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August 23, 2021

Peter Bach, MD, MAPP
Chair

Medicare Evidence Development & Coverage Advisory Committee
Centers for Medicare and Medicaid Services
7500 Security Boulevard
Baltimore, MD 21244

RE: MEDCAC Panel on Health Outcomes in Cerebrovascular
Disease Treatment Studies

Dear Dr. Bach and Panel Members:

On behalf of the American Stroke Association (ASA) division of the American Heart Association (AHA) and our Stroke Council volunteers, thank you for the opportunity to submit comments on the questions posed to the panel about the health outcomes that should be of interest to CMS in studies for cerebrovascular disease treatment. We asked a number of our leading Stroke Council professional members to respond to MEDCAC's questions and have summarized their comments below. Please note that a number of different perspectives are represented in commenting about the appropriateness and utility of different outcome measures, including statistical, clinical, patient, caregiver, health system and public health perspectives, among others. All of these are important and may have differential weighting or meaning depending on the question being addressed.

Please see our compiled responses below.

Question 1 – Modified Rankin Scale (mRS) as a Meaningful Primary Outcome

- a. Major disabling stroke: defined as stroke in the treated vascular territory that results in a Modified Rankin Scale (mRS) ≥ 3

On average, our reviewer experts have intermediate confidence in mRS as a meaningful primary health outcome for major disabling stroke. We note, however, that there was considerable

variation among our reviewers in their confidence in mRS ≥ 3 for major disabling stroke. Reviewers who had low confidence in the mRS pointed out that this score does not take into account baseline (pre-stroke) mRS and also that the ≥ 3 outcome may miss a treatment that avoids non-disabling or somewhat disabling strokes. The ≥ 3 outcome would be appropriate if evaluating a treatment for a patient population limited to severe strokes, such as delayed treatment of large core infarcts or surgery for large intracerebral hemorrhage. In addition, many trials have now begun to consider a shift of the mRS along its full continuum as more meaningful than a binary outcome, and others have used a utility-adjusted mRS as a more comprehensive, nuanced, and patient-oriented outcome, since it accounts for the fact that the spectrum of mRS scores are not truly linear in patients' perceptions.

Other reviewers had high confidence in mRS ≥ 3 as an outcome indicator for major disabling stroke. As one reviewer said, "A disability which renders a person totally dependent on others by definition is a major disabling stroke." These reviewers pointed out that the length of time and type of therapy are important factors when answering this question. These reviewers felt that mRS at 90 days after stroke onset is typically used for acute therapies, but a more longitudinal follow-up is needed to assess for long-term effects, especially if the technology in question is intended to be a restorative therapy. One reviewer recommended that an mRS of >4 would be a preferred definition of major disabling stroke because they feel independent gait is over-weighted in the mRS schema.

b. Decrease in mRS of ≥ 2 points compared to baseline

Our reviewers also had intermediate confidence in the decrease in mRS of ≥ 2 relative to baseline as a meaningful primary outcome measure. However, variations in confidence for this measure may depend in some or large part on how the question was interpreted (i.e., what was meant by baseline and the direction of the change in score). For instance, does baseline refer to the pre-stroke mRS, or to the perceived mRS at time of the stroke? Attributing an mRS at the time of the stroke does not make sense since the mRS refers to the patient's ability to function in their normal social role, which by definition is abnormal at the time of hospitalization. Does the decrease in points refer to a decline in function (a higher mRS) or score (greater function)?

Reviewers made the following comments:

- There is theoretical rationale in comparing the post-stroke mRS to a baseline score, but the reliability of premorbid mRS measurement is marginal at best.

- I think you mean a change or increase in mRS of > 2 points compared to baseline. A change in mRS from baseline would be appropriate if patients were included with baseline disability (e.g. mRS > 2).
- This is preferred over an absolute mRS as it takes baseline functioning into account. A 90-day outcome is acceptable, but again demonstrating durability of treatment effect with 1-year outcomes is desirable.
- A good outcome can be defined by an improvement of 2 points or more on mRS disability score. However, this is limited by the degree of comorbidities a patient may possess.

c. mRS of ≤ 2 or equal to pre-stroke mRS (if the pre-stroke mRS was > 2)

See 1e below for comment on the length of follow up for this measure.

d. Other kinds of stroke, such as major ipsilateral stroke or morbid stroke

No comment.

e. Appropriate length of follow-up post intervention for assessing this outcome

In general, 90 days was felt to be an appropriate length of follow up for each of the first 3 measures. As noted above, a longer (i.e. one-year) follow up may be appropriate for some technologies or therapies.

