Workshop 1 – Discussion Guide

To Develop Recommendations for:

THE NEXT GENERATION OF ENDOVASCULAR TRIALS

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Goal: This workshop will generate a roadmap for the next generation of endovascular trials in acute ischemic stroke. Recent publications on the primary results and related secondary analyses of positive endovascular trials have established the unequivocal benefit of mechanical thrombectomy for revascularization of proximal arterial occlusions in selected patients. However, at least 50% of patients presenting with stroke due to large vessel occlusion within 6 hours do not achieve functional independence despite undergoing endovascular therapy and approximately 15% will not survive. Further research is critical to establish new approaches that will substantially improve outcomes. The goal within the next decade is to achieve independent level of functioning in at least 75% of LVO patients and to lower stroke mortality to less than 10%. Key unanswered questions remain and may be addressed in future or ongoing randomized controlled trials and phase IV registries. Selection of optimal candidates based on clinical and imaging variables may be further refined and new approaches should be sought that may extend therapeutic opportunities to broader stroke populations. Given the fundamental time sensitive nature of reperfusion therapies in acute stroke, pre-hospital triage, delivery and management of stroke patients should be developed around systems of care that ensure the fastest possible access to endovascular centers of patients identified as candidates while novel adjunctive approaches aimed at penumbral preservation offer opportunities for increasing the number of patients that may benefit from intervention. The workshop discussion will explore and then summarize consensus statements on research priorities for endovascular trials across various geographical regions.

1. **Next steps following the initial positive endovascular trials: key unanswered questions**
    a. Is prospective enrollment in an RCT required or can retrospective analyses and ongoing registries be used to answer these questions?
        i. Which study format is best for each question raised here?
        ii. How do we address prior gaps in trial screening logs and generalizability?
    b. What are current barriers in conducting RCTs and what are potential ways to overcome these barriers?

    i. What is the impact of the consenting process in time-sensitive trials? Are novel forms of consent or lack thereof necessary?
    ii. Are there reimbursement barriers to testing new approaches?
    iii. Are there regulatory barriers to testing new approaches?
    iv. Do competing trials constitute barriers?
c. NIHSS criteria? Is there a need to establish benefit through further studies?
    i. Mild stroke (NIHSS<6)? What is the stroke severity threshold below which benefit is not clearly established?
d. Large core (low ASPECTS (<6) or baseline infarct > 70 cc)
    i. How large is too large for revascularization? Are there core thresholds that predict futility or even harm?
    ii. Should core thresholds studies be age-adjusted?
    iii. Should studies be stratified by individual baseline core grade?
e. Are there other subgroups of patients that derive harm from intervention and is there a clinical need to conduct studies addressing these patients?
f. How do we define and measure reperfusion?
    i. Can we measure TICI reperfusion dynamically in real-time at angiography?
    ii. Intermediate goals for reperfusion – do all patients require the highest TICI?
g. Should different outcome measures be used depending on the research question to be answered?
    i. Do our chosen endpoints matter to patients and should we adopt a patient-centered approach?
    ii. Are we using optimal time points for outcome measure? Would earlier time points more accurately and objectively measure the intended purpose of intervention
    iii. Surrogate markers (final infarct volume or 24 hour ASPECTS)
    iv. Cognition, mood and quality of life
    v. Major confounders of outcome measure (economic status, access to health care, family and social support other comorbidities)
    vi. Health economics and cost effectiveness analyses
h. Can we treat independent of time windows?
    i. DAWN and DEFUSE 3?
i. Collateral status – selection based on collateral circulation
    i. Are certain subgroups more time sensitive than others?
    ii. Do patients with poor collaterals benefit from reperfusion?
    iii. What are the extended time windows for those patients with robust collaterals?
    iv. Can intra-procedural collateral imaging substitute for pre-intervention assessment of core?
j. Location of arterial occlusion?
    i. Basilar occlusions?
    ii. M2 definitions and benefit from intervention

k. Tailored endovascular therapy in the setting of atherosclerosis
    i. Intracranial stenosis?
    ii. Extracranial carotid stenosis or occlusion?
l. Are certain device technologies superior to others?
m. Are alternative access strategies likely to improve outcomes by shortening procedure time (direct carotid approach, radial approach)?

2. How to get the right patient to the right places

a. Triage in varied systems of care and geographical regions
    i. Does preferential delivery to endovascular centers lead to better outcomes for a higher proportion of patients at the population level?
    ii. Criteria for diversion or secondary transfer to endovascular centers?
    iii. Prehospital and ED strategies
    iv. Criteria for endovascular centers – interventional specialties, post-reperfusion care in the NICU
b. Imaging in the community – can multimodal imaging (CT/CTA at a minimum) be efficiently acquired in the community and is it necessary?
c. Telestroke imaging triage in clinical context
    i. Remote ASPECTS and CTA interpretation in real-time
    ii. Can a national stroke expert panel triage for endovascular therapies?
d. mobileCT – role and impact in various geographical regions
e. Establish concrete data on reasons behind time delays and the relative impact on clinical outcomes
    i. Systematic analyses of reasons behind time delays and failure to meet mandated standards
    ii. Development of region or system-specific approaches to eliminate such delays
f. Can we triage patients in based on collateral flow status to define individual time windows? (precision medicine of collaterals)
g. Can we eliminate intra-hospital workflow steps and if so do we improve outcomes?
    i. Can we bypass the ED?
    ii. Can we go straight to the angiography suite and perform imaging on the angiography table?
    iii.

3. How to preserve penumbra while waiting for reperfusion

a. Do we need to identify “penumbra” or can empirical therapies be used to save brain before imaging?
b. Hemodynamics and collateral augmentation
    i. Can we define optimal head positioning?
    ii. Fluids and manipulation of volume status?
    iii. BP management – can we define universal parameters to avert ischemia?

c. IV tPA
    i. Why not always give it?
    ii. What is the role of IV tPA within the new treatment paradigm and is tPA administration still beneficial especially in certain subgroup of patients (ICA terminus or tandem occlusion)?

d. Combining reperfusion with neuroprotection
    i. Hypothermia
    ii. Pharmacological neuroprotection
    iii. Preconditioning
    iv. Optimal timing and administration venues (prehospital, pre-intervention, post-intervention)
e. Measuring the impact of anesthesia on endovascular reperfusion and subsequent clinical outcome
f. Can we prevent the evolution of malignant edema at the time of endovascular therapy?