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The utility of domain-specific endpoints in acute stroke trials

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Conflicts of Interest

Dr. Cramer has served as a consultant for Constant Therapeutics, MicroTransponder, Neurolutions, SanBio, Fujifilm Toyama Chemical Co., Medtronic, and TRCare. Dr. Saver co-created the Rankin Focused Assessment (RFA) while a University of California employee, and Dr. Saver, collaborators, and the University of California Regents have made the RFA freely and permanently available as a no-fee public resource under a Creative Commons, use-freely-with-attribution license. Dr. Saver also co-created a written vignette rater certification program for the RFA while a University of California employee. The written vignettes are an optional system for training and certifying raters in the use of the free RFA resource. The University of California Regents, along with Dr. Saver and collaborators, hold a copyright for the written vignette rater certification system. Any revenues received under that copyright are used to support the training of Vascular Neurology Fellows at UCLA. Dr. Wolf has served as a consultant for SAEBO, Inc., Motus Nova, MicroTransponder, and Fujifilm Toyama Chemical Co. Dr Lansberg has served as a consultant for Biogen, Nektar Therapeutics, and Roche/Genentech. Dr. Khatri's department has received funds for her efforts from Cerenovus (Investigator-Initiated Study), Nervive (NIH SBIR co-investigator), Lumosa (consultant), and Diamedica (Scientific Advisory Board). She has also received funds from Bayer (National Trial PI) and UpToDate, Inc. (royalties). Dr. Broderick's department received funds from Genentech for his role on steering committee of TIMELESS Trial, and from Ono Pharmaceuticals for consulting work. Dr. Lansberg reports consultancy for NuvOx Pharma. Dr. Smith reports other from MindRhythm, Inc

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Abstract

Domain-specific endpoints are assessments that correspond to the output of individual neural systems and are useful for capturing treatment effects on specific behaviors. By contrast, global endpoints combine several attributes into a single score and are useful for capturing broad treatment effects in a summary way. While global endpoints have become the de facto mechanism required to define benefit in stroke trials, they also have important limitations, some of which might be addressed by simultaneously measuring domain-specific endpoints. Substantial opportunity remains to identify quantifiable patient benefit that would otherwise not be captured by global endpoints. Potential advantages of incorporating domain-specific endpoints in acute stroke trials are discussed, such as increased granularity of measurement, improved understanding of how therapies affect the brain between acute treatment and day 90, and optimized therapeutic translation. Potential disadvantages are also considered, including time and cost of administering domain-specific endpoints, as well as statistical implications. Domain-specific endpoints and global endpoints are not mutually exclusive, and both capture clinical benefits to patients. Incorporating a broader set of outcome assessments in stroke trials, including both global and domain-specific endpoints, is warranted.

Indexing terms:

stroke; clinical trial; outcome assessment

Subject terms:

cerebrovascular disease

Introduction.

Acute stroke trials generally enroll patients within 24 hours after stroke onset, with the aim being to salvage threatened tissue, e.g., through reperfusion. Because large volumes of brain are often prevented from infarction, clinical benefits can be substantial when patients are assessed 90 days later. Acute stroke trials have generally relied on global endpoints to capture treatment efficacy.

Global endpoints can be defined as measures that combine several attributes into a single score, often with an emphasis on functional outcomes[1, 2]. The global endpoint most commonly used in acute stroke trials is the modified Rankin Scale (mRS) assessed at day-90, which has been the primary[3–8] or secondary[9] outcome measure in positive reperfusion trials. The mRS is often endorsed by the FDA as the primary endpoint for acute stroke trials[10] and is included with the definition of stroke disability co-developed by the

FDA[11]. The mRS is a 7-level functional outcome scale that ranges from no functional deficits (score of 0) to death (score of 6)[10].