For comparing groups, a 1-month mRS could be used for outcomes a, b, or c, but the result for each group would not be an accurate reflection of long-term outcomes. In other words, one might be able to say treatment x was better than y, but one would not know how good the eventual outcomes would be in group x. With respect to 1c, 1-month mRS could be used, but since good outcomes are being compared, it may take longer for patients to recover to this level.

We note that discharge mRS really does not make sense as a measure, since mRS refers to the patient's ability to function in social roles (job, family care etc.). No one is doing these things at time of discharge from hospital; they haven't had chance to reintegrate into their role. mRS is not the same as assessing activities of daily living.

f. Appropriate cutoff points of mRS and NIHSS for assessing these outcomes

For proposed outcome 1b, a worsening of 2 or more points is reasonable but depends on the transition. For instance, a 1-point change from mRS of 3 to 4 or from 4 to 5 would be very important to a patient compared to a

change from mRS 0 to 1 or 5 to 6, and probably comparable to a 2-point change from 0-2 or 4-6. One way to address this could be to convert each patient's mRS to a utility value that "weights the transitions of the mRS based on patient preferences and could be averaged."

For proposed 1c, a mRS of 0 or 1 for treatments begun very early would be preferable where there is an opportunity for "cure". While the numbers of patients achieving this outcome is smaller, it would be a powerful way of detecting the effect of early treatment, as proven in the trials of early thrombolysis. A 30 percent improvement in total NIHSS from baseline to 24 hours or hospital discharge or similar measures of early NIHSS improvement are also sensitive to early reperfusion therapies and can detect treatment group differences. However, change in NIHSS has not been used or validated for detecting differences in treatment effect for severe strokes or ICH.

Considerations when using composite outcomes.

Reviewers highlighted a number of important considerations for developing and using composite outcomes:

- Clinical interpretability of composite outcomes is important to allow clinical providers to understand the effect of treatment on their patients.
- A big advantage of using composite outcome is statistical efficiency. However, the treatment effect can be diluted if any one of the individual measures included in the composite is not affected by the treatment or is not sensitive to change. At worst, the effect of intervention on individual components could be contradictory. Preliminary data, therefore, are critically important when selecting outcome measures.
- Likewise, the severity of the components of a composite outcome should be similar – not lumping minor and major effects.
- Individual measures included in the composite outcome may have different degrees of importance to patients (for example, length of stay vs mortality) and treating them as equivalent is suboptimal. Weighting using patient input may be an option but adds significant complexity and potentially reduces clinical interpretability.
- Protocols should be in place to deal with instances where individual outcomes comprising the composite can lead to "double-counting" (such as hospital admission and recurrent stroke) or occurrence of an individual outcome precludes the occurrence of other outcomes in the composite (such as mortality vs hospitalization).

- One potential use of composite outcomes is to evaluate the simultaneous effects of a technology on multiple, predefined outcome measures that provide alternative approaches to measuring same or similar phenomena. For example, this type of analysis was used in the second part of the NINDS tPA trial and evaluated treatment effects on four outcome measures: the mRS, the Barthel Index, the Glasgow Outcome Scale, and the NIHSS. Although each individual outcome measure demonstrated a significant difference, the global test showed the most robust treatment difference between tPA and placebo patients. Careful consideration should be given to using a global test of composite outcomes as the primary outcome measure with individual decisions about what specific outcome measures should be included to assess the intended effects of a specific technology.

