

MEDCAC Meeting: September 22, 2021
Health Outcomes in Cerebrovascular Disease Treatment Studies

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1. How confident are you that each of the following are standalone, meaningful primary health outcomes in research studies of cerebrovascular disease treatment technologies:
 - a. Major disabling stroke: defined as stroke in the treated vascular territory that results in a Modified Rankin Scale (mRS) ≥ 3 ;
 - b. Decrease in mRS of ≥ 2 points compared to baseline;
 - c. mRS of ≤ 2 or equal to pre-stroke mRS (if the pre-stroke mRS was > 2);
 - d. Other kinds of stroke, such as major ipsilateral stroke or morbid stroke.

Discussion:

- e. For each health outcome with greater than or equal to intermediate confidence (≥ 2.5), please discuss the appropriate length of follow-up post intervention for assessing this outcome;
- f. For each health outcome with greater than or equal to intermediate confidence (≥ 2.5), please discuss the appropriate cutoff points of mRS and NIHSS for assessing this outcome;
- g. Please discuss important considerations when using composite outcomes in research studies of cerebrovascular disease treatment technologies, which may include the combination of mortality, stroke, hospitalization/hospitalization equivalent events, and neurologic functional evaluations.

Response: We are not confident for Intracerebral Hemorrhage (ICH). EQ-5D should be utilized at 365 days. Outcomes are best measured at 365 days or possibly 180 days. mRS > 4 is a threshold that best correlates with living at home. Decreased mortality is important to most ICH patients and their families.

2. How confident are you that each of the following are standalone, meaningful primary health outcomes in research studies of cerebrovascular disease treatment technologies:
 - a. Hospitalization length of stay for index procedure;
 - b. Number of unscheduled re-admissions that are related to cerebrovascular disease;
 - c. Discharge disposition to rehabilitation (home vs. inpatient facility).

Discussion:

- d. For each health outcome with greater than or equal to intermediate confidence (≥ 2.5), please discuss the appropriate length of follow-up post intervention for assessing this outcome (applies to "b." only);
- e. Please discuss important considerations when assessing the merits of composite outcomes in research studies of cerebrovascular disease treatment technologies, which include the combination of mortality, stroke, healthcare resource utilization for index procedure, post-procedure and re-hospitalizations, and neurologic functional evaluation.

Response: For ICH, we are confident in 2c, but not a or b. Return to home and independence in the home are important outcomes as identified by survivors in ICH.

3. How confident are you that each of the following functional assessments are standalone, meaningful primary health outcome measures in clinical research studies of cerebrovascular disease treatment technologies:
 - a. The Modified Rankin Scale (mRS);
 - b. The National Institutes of Health Stroke Scale (NIHSS).

Discussion:

- c. For each health outcome with greater than or equal to intermediate confidence (≥ 2.5), please discuss the appropriate length of follow-up post intervention for assessing this outcome;
- d. For each health outcome with greater than or equal to intermediate confidence (≥ 2.5), please discuss the appropriate cutoff points for assessing this outcome;
- e. Please discuss important considerations when assessing the merits of composite outcomes in research studies of cerebrovascular disease treatment technologies, which include the combination of mortality, stroke, hospitalization/ hospitalization equivalent events, and neurologic functional evaluation;
- f. Are there any other functional assessments (e.g. the Barthel Index (BI), the Fugl-Meyer (FM) Upper and Lower Extremity scales) that we have not discussed whose use you believe would result in important information pertaining to meaningful primary health outcomes in clinical research studies of cerebrovascular disease treatment technologies?

Response: For ICH, mRS is best coupled with EQ-5D. Barthel index is useful for mRS 3,4,5 subjects.

4. How confident are you that using EQ-5D to measure quality of life:
 - a. Is adequate measure which reflects the patient experience in the context of cerebrovascular disease studies;
 - b. Should be included as standalone, meaningful primary health outcome measure in research studies;
 - c. Should be included as part of a composite, meaningful primary health outcome measure in research studies;
 - d. Should be included as secondary health outcome measure in research studies.

Discussion:

- e. Please discuss whether additional patient-reported measurement [e.g., Short Form-36 (SF-36), Stroke Impact Scale-16 (SIS-16)] should be considered to capture quality of life and burdens associated with the cerebrovascular disease treatment under study;
- f. Please discuss the minimal clinically important differences (MCIDs) for the instruments;
- g. Please discuss the appropriate length of follow-up post intervention for assessing patient-reported measurements.

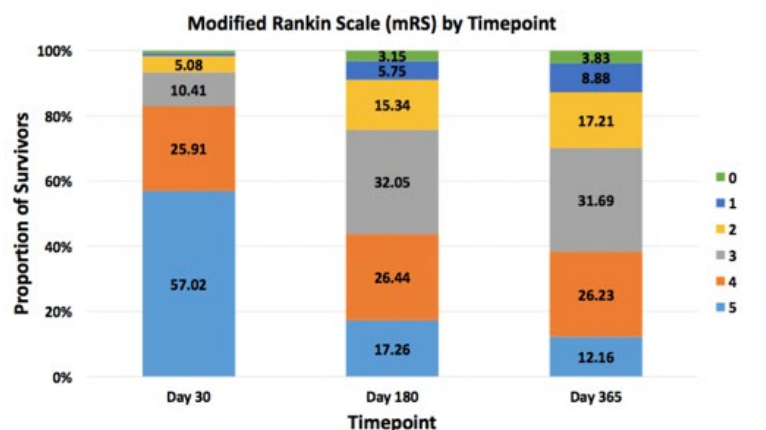
Response: We believe 4b is correct. We do not have SF-36 data. However, our Stroke Impact Scale data is similar to SF-36, but stroke specific. It correlates quite well with EQ-VAS, a component of EQ-5D. This data is best assessed at 180 and 365 days. However, it is simpler to assess EQ-VAS.

