Competing Trial Issues Update
April 2019

Prior Work: StrokeNet originally developed a white paper for stroke trials with competing enrollment criteria under the leadership of Jenny Majersik. We have attached this document for guidance. At that time, for most sites, the issue was more theoretical and a future concern, rather than a reality. The bottom line recommendation was that **every StrokeNet site had to have a locally defined process for competing trials and communicate the plan with the National Coordinating Center but we didn't legislate how this was to be done**. *This recommendation remains unchanged*.

New Trials: The overlap of ARCADIA and Sleep Smart and the upcoming SATURN and ASPIRE trials have again highlighted this issue. The first two, both ischemic stroke trials, have potentially substantial overlap. ARCADIA has narrow criteria, with a two-stage consent process that includes randomization only after testing with a send-out lab and TTE/EKG adjudication. Identification of patients is typically in-hospital but patients can enroll from clinic after hospitalization. ARCADIA's enrollment is currently behind its projected rate. Sleep SMART has broad entry criteria, and identifies stroke/TIA patients in-hospital within 1-2 days. It also utilizes a two-stage consent process with randomization only if patients are diagnosed with OSA on an overnight PSG and then tolerate CPAP. The overlap of SATURN and ASPIRE is much less but also present.

After excellent and thorough discussion by the Executive and Steering Committees, we have identified several options that sites can consider when running competing trials. They are listed in order by what some RCCs have indicated have worked well. Any are acceptable but each site should indicate which of the following, or another method, is their chosen approach.

Acceptable options discussed include:
1. Rolling Prioritization Enrollment Grid: Trials are placed in order from first to last in which they would be offered to patient. Priority should be given to NIH-funded trials (expectation). When an enrollment in one trial occurs, the next trial on the list then assumes the first position. One may decide to place trials with narrower criteria first (like ARCADIA).
   - Example: Enroll in ARCADIA first, Sleep Smart second. During the first stage of ARCADIA enrollment, the stroke subtype is required to be ESUS and thus most (4/5) patients will not qualify for ARCADIA; these non-ESUS patients will be immediately considered for the first stage of enrollment of Sleep Smart. If the patient does have ESUS, then s/he would be consented for ARCADIA with stage 2 of the enrollment process including determination of eligibility by one of the three cardiac criteria. If the patient qualifies in this second stage of ARCADIA enrollment and is randomized, then Sleep Smart would move to the top of the list for trial presentation, until someone is enrolled in Sleep Smart. At that point, ARCADIA would move to the top of list, and so on. Likely four-fifths of the time, a patient will not be an ESUS patient and they will be evaluated for SleepSmart. However, there will still be the potential for ESUS patients to be enrolled in Sleep SMART, when Sleep SMART is at the top of the list.

- Comment: This method minimizes impact of Sleep SMART's wide inclusion criteria on ARCADIA while still allowing for ARCADIA's sub-population to enroll in Sleep SMART. It can easily be adapted to all overlapping trials.

2. Equal Opportunity Enrollment Grid: Develop a site-specific enrollment grid where each trial is given equal opportunity for enrollment based on time up first. If there are two trials, perhaps one trial is offered first on odd days and one is offered first on even days.
   - Comment: This would more negatively impact ARCADIA and other trials with narrower criteria. It also becomes difficult to implement if there are many overlapping trials.

3. Prioritize Laggers: Put the trial lagging in recruitment at the top of the enrollment grid to maximize recruitment. Once no longer lagging, can change the order.
   - Comment: This may bias the type of patients enrolled. For example, if a site is behind in ARCADIA, and thus prioritizes it to first place, then that site will never enroll ESUS patients into Sleep Smart. However, since some sites will only be enrolling in Sleep Smart, this enrollment bias will not extend across the entire network. Also, if a site is behind in enrollment in multiple trials, this method does not address that problem.

4. Maximize Patient Autonomy: Offer all trials to patients and let them choose. This can be overwhelming to stroke patients and families and requires very knowledgeable coordinators/investigators with excellent communication skills but is an option in the subacute and recovery settings.

5. Minimize Trial Participation: Some sites in an RCC may do just a single trial, avoiding the issue of competing trials altogether and allowing for simpler site management. However, it is the collective experience of StrokeNet that sites tend to improve enrollments when there are more trials because of more attention on screening. Additionally, having more trials allows for more income for research infrastructure (coordinators) which can be an important consideration.

Future Questions: A question for the long term is whether or not someone could participate in two trials at once, for example, acute and prevention, or acute and recovery. There would need to be statistical approaches to manage this issue but ideally this would benefit recovery trials or any trial which is further downstream from the stroke event. While this is a complex issue from trial design and ethical considerations, we will be exploring this (there are examples in the literature for this), including inclusion of the cIRB. Another intriguing question is whether for the 2-stage trials, patients could consent to both trials (e.g. ARCADIA and Sleep SMART), proceeding with the second stage screening simultaneously (overnight PSG for Sleep SMART, send-out labs for ARCADIA) and then randomizing into only the one in which they are eligible. StrokeNet would need to find valid methods for determining in which trial to randomize in the event that after 2-stages of screening, a patient was eligible for both.

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