Question 2 – Hospitalization Length of Stay, Re-admissions, and Discharge Disposition as Meaningful Primary Outcome Measures

a. Hospitalization length of stay for index procedure

Our reviewers were in agreement in having low confidence (with an average confidence score of 1.75) in hospital length of stay as a meaningful primary outcome measure. Reviewers felt there were too many confounding factors at both the patient and hospital levels to make this a reliable measure for evaluating the effectiveness of a stroke intervention. For example, patient socioeconomic factors, insurance status, comorbidities, and family support may all have an impact on a patient's hospital length of stay. Similarly, hospital or system-level variables, such as availability of case management support, strength of discharge planning, or availability of rehab beds, may all impact length of stay in a manner not necessarily reflective of a patient's state of health.

b. Number of unscheduled re-admissions that are related to cerebrovascular disease

Our reviewers generally had low confidence in unscheduled re-admissions related to cerebrovascular disease as a meaningful primary outcome measure (average confidence level of 1.6). Here again, the reviewers felt that other factors unrelated to the effectiveness of a treatment can impact this measure. For example, certain etiologies of stroke have a natural history of higher risk of recurrence than others. Conversely, stroke or TIA recurrence that does not lead to re-admission may be missed. In addition, patient factors, such as social determinants of health, medication adherence, and others may also impact re-admissions

c. Discharge disposition to rehabilitation (home vs. inpatient facility)

Our reviewers have relatively low confidence (average score of 2.3) in discharge disposition to rehabilitation as a primary outcome measure. Our reviewers felt that, although there is a correlation between discharge disposition and functional status at 3 months, this measure is also confounded by variables unrelated to stroke outcome or treatment technologies. For example, discharge to home versus an inpatient facility can be affected by resource (bed) availability, socioeconomic factors (insurance coverage), caregiver availability, and patient or family preference.

Discharge disposition is perhaps best viewed as a surrogate measure for functional status at 3 months in studies where direct assessment of functional status is not possible.

One reviewer suggested that, rather than discharge disposition, place of residence or "home-time" over 1 year would be a more meaningful outcome.

d. Appropriate length of follow-up post intervention

Several reviewers argue for an ideal follow up time of one year after the index stroke for a measurement of health care utilization or home time. Inpatient rehabilitation and skilled nursing facility stays may be long, so six months should be the minimum length.

e. Considerations when assessing the merits of composite outcomes, which include the combination of mortality, stroke, healthcare resource utilization for index procedure, post-procedure and re-hospitalizations, and neurologic functional evaluation

This question has the same limitation expressed above in 1g. Cerebrovascular diseases are a heterogeneous group of disorders that affect individuals of different ages, have different degrees of severity, and exhibit natural histories with non-homogeneous course and risk of recurrence. As such, consideration for composite outcomes should be based on condition-specific characteristics including considerations of the peculiar natural history of each condition, degree of premorbid function, magnitude of acute damage produced by the disease, and comorbidities.

Health care utilization could be a good addition to a composite outcome but it would be best to include total health care utilization and not just a single measure such as length of stay, re-admission, or discharge destination. As explained above, single care process measures such as length of stay, re-admission, or discharge disposition are influenced by a number of heterogeneous determinants.

Question 3 – Functional Assessments as Meaningful Primary Outcome Measures

a. The Modified Rankin Scale (mRS)

Overall, our reviewers have relatively high confidence in the mRS, with an average score of 4.2. Our reviewers noted that there are some significant, well-known limitations of using mRS as a sole outcome measure in clinical trials (it's heavily weighted towards mobility, can be substantial interobserver variability in scoring, and ability to detect meaningful change and differences in outcomes among treatment groups is limited). Nevertheless, alternate options have limitations that are equally problematic. Because of this, inclusion of relevant secondary outcomes or the use of composite outcome that includes a measure of health status are important to understand the impact of intervention on patients with stroke

b. The National Institutes of Health Stroke Scale (NIHSS)

Reviewers were also relatively confident in the use of the NIHSS assessment as a meaningful primary outcome measure, with an average score of 4.0. One reviewer noted that, although reporting the final score is useful, perhaps more useful is reporting the mean and median for each NIHSS parameter for each stroke classification. Another reviewer stated that the 90-day change in NIHSS (relative to pre-stroke) is a good granular outcome measure.

