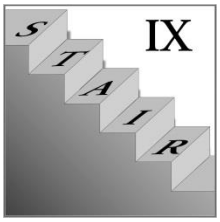

Workshop 2 – Discussion Guide

To Develop Recommendations for:

ORGANIZING A TRIAL TO COMPARE IMAGING MODALITIES TO SELECT PATIENTS FOR ACUTE STROKE TREATMENT

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Recommendations on Final Infarct Imaging and Its Use as a Biomarker of Treatment Efficacy

1) **Final infarct volume as a prognostic and therapeutic biomarker**
    a. Rationale
        i. Biological rationale:
            1. FIV is a closer biological outcome to the treatment intervention. The reduction in the volume of infarcted brain is the key objective of revascularization. It is closer to the intervention and therefore likely to be a more responsive outcome.
            2. Potentially strong clinimetric characteristics. Measurement can be agreed upon, is reproducible and sensitive to change (Note: These must be demonstrated. See Section 3.)
        ii. Advantages of FIV for trial design
            1. Ability to distinguish smaller treatment effects.
                a. Imaging selection approaches (e.g., NCCT ASPECTS vs. CTP selection)
                b. Intra-arterial treatment approaches (e.g., Stentriever vs. Thromboaspiration)
            2. Efficient and cost-effective
                a. Reduce sample size
                b. Decrease time to patient follow up
        iii. Disadvantages of clinical endpoints (**Jovin**)
            1. Non-stroke related morbidity and mortality between early phases and day 90.
            2. Inter-rater variability/greater subjectivity
            3. Exclusion of patients with pre-stroke mRS>1 due to orthopedic or neurologic morbidity
            4. Loss to follow up

iv. Disadvantages of angiographic endpoints **(Liebeskind, Menon [CTA])**
    1. Futile revascularization
    2. Neglects intra-procedural time to revascularization
    3. No measure for IV rtPA or neuroprotection strategies

b. Evidence to date
    i. Criteria for biomarker validation (**Yoo**)
        1. Strong relationship to disease severity/outcome (i.e., prognostic)
        2. Modifiable and closely linked to treatment success/harm (i.e., therapeutic)
        3. Easily and reliably measured (**Luby**)
    ii. Current data (**Luby, Muir, Yoo**)
        1. IV thrombolysis (alteplase/tenecteplase)
        2. IAT

2) Technical issues for optimizing and standardizing final infarct volume measurement and reporting

a. Timing of imaging
    i. Early: (1) avoids volume expansion from cerebral edema, (2) minimizes loss of data due to early mortality
    ii. Late: (1) infarct volume may continue to grow in non-reperfused patients beyond 24 hours mostly in the setting of borderline and late-failing collaterals, (2) avoids issue of transient post-reperfusion DWI reversal; (3) new events may occur to patients obscuring an early outcome; (4) variability in the evolution of atrophy and measurement of atrophy make late outcome(Infarct volume) determination problematic

b. Imaging modality
    i. MRI volume
    ii. NCCT volume
    iii. NCCT ASPECTS

c. Confounders: (**Yoo**)
    i. Cerebral edema
    ii. Hemorrhagic conversion
    iii. “Fogging” (on CT)
    iv. Hemicraniectomy
    v. Leukoariosis/Senile volume loss
    vi. Atrophy

3) **Methodology for establishing final infarct volume/size as a biomarker** (note: the methodology may be different depending on the population and treatment of interest: IV rtPA, IAT, neuroprotection)

a. Datasets
b. Outcomes used as reference standards for validation
    i. Dichotomized 90-day mRS (0-1, 0-2, 0-3)
    ii. Ordinal 90-day Mrs
    iii. Early NIHSS change?
c. Comparators (e.g., revascularization, intermediate clinical endpoints)

d. Statistical analysis
    i. Thresholds for validation
        1. ROC
        2. Correlation
    ii. Establish interobserver reliability
    iii. Automated infarct volume quantification: Standardization of the different imaging softwares **(Majoie et al.)**
e. Determination of FIV endpoints (MCID) for trials (**Menon**)

4) **Future directions** (**Hill**)
    a. Final infarct volume vs. Infarct growth: Latter removes the influence of baseline infarct size which is non-modifiable; however, it is limited by less accurate detection of baseline infarct core volumes on NCCT and CTP.
    b. Eloquence weighting: More clinically relevant but a random phenomenon (i.e., not procedure-related). May be better as a prognostic biomarker rather than a therapeutic biomarker.
    c. Combined final infarct volume + early clinical scales