FDA Stroke Devices Meeting, October 6, 2015

Breakout Session Questions Follow Up from AANS/CNS Joint Section on Cerebrovascular Neurosurgery Attendees

The consensus comments below were developed by the members of the American Association of Neurological Surgeons (AANS) and the Congress of Neurological Surgeons (CNS) Joint Section on Cerebrovascular Neurosurgery who attended the October 6, 2015 workshop. The following individual neurosurgeons contributed to the consensus document:

Adam Arthur, MD, Brian Hoh, MD, William Mack, MD, J. Mocco, MD, Peter Rasmussen, MD, and Adnan Siddiqui, MD. Their consensus comments are in red.

Clinical Study Design

1. **For acute ischemic stroke medical devices, what are appropriate control therapies?**

    - *If a control arm is "standard of care," should it be limited to relatively few treatments? A potential concern with unlimited choice in standard of care is that the observed control group performance may be difficult to characterize and interpret due to heterogeneity of treatment strategies.*

Level 1 evidence from multiple prospective multicenter randomized controlled trials convincingly demonstrates that mechanical thrombectomy for emergent large vessel occlusion (ELVO) within 6 hours of symptom onset has become the new standard of care.

The following are the most appropriate control arms patient populations for future trials:

1) IV tPA-eligible patients with ICA and/or MCA ELVO: standard dose IV tPA (0.9mg/kg) plus mechanical thrombectomy

2) IV tPA-ineligible patients less than six hours from symptom onset with ICA and/or MCA ELVO: mechanical thrombectomy

3) Patients six hours or greater from symptom onset: best medical therapy

4) Patients with 1/3 or greater territory area of infarct: unclear

2. **What criteria or mechanism(s) can be used to allow data borrowing among multiple studies or subgroups?**

- *For example, if a pivotal study has a sparse number of patients for a certain patient/stroke subgroup, how can we make study conclusions regarding the subgroup by borrowing information from other subgroups that are deemed to be sufficiently "similar"?*

Data borrowing from previous studies would likely have to come from patient populations with the same characteristics according to the following criteria:

1) similar age distribution

2) similar gender composition

3) similar time from symptom onset

4) similar anatomic location of occlusion

5) similar additional treatment (e.g. IV tPA)

6) similar advanced imaging findings

- *Under what circumstances can borrowing among multiple studies or subgroups be useful?*

Data borrowing can be useful when patient populations are similar according to the criteria above and when they can reduce the number of patients required for a study thus reducing cost, resources, time, and risk to patients. In addition, when proposed study designs will face enrollment challenges secondary to concerns around equipoise, borrowing can be very useful in expediting the speed of the trial.

One of the major potential issues with this approach is the fact that it requires patient-level data and these data are often owned by the sponsors of previous trials. Therefore this approach is useful only in the unusual circumstance where a sponsor has already completed a large trial and wants to do another trial for a similar patient population. To develop a policy wherein data borrowing is seen as the mechanism to circumvent strokes relative low disease prevalence and large number of patients needed for clinical trials would create an unfair bias towards one or two device vendors and, as a result, would stifle continued innovation in the field.

- *What criteria or clinical trial designs can be used to leverage such data borrowing?*

Data borrowing can be useful under two conditions

1. Development of a performance standard utilizing multiple approved devices through data from FDA approved randomized trials, FDA approved post market registries, as well as

international studies carried out using rigorous trial methodology. This performance standard can obviate the need for control arms with varied approved devices (different types of stent retrievers, aspiration, combination) and treatment heterogeneity, which make interpretation difficult.

2. Data borrowing may also be useful for prospective randomized trials that require large sample sizes in potentially reducing control arm size. However, unless appropriate level data is available to all parties, data borrowing may significantly limit device development in stroke.