The NIHSS, which is a marker for stroke severity, is primarily of use as an inclusion criterion for acute stroke studies and to detect improvement or deterioration compared to baseline. Because the NIHSS has a ceiling effect and does not adequately capture outcomes most relevant to patients with stroke (such as mortality and functional outcomes), it is not an appropriate primary outcome in most clinical trials of acute stroke interventions.

c. Appropriate length of follow-up post intervention for assessing this outcome

Our volunteers noted that the mRS is a better longer-term outcome measure, while NIHSS is best used as a short-term measure. As noted above, reviewers felt that mRS follow up should be 90 days. Longer follow up (e.g. 1 year) can be used to evaluate durability, and a mRS of <3 should constitute a good outcome after severe stroke.

If NIHSS is used as an outcome, the timeframe should be short (24-48 hours after the stroke intervention).

d. Appropriate cutoff points for assessing these outcomes

Multiple reviewers recommend use of shift analysis of the mRS scale, which can assess transition across levels of the scale rather than differences across a dichotomy. In using the mRS, the ordinal "shift" analysis seems most sensitive.

Sometimes the requirements for shift analysis are not met by the distribution of the data, in which case a categorical analysis is the default. In this case, the reviewers expressed that the cutoff or threshold would be based on the severity of the patient population enrolled in the trial, as well as what the investigator thinks the treatment will accomplish, and the existence of baseline disability. For acute reperfusion therapy in non-disabled patients, the best threshold would be a mRS of 0 or 1; for later treatment 0-2. For patients with severe strokes or ICH, the cut point would be 0-3.

As introduced above in 1f, one reviewer recommends use of utility weighted (uw) mRS—i.e. the mean uw-mRS in each group. A difference between groups in mean uw-mRS of 0.03 or more is clinically meaningful; a difference of 0.06 is substantial; the difference between tPA and placebo within 3 hours is about 0.09.

For the NIHSS, a 30 percent improvement in the baseline NIHSS to 24 hours correlates well with improved mRS outcomes in reperfusion studies. Similar results have been seen with either an 8-point improvement from baseline or a total score of 0 or 1.

e. Important considerations when assessing the merits of composite outcomes, which include the combination of mortality, stroke, hospitalization/ hospitalization equivalent events, and neurologic functional evaluation

See the responses to question 1g above. Cerebrovascular diseases are a heterogeneous group of disorders that affect individuals of different ages, have different degrees of severity, and exhibit natural histories with non-homogeneous course and risk of recurrence. As such, consideration for composite outcomes should be based on condition-specific characteristics including considerations of the peculiar natural history of each condition, degree of premorbid function, magnitude of acute damage produced by the disease, and comorbidities.

f. Other functional assessments (e.g. the Barthel Index (BI), the Fugl-Meyer (FM) Upper and Lower Extremity scales) not discussed

With respect to the Fugl-Meyer Upper and Lower Extremity scales, our reviewers generally agreed that they would be useful as primary outcomes specifically for intervention trials targeting motor function for patients with chronic stroke. Both of the scales have been validated as best evidence instruments, used extensively in rehabilitation research, and have the added benefits of being easy to learn and feasible to use in large studies.

There was less consensus about the utility of the Barthel Index (BI). Some reviewers support its use as a secondary functional measure in studies of stroke treatment or as part of a “global statistic” as in the NINDS tPA trial. It can be performed via the phone and provides information about activities of daily living that can be helpful to researchers. However, other reviewers felt that it’s less useful because it has a significant ceiling effect except in the most severe stroke patients.

Additionally, one reviewer commented that the following tests assess more specific outcome measures and may be appropriate for selected studies of technology treatments of stroke (such as rehabilitation interventions) that are expected to have a narrower effect on outcomes:

1. Walking Speed, which assesses locomotion and has demonstrated validity, reliability, and is responsive to change.
2. Additional scales with psychometric support that may be reasonable to include as a primary or secondary outcome depending on the specific study intervention and study context include the Wolf Motor Function Test, the Action Research Arm Test, the Ten-Meter Walk Test, the Six-Minute Walk Test, the Stroke Impact Scale (SIS) and SIS-16. (Circ Cardiovasc Qual Outcomes. 2015;8:S163-S169).