Global endpoints are useful for capturing broad treatment effects in a summary way. For example, the parsimony, simplicity, and clinical relevance of mRS scoring have enabled measurement of treatment effects across numerous studies. However, global endpoints also have important limitations, as discussed below, and some of these might be addressed by simultaneously measuring domain-specific endpoints. While global endpoints have become the de facto mechanism required to define benefit in stroke trials, substantial opportunity remains to identify quantifiable patient benefit that would otherwise not be captured by global endpoints, particularly as novel concomitant therapies or expanded indications for treatment are evaluated.

Domain-specific endpoints, also known as modality-specific endpoints[12], are behavioral measures that correspond to the output of individual neural systems. The brain is composed of dozens of interconnected neural systems, each defined as a circuit of neurons that gives rise to a specific behavior[13]. For most neural systems, the behavioral output can thus be measured using a domain-specific measure, either once as a day-90 cross-sectional endpoint, or serially to capture stroke recovery; domain-general circuits support diverse processes[14] and are not further considered here. Examples of domain-specific endpoints appear in Table 1; more detailed lists appear elsewhere[15–18]. Abnormalities in domain-specific endpoints, such as hemiparesis and aphasia, are often useful for diagnosing acute stroke[19], but detailed assessment is not commonly performed. For many domain-specific endpoints, validity and reliability have been documented, sensitivity to change has been established, and the minimal clinically important difference has been defined. Domain-specific endpoints have been successfully used in neurological clinical trials outside of stroke (e.g., a common endpoint in multiple sclerosis trials is the MS Functional Composite, which measures gait via a 25-foot walk test, hand dexterity via the nine-hole peg test, and memory/attention via the paced auditory serial addition task) and in trials focused on stroke recovery therapeutics, but to date have been uncommon in acute stroke trials and in stroke prevention trials. Domain-specific endpoints have been the basis for FDA approval of neurological therapies, such as 4-aminopyridine, which was approved for walking ability in patients with multiple sclerosis[20, 21].

The use of domain-specific endpoints has several potential advantages for acute stroke trials in terms of understanding and measuring the recovery processes that occur between acute treatment and outcome assessment 90 days later:

1. Increased resolution of measurement.

The most commonly used global endpoints in acute stroke trials, such as the mRS or the Barthel Index, are ordinal scales with a limited number of scoring levels[10]. Fewer scoring levels means lower resolution and less biological information to detect smaller but still clinically meaningful changes. In addition, lower resolution scales sometimes increase the study's required sample size[22]. With continuous variables, there is the same difference across successive numerical intervals, for example, the difference in volume of cerebral infarction is precisely the same when going from 25 to 30 cc as compared to going from 55

to 60 cc. However, ordinal variables have intervals with marked differences between single steps across the range of the scale. For example, the step between mRS scores of 0 and 1 represents the clinical difference of no symptoms versus symptoms with no limitations, whereas the step between mRS scores of 5 (severely disabled) and 6 (death) is a large clinical difference. Because ordinal variables often treat interval values as homogenous, they are a comparatively weaker form of measurement as compared to continuous variables[23, 24]. This comparison is not universal: not all global endpoints are ordinal, although the one used most often in acute stroke trials[10] (mRS) is, and not all domain-specific endpoints are continuous, although even when they are not they tend to have a large number of intervals (Table 1).

Achieving finer resolution may increase the ability to detect smaller treatment-related benefits. This level of resolution might not be a priority when salvaging large volumes of brain, but could be important when evaluating a therapy for which benefits might be smaller, such as when (1) targeting specific subpopulations, as seen among the oldest old or patients treated with greater delay or patients with distal vessel occlusion; (2) trying to detect differences related to a variant treatment, such as higher number of catheter passes, different approaches to anesthesia, or tighter blood pressure control; or (3) examining the added value of a combination therapy, such as when comparing endovascular therapy (EVT) plus neuroprotection vs. EVT alone. Identifying small benefits may not be important if the differences detected are not clinically important.

Serial measurement of a domain-specific endpoint that has good resolution may be useful to understand which patient features (and their change over time) are most associated with a good treatment response, or to understand how an acute