- *What are acceptable sources of information for developing an OPC or PG, if appropriate, in addition to prior clinical studies and/or registries?*

OPC data should, at a minimum, be derived from studies in which the outcome is adjudicated by an impartial source. Single center self-adjudicated case series are notoriously unreliable and should not be used for OPC. We suggest any study utilized should have an independent core lab imaging adjudication with independent CEC for clinical events. Studies to utilize may include:

1. FDA approved randomized trials for approval of devices
2. FDA approved post market registries,
3. International studies carried out using rigorous trial methodology (single arm or randomized) meeting above criteria

3. **What are the benefits and challenges of using consistent imaging assessments before and after treatment within the patient population in the same clinical trial and across all acute ischemic stroke clinical trials?**

- *How can the challenges be minimized?*

Consistent imaging assessments before and after treatment within the same clinical trial and across all acute ischemic stroke clinical trials is essential for accurate analysis of outcomes from stroke device treatment. We suggest the following to promote consistent imaging assessments:

1) Well-defined imaging modalities and parameters for pre-treatment and post-treatment assessment to be consistent across centers in the same clinical trial

2) Standardized application of revascularization scales such as the modified TICI score for use across all studies so that populations can be merged and risks to additional patients be mitigated

3) Well-defined imaging modalities and parameters for pre-treatment and post-treatment assessment to be consistent across all acute ischemic stroke clinical trials. One potentially useful tool would be the NIH/NINDS Stroke Common Data Elements (CDE).

4) The use of central core labs to adjudicate pre-treatment and post-treatment imaging is also an important measure to limit bias.

4. **In some cases, patients may require concurrent therapies (such as an acute ischemic stroke medical device in addition to carotid stenting). How should these multiple-therapy patients be analyzed if the active treatment group is the acute ischemic stroke device?**

Patients that require concomitant therapies such as carotid stenting for a tandem proximal occlusion complicate the analysis because it is difficult to ascertain whether the outcome is related to the acute ischemic stroke device being studied or from the concomitant treatment. However, it is not always possible to predict when a patient will require a concomitant treatment before they are enrolled, so these patients should not be given the worst outcome in an FDA trial because they are deemed a protocol deviation. The best possible approach may be to include them in a separate a priori subgroup analysis. There is evidence from MR CLEAN that this group may be specifically exposed to harm by exclusion from trials and withholding of treatment since greatest treatment effect was noted in this cohort. A predefined subgroup analysis will allow for dissection of combined effect of more than one intervention in this group. The heterogeneity of patient presentation is part of what makes pragmatic trial designs promising in advancing clinical care, but challenging for device approval analysis.

5. **In what situations in the development of an acute ischemic stroke medical device could a clinical trial not be necessary or should it be required for all acute ischemic stroke technologies given that this is a high-risk patient population?**

It may be that, moving forward, device trials should focus on recanalization (TICI 3) and safety endpoints rather than being limited to only clinical outcomes (mRS), as we have definitive evidence that reperfusion equates to better clinical outcomes. Perhaps clinical outcomes should be reserved for trials incorporating neuroprotection, imaging, ICU management, etc.

We suggest that a clinical trial may not be necessary if:

1) the device is significantly similar to an approved device

2) if it's a iterative refinement or modification of an approved device

3) or refinement or modification of an indication for an approved device

4) The change is not in the actual device but in delivery or other mechanism which are not considered substantial change to expected performance

Patient Populations and Selection

1. **For novel acute ischemic stroke treatment, is there a patient population that can be defined in which clinical equipoise still exists? If so, how can we define these patients?**

Clinical equipoise exists for too many patient populations to list here, and includes but is not limited to:

1) Patients six hours or greater from symptom onset
2) Patients with uncertain time of symptom onset.
3) Patients with vessel occlusions beyond M1, A1, P1
4) Patients with poor perfusion profiles on CT or MR Perfusion

5) **How can we design studies to select patients most suitable for particular acute ischemic stroke medical devices?**

   a. *This may include selecting certain types of patients (e.g., specific anatomical location) or including assessments such as validated instruments or imaging tools.*

   Targeted patient populations are going to be device-specific and difficult to define ahead of time. Assessments can be defined and should aim to be consistent across acute ischemic stroke device trials. One way to do this is to use the NIH/NINDS Stroke Common Data Elements (CDE).