Question 4 – Using EQ-5D to Measure Quality of Life

a. Adequacy of measure in reflecting the patient experience

On average, our reviewers had intermediate confidence in the use of the EQ-5D instrument in the area of stroke, with average scoring of 3.25. However, there was significant variation in opinion on this question among our reviewers.

Reviewers who have more confidence in the EQ-5D feel that the long version in particular does a good job of assessing quality of life and has among its benefits that it is easy to use, can be used via phone or in-person, and is available in multiple languages.

Reviewers who have less confidence in the EQ-5D expressed concern that it is not commonly used in the area of stroke and has not been broadly

validated for use with cerebrovascular disorders. They also express concern that it includes factors that may be unrelated to the stroke and the value of treatment interventions and instead are more subjective than standard functional factors, such as those captured in the Barthel.

b. Inclusion as standalone, meaningful primary health outcome measure in research studies

Even among those who had higher confidence in the EQ-5D as a measure reflecting patient experience, our reviewers were less confident in its use as a standalone outcome measure, garnering an average confidence score of 2.3. Reviewers generally felt that it has not been used enough in stroke studies to be able to make an adequate judgment of its utility as a standalone measure.

The lack of validated assessment tools to determine baseline patient-reported health is a limiting factor when using patient-reported outcomes in clinical trials of treatment interventions in acute stroke. The heterogeneity in patients' perceived health at baseline will reduce power to detect treatment effects, and adjustment for these baseline differences is difficult. However, the primary goal of most health care interventions is to improve patient well-being, which is best assessed through patient self-report. Because of this, the AHA/ASA has long advocated for the inclusion of patient-reported health status in clinical research (Circulation. 2013;127:2233-2249).

c. Inclusion as part of a composite health outcome measure

In general, reviewers were supportive of including quality of life measures in a composite outcome measure in many stroke studies and had moderate confidence (average score of 3.6) in the inclusion of the EQ-5D specifically as part of a composite primary outcome measure.

The reviewers feel that quality of life measures are needed to assess quality-adjusted life years and cost effectiveness, which should be included in assessments of new technologies. Several reviewers expressed that quality of life has not been included appropriately as an important research measure and is overdue for inclusion as a composite or secondary outcome measure in stroke studies.

d. Inclusion as secondary health outcome measure

Our reviewers have slightly more confidence in the inclusion of the EQ-5D assessment as a secondary health outcome measure, giving it an average score of 3.7 for this purpose. Some reviewers expressed that its use may depend on the type of study.

- e. Consideration of additional patient-reported measurement [e.g., Short Form-36 (SF-36), Stroke Impact Scale-16 (SIS-16)] to capture quality of life and burdens associated with cerebrovascular disease treatment

We received a variety of viewpoints from our volunteers on this question. Some reviewers felt that the SF-36 and SIS-16 are valuable tools that should be included. Others felt that these tools don't offer an advantage over the EQ-5D. More specifically, reviewers commented:

- The SIS-16 measures the physical domains of functional status and thus serves as a disability measure rather than a quality of life measure.
- SIS-16 is limited by measuring only physical domains of functional status.
- The SIS-16 is a well-known psychometrically robust measure that is appropriate for inclusion in clinical trials; however, the PROMIS Physical Function has recently been demonstrated to provide more efficient assessment of the patient-reported physical function with less ceiling effects. See more about the PROMIS Physical Function below (Neurology 2016;86:1801–1807).
- The Stroke-Specific Health related quality of life (SS-QOL) or Stroke Impact Scale (SIS) have been validated in the stroke population to measure health-related quality of life after stroke. As compared to the Barthel Index, the SIS-16 contains more difficult items that can differentiate patients with less severe limitations and therefore has less pronounced ceiling effects. SIS-16 scores were significantly different across Rankin levels 0 to 1, 2, 3, 4, and 5, whereas BI was significantly different only across Rankin levels 0 to 2, 3, 4, and 5.
- The SF-36 is a reasonable tool and there is experience with SF-36 in stroke. The physical function component does not cover severe strokes as well as the SIS-16. In addition, the SF-36 is longer and more difficult to use and the proprietary nature of the tool makes it less appealing than some of the newer tools, which are likely to replace SF-36 in many situations in the future.
- Alternatively, another reviewer favors the SF-36 over the EQ-5D because the SF-36 queries more thoroughly about the impact of various limitations on a person's actual functioning in society. This reviewer doesn't favor using the SIS-16 because it poorly measures problems experienced by high-functioning stroke survivors and people with cognitive occupations. If choosing between EQ-5D, SF-36, and SIS-16 for a single secondary measure in a stroke treatment study, this reviewer would recommend the SF-36. In general, the

ideal secondary outcome for an individual treatment trial should reflect whether the intervention is intended to provide narrow benefit (e.g. specifically on disability or mental health) or a holistic benefit (in which case a score with more heterogeneous components included is preferred).

