of treatment modality for eradication of brain AVMS remains a complex therapeutic decision, which depends heavily on local expertise. Variation in treatment approach will undoubtedly continue for some time to come. Thus, the standard for comparing alternative treatments is the range of available treatment approaches. This is the rationale for the large simple trial design selected for ARUBA, where on a case-by-case basis local experts determine the optimal approach to AVM eradication.

Despite the variations in treatment options, outcome rates for the range of interventions appears relatively stable over the last 2 decades.^{24, 41, 42} However, assessing the functional details of the outcomes for interventions has proved difficult. The descriptive terms used to characterize adverse events leave many readers unclear what is meant by “permanent”, “major”, or other terms describing the deficits. Few reports cite more quantitative assessments like the modified Rankin Scale (mRS, the usual break point for “minor” versus “major” being 0–1 vs. ≥ 2) or Barthel Index (BI). Almost none cite quality of life

In the submission and protocol, the ARUBA investigators cited the range of complication rates (and, where reported, by severity) by intervention(s). These values were used in calculating sample size and post-randomization time course for the trial to allow comparison against hemorrhage rate and severity for the medical management arm. The trial is based on the good faith assumption that clinical teams would use their best judgment for the selection of procedure(s) for the cases randomized to intervention and for those in the medical management arm who experience hemorrhage during follow-up. The modified Rankin Scale status at the end of the trial will also provide a means of assessing the late outcome for all patients in the trial. The protocol calls for subset analyses wherever feasible. The larger the cohort randomized in ARUBA the better such opportunities.

Results from a randomized clinical trial have long been shown preferable to relying on the wide range of outcomes based on case series. The current concern is that failure to complete the trial as planned could leave referring clinicians and insurers unclear whether intervention in any form should be delayed pending hemorrhage, when or whether it occurs in the useful lifetime of the patient, or undertaken in hopes of its prevention.⁴³ Considerable resources are used in BAVM management.⁴⁴ The matter could be left to outcomes research or effectiveness research, which, if applied to pre-trial data in the past, might well have ended carotid endarterectomy,^{45, 46} or continued the enthusiasm for anticoagulation for non-embolic stroke.^{47, 48}

There is also a rising interest in the basic biology of BAVMs.⁴⁹ Although the outcomes for those already bled and those too daunting for intervention have no relevance to the ARUBA trial, they pose a need for innovations in therapy. The large number of cases being screened for the ARUBA trial provides a database for studies of biomarkers of hemorrhage risk,⁵⁰

assessment of the utility of tensor diffusion tractography on management options.⁵¹ They may even permit the eventual posing of a minocycline medical trial to delay vascular changes and hemorrhage risk.⁵² Recent studies of functional reorganization following non-ischemic focal infarct raise hopes that similar outcomes might apply for BAVMs after hemorrhage or intervention,^{53, 54} The periodic assessments of functional status during long-term follow-up planned for ARUBA participants will allow such insights, but await the data. The tide is running strongly for evidence-based treatment plans. We encourage intrepid interventionists to join the effort for ARUBA.

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