   What specific patient characteristics can and cannot be generalized? For example, most studies to date included subjects with predominantly anterior circulation strokes, can results be generalized to subjects with posterior circulation strokes? Why or why not?

   While one is typically hesitant to generalize findings in predominantly anterior circulation stroke subjects to subjects with posterior circulation stroke because differences in collaterals, anatomy, areas of brain affected, and historically known outcomes in patients. However, the common element here is revascularization and reperfusion of tissue at risk (i.e. non-infarcted). Generalizing results of a device that is safe and highly efficacious at removing occlusive lesions to these other areas, as above, is appropriate. It should be noted that posterior circulation large vessel occlusion particularly dominant vertebral and basilar artery occlusion have an established natural history which is almost uniformly devastating. This group may be best studied in a single arm prospective study so as to allow evaluation of efficacy of devices without subjecting patients to known risks of natural history. That being

said it is unclear the benefit of revascularization beyond basilar artery such as P1 P2 and at such locations equipoise does exist.

6) **What subgroups of patients warrant examination in future mechanical neurothrombectomy studies to expand the safe and effective clinical use of these devices to a wider patient population?**

Subgroups of patients that warrant examination in future mechanical thrombectomy studies are too many patient populations to list here, but includes although not limited to:

1) Patients six hours or greater from symptom onset
2) Patients with PCA occlusions (the posterior circulation beyond the basilar)
3) Patients on novel anticoagulation agents
4) Patients with uncertain time of symptom onset.
5) Patients with vessel occlusions beyond M1, A1, P1
6) Patients with poor perfusion profiles on CT or MR Perfusion

7) **What key criteria can be used to allow combining patients across seemingly heterogeneous subgroups (e.g., with different locations, size and etiology of stroke) within a study in order to make a broader device indication (e.g., to include acute ischemic strokes in vascular territories that may present less frequently than others)?**

    a. *What clinical trial approaches are preferred to adequately capture and appropriately interpret such information?*

    Including large populations of patients and utilizing data borrowing across properly matched clinical trials would be an effective approach if feasible. As previously iterated, our concern is that this approach seems impractical in the real world given the problems accessing data of appropriate detail.

    It is in these situations that single arm post market studies can be best utilized allowing for collation of data from large populations and determining effects in smaller groups of patients where trials may fail.

    It would seem reasonable that a physiologic or imaging correlate could be used. For instance, if pre-treatment tissue “at risk” from a vessel occlusion can be assessed, and then after the intervention that tissue is no longer imaged as “at risk”, that would be a successful result for infrequent vessel territories.

8) How can we use enrichment strategies so that devices benefit the most appropriate patients?

a. *Certain enrichment strategies can help select an appropriate patient population based on the prospectively specified characteristics (e.g., the acute ischemic stroke presentation or imaging assessment) of patients who may respond best to a therapy. In adaptive enrichment trials, the enrollment criteria may be also adapted in a prospectively specified manner based on interim analysis results.*

In mechanical thrombectomy for acute stroke trials the following enrichment strategies might be applicable:

Decrease heterogeneity: Possibilities include restricting inclusion criteria by imaging characteristics, time criteria, clot location, premorbid Rankin scores, age range. This could also include use of a single device in a given trial. Many of the previous stroke trials have aimed to decrease heterogeneity.

Prognostic enrichment: In acute stroke trials this might be achieved by focusing on patients with basilar artery embolic occlusions, those with high NIH stroke scales, those with good premorbid mRS scores or those with very little initial injury on imaging yet an M1 occlusion. The goal would be to increase the disparity between responders and non-responders on 90 day mRS.