- The PROMIS Global Health should be considered as a potential outcome for future trials. This 10-item scale is recommended as an outcome measure for stroke by the International Consortium for Health Outcomes Measurement as it captures domains felt to be relevant for patients with stroke (Stroke 2016;47(1):180-186). Data on its psychometric properties in stroke are available. Because of the minimal experience with the use of PROMIS GH in clinical trials of patients with stroke, it may be most appropriate to include this scale initially as an exploratory outcome then as secondary outcome or part of a composite outcome measure.
- PROMIS Physical Function (PF) - The efficiency of assessment using computer adaptive testing (CAT) is appealing. One can obtain good precision on this metric typically with 4-5 questions. In addition, because of the large number of items in the item bank, there is less ceiling and floor effects. Similar to PROMIS GH, data on its use in clinical trials is limited; including the PROMIS PF CAT in an exploratory aim of clinical trials may be helpful to better understand the distribution of responses and association with other variables to inform its potential use in future trials.

f. Minimal clinically important differences (MCIDs) for the instruments

The approach to MCID in patient-reported outcome measures is evolving and an area of active discussion. The MCID values likely depend in part on patient severity and ranges quoted in literature vary. In general, though, our reviewers cited a MCID range for EQ-5D of between 0.03 to 0.54, with 0.1 cited as a specific typically valid difference.

For PROMIS tools, including PROMIS GH summary scores and PROMIS PF, conservative estimate of MCID at a group level is 5 points, although there are some instances (mild deficits) where a smaller MCID of 3 or 4 points is likely sufficient.

For SIS-16, a MCID range of 9-14 points has been reported. One reviewer recommended a difference of 10 points at minimum. The change scores an individual patient has to reach are 24.0, 17.3, 15.1, and 25.9 on the 4 subscales to indicate a true change (DOI: 10.1177/1545968309356295).

For SF-36 summary scores, reviewers cited a MCID range of 4-8 points. A reviewer commented that the MCID should be informed by the patient perspective for each trial because the MCID should reflect patients' minimum desired difference for which they are willing to incur the risk of a given intervention. Whether the physical or mental components should be combined or treated separately should be determined based on the nature and mechanism of the intervention.

g. Appropriate length of follow-up post intervention for assessing patient-reported measurements

There were a variety of viewpoints among our reviewers about the optimal length of post-intervention follow-up to assess patient-reported measures. It seems useful to factor in the risk and length of the intervention when determining the length of the outcome. For a low-risk, short-term intervention, shorter outcomes (e.g. 90 days) would be acceptable. For major high-risk or high burden interventions, a durable benefit extending for a longer time (6-12 months) would be preferable. Another reviewer commented that the standard time-point of 3 months seems reasonable for acute stroke trials. However, perhaps more than other outcomes, it would seem important for the assessment of patient-reported health to occur at a time beyond the acute period, so participants have a chance to fully understand the impact of stroke on their health status. Delaying the timing of outcome assessment beyond 90 days, however, has the added feasibility disadvantage in a clinical trial of loss to follow up.

Thank you again for the opportunity to comment on these questions. We look forward to continuing to work closely with you to advance research on and selection of cerebrovascular patient outcomes. If you have any questions about these comments, please feel free to contact Tyler Hoblitzell, AHA/ASA regulatory affairs manager, at Tyler.Hoblitzell@heart.org.

Sincerely,

A handwritten signature in black ink, appearing to read "Don Lloyd-Jones", with a stylized flourish extending to the right.

Donald M. Lloyd-Jones, MD, ScM, FAHA
President