Overall Response:

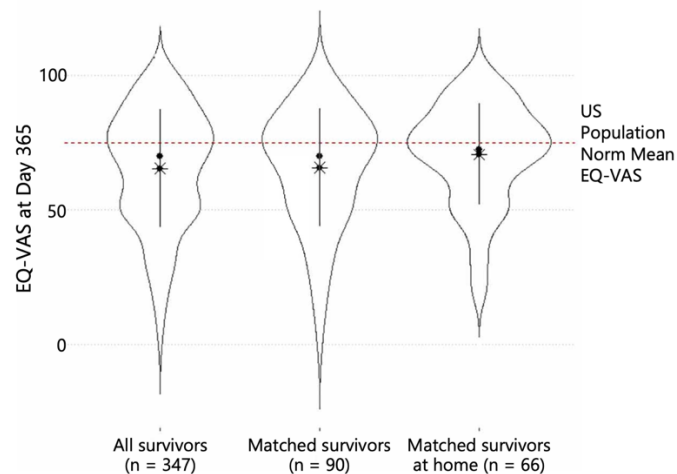
Intracerebral hemorrhage (ICH), a devastating subtype of stroke, accounts for an estimated 30% of all stroke-related deaths and leads to catastrophic disability among survivors each year.^{1,2} Despite advances in care, approximately 50% of patients with ICH die within 30 days and only 20% of ICH survivors are expected to have a full functional recovery at 6 months.^{2,3} The course of recovery in ICH is prolonged and unpredictable, resulting in considerable challenges in estimating a long-term meaningful outcome in regards to functional recovery and health-related quality of life (HRQoL).⁴ Consequently, prognostication following devastating brain injury has been recently identified as an area of critical importance in ICH.^{4,5}

Important components of prognostication for patients with ICH involve the perception(s) of severity of disease on outcomes and the use prognostication models. However, current prognostication models for ICH and other forms of devastating brain injury is limited mostly to functional disability and does not generally involve HRQoL domains.⁴ While professionally determined functional outcomes are commonly used as the primary endpoints of therapeutic interventions for stroke and other forms of brain injury, current prognostication addresses the question of whether or not the patient will recover to the extent of being able to function independently again.⁴ Functional outcome alone ignores a person's ability to adjust to a new life of disability, and fails to account for the dynamic process involved in a person's capacity to reframe their values and perceptions of quality of life in a new health state.^{4,6,7} Thus, an observer's measure of functional outcome does not capture the complex nature of a person's self-reported HRQoL in a new state of disability. Such discrepancies between functional outcome and HRQoL have been described in patients with ischemic stroke.^{8,9}

To evaluate the long-term functional outcome of ICH survivors (N=732) over time, we evaluated data from the phase 3 Clot Lysis: Evaluating Accelerated Resolution of Intraventricular Hemorrhage (CLEAR III) and Minimally Invasive Surgery Plus Alteplase in Intracerebral Hemorrhage Evacuation (MISTIE III) trials. The figure below shows the proportion of ICH survivors by mRS and timepoint. At day 30, 14.5% of ICH survivors had a mRS of ≤ 3 , while 82.9% of survivors had a mRS of 4-5. At day 180, 56.3% of ICH survivors had a mRS of ≤ 3 and 43.7% of survivors had a mRS of 4-5. At day 365, 61.6% of ICH survivors had a mRS of ≤ 3 , while 38.4% of survivors had a mRS of 4-5.



Using longitudinal one-year data from the MISTIE III trial, we performed a matched cohort analysis with a modified severity index to compare Intracerebral Hemorrhage (ICH) survivors to patients who had withdrawal of life-sustaining treatment (WLST) after the first 72 hours. Patient disposition and EQ-5D visual analog scale (EQ-VAS) of matched survivors were evaluated at days 30, 180, and 365. The mean EQ-VAS at day 365 was compared to the mean EQ-VAS US population norm for persons aged 45–75. Of 379 survivors at one year, 90 were matched to patients who had WLST (n = 61). Of the 90 matched survivors, 11.1%, 65.6%, and 73.3% returned home by days 30, 180, and 365. The mean (SD) EQ-VAS of matched survivors at days 30, 180, and 365 was 41.9 (24), 62.2 (20.8), and 65.6 (21.8). At day 365, matched survivors living at home (n = 66) had mean (SD) EQ-VAS of 70.6 (18.9) as compared to the mean EQ-VAS US population norm of 74.9. The figure below displays a Violin plot of mean EQ-VAS distribution at day 365 for all survivors, matched survivors, and matched survivors living at home. The mean EQ-VAS of matched survivors and matched survivors living at home at day 365 approach the mean EQ-VAS US population norm for age-matched persons.



Our data suggest that patients with ICH demonstrate improvement in functional recovery and HRQoL over time. The majority of ICH survivors that had comparable baseline demographic and clinical characteristics to patients who had withdrawal of life-sustaining treatment returned home by one year. The EQ-VAS of matched survivors, specifically those living at home at one year, approached the EQ-VAS US population norm for age-matched persons. Our results indicate that early prognostication of pessimistic outcomes, for both functional recovery and quality of life, do not appear to match the potential for acceptable outcomes. To understand the recovery trajectory of patients with ICH, functional outcome in conjunction with patient-reported HRQoL, should be measured at 365 days or possibly 180 days in ICH treatment trials. The evaluation of HRQoL, in addition to traditional functional recovery measures, has the potential to mitigate the discrepancy between observed outcomes and patient-generated outcomes and improve resources for neurorehabilitation and reintegration into society for patients with ICH.¹⁰

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