Predictive enrichment: Ultimately genomic profiling and issues such as clot composition and collateral circulation etc. may come into play. As we are not at the point where these factors are being incorporated into acute stroke care, focusing on patients with a low stroke burden on admission imaging and younger, healthier patients might be other possibilities to leverage predictive enrichment. Another possibility might be segregating patients according to aortic arch subtype and ease of endovascular access. Excluding patients taking novel anticoagulant agents that might be more likely to hemorrhage is also a consideration. Any factor that could influence a patient to dropout before the primary endpoint (90 days), such as comorbid disease or social factors, might be considered

Adaptive Clinical Trial Design could benefit mechanical thrombectomy trials: Designing trials that factor in the data at interim analyses could serve to shorten trials, decrease patient numbers and decrease costs. Possible adaptations could include modifying eligibility criteria (age, last know well time, etc.), change of mechanical thrombectomy device as new iterations are developed, and randomization procedure/ allocation (i.e.: need for less patients in the comparator group)

However, while the aforementioned enrichment strategies may provide benefit, it is as yet unclear of this will be the case. Across the seven recently completed prospective randomized stroke treatment trials, various enrichment strategies were used with varying degrees of benefit or value. It would be premature to conclude that we, as a community, know the appropriate enrichment strategy.

Clinical Outcomes

1. **What are key primary and secondary outcome measures that should be used routinely in clinical trials for acute ischemic stroke medical devices?**

    - *What is the range of scores on outcome assessment scales (e.g., modified Rankin Scale (mRS), National Institutes of Health Stroke Scale (NIHSS), Thrombolysis in Cerebral Infarction (TICI), Stroke Impact Scale (SIS)) that is most indicative of a clinically meaningful improvement?*

    The following outcome measures are reasonable:

    1) modified Rankin Scale (mRS) 0-2 at 90 days or mRS shift analysis

    2) NIHSS change at 24 hours (or 48 hours) since many are not available for 7 days and there may be additional morbidity, which may come into play at 30 or 90 days from underlying disease complicating effect size of actual intervention.

    3) NIHSS 8 point drop or NIHSS score 0-1

    4) TICI 2b/3a

    5) NIHSS shift analysis

    6) It would also be of value to pursue outcome metrics that assess the function of the "tissue at risk" which is specific to the vessel that is occluded. As an example, living situation at 6 months may be appropriate for basilar occlusions.

    7) There needs to be evaluation of patient reported outcome measures as exploratory endpoints in future studies to fully evaluate impact of these interventions on patients.

    8) It is critical that socioeconomic endpoints be also explored as we consider effectiveness of these comparative therapies. Including length of stay, direct costs etc.

    - *Are incremental improvements in ordinal rankings such as the mRS clinically meaningful to patients and physicians, or must a device increase the likelihood of being a "responder" (e.g., mRS ≤ 2) compared to a control in order to be considered effective?*

    For incremental improvement, we suggest considering an improvement in the NIHSS. Modified Rankin Scale is a relatively crude scale.

    - *Can a treatment that shifts the assessment toward the more favorable end of the scale be meaningful even if the treatment does not significantly increase the proportion of "responders?"*

Absolutely

- *What is the role of patient reported outcomes (PROs) and what are the PROs that are most meaningful to patients?*

A short self-reporting tool such as the SF-12 or the stroke specific quality of life tool could be utilized. The WHODAS also assesses a wide-variety of meaningful life experiences for patients.

Others to consider include EQ-5D, SF-36 and other national initiatives such as the NIH lead PROMIS (patient reported outcomes measures information system)

2. **Given our concerns for the translation of patient safety in the clinical trial setting to the "real world" following premarket approval or clearance of acute ischemic stroke medical devices, how can registries be leveraged in the design of new acute ischemic stroke studies?**

- *What information should be collected in the Registry?*

- *If you were to be entering outcome data for the purposes of a Registry, what are the common data elements you would enter for a trial for device evaluation?*

We suggest also consulting the NIH/NINDS Stroke Common Data Elements (CDE), the N2QOD and the NVQI to identify appropriate elements. That said, we would include these data elements for outcome:

1) mRS at 90 days

2) NIHSS improvement

3) Mortality

4) Symptomatic ICH

5) TICI scale

6) Patient reported outcomes

- *What procedures should be used to construct new registries, if existing ones are not accessible or lack important information?*

A number of professional medical societies have prospective registries that would address this issue. Neurosurgery has N2QOD, and SNIS has NVQI. We recommend the FDA seek to partner with those societies rather than creating further competing efforts.

- *How can we support the development of common definitions and develop common data elements that are entered into Registries?*

One channel is working through the NIH/NINDS Common Data Elements (CDE) project. Another is to partner with physician organizations such as the AANS or SNIS to support the use of the N2QOD and NVQI.

- *What is the role of professional medical societies and FDA in this effort?*

Professional medical societies and FDA should work closely together on this effort. The medical societies can nominate representatives to work closely with FDA towards registries and clinical trials for the evaluation of new acute ischemic stroke devices. In addition, the Joint Section of CV surgery and the SNIS have developed AIS registries for their members in the form of N2QOD and NVQI.

Safety Endpoints

1. **What common risks can be applied to all acute ischemic stroke patients when designing safety endpoints for clinical studies of acute ischemic stroke medical devices?**

    - *What risks (besides intracerebral hemorrhage, new stroke, or death) are unique to patients eligible for mechanical neurothrombectomy and warrant further investigation?*

    The main considerations are intracerebral hemorrhage, subarachnoid hemorrhage, hemorrhagic conversion of ischemic stroke, new stroke, death, new embolic stroke in the territory of the mechanical thrombectomy, device adverse events such as device fracture, vessel perforation

    - *Have any signals emerged from the recent published literature that suggests there are unique risks or adverse events associated with current or novel acute ischemic stroke medical devices?*

    There has been some concern for distal emboli or emboli into previously uninvolved territories with some devices

2. **We have previously required intracranial hemorrhage with a change in the National Institutes of Health Stroke Scale (NIHSS) of ≥ 4 points as evidence of neurologic deterioration in acute ischemic stroke device trials. What alternative or more meaningful methods of assessing neurologic deterioration could be included in clinical studies to assess the safety of novel acute ischemic stroke medical devices?**

We agree with continuing NIHSS increase of 4 or more points.

3. **What stopping rules should be utilized to best protect patients from unknown or known risks associated with acute ischemic stroke medical devices?**

If stopping rules refers to number of passes of a device in an individual procedure, then we do not believe that there is any evidence to support hard and fast rules upon which device passes should be stopped. This should be according to the clinical judgement of the physician.

If stopping rules refers to stopping of a trial, then we believe this should be a decision of the Data Safety Monitoring Board (DSMB) of the trial, according to pre-defined criteria following appropriate statistical methodology or new external information resulting in a loss of equipoise.

4. **With the development of novel acute ischemic stroke medical devices, in order to specify an appropriate patient population, the patients selected may have been treated with previous medical therapies. What are the increased risks to patients if multiple acute ischemic stroke**

medical therapies are used on the same patient and how should these risks be captured/mitigated in the clinical trial design?

1) The use of IV tPA concomitantly with acute ischemic stroke devices has been shown to be safe and proven in randomized clinical trials.

2) The use of carotid stenting for a tandem proximal occlusion when using an acute ischemic stroke device intracranially has not been adequately studied in previous studies. It is difficult to ascertain whether the outcome is related to the acute ischemic stroke device being studied or from the concomitant treatment. However, it is not always possible to predict when a patient will require a concomitant treatment before they are enrolled, so these patients should not be given the worst outcome in an FDA trial because they are deemed a protocol deviation. The best possible approach may be to include them in a separate subgroup analysis.

3) The use of multiple ischemic stroke devices such as the use of a distal suction catheter with a stent retriever is a question with clinical equipoise and may be of interest for further study. However, clinical practice often develops and out paces device assessment trials. This is a major limitation of modern trials, in that associated technology becomes difficult to tease out in the evaluation of a particular device. When a thrombectomy device is variably used with any of a number balloon guide catheters or with distal aspiration or with a proximal angioplasty and stent, the relative contribution of that one device becomes difficult to asses, particularly with the limited numbers of patients able to be enrolled in randomized trials. This may potentially be addressed in large post-market studies that allow adequate data volume to work out such issues.

4) There very likely exist patient safety concerns when evaluating multiple medical treatments that impact the clotting cascade and platelet function. This likely will need to be very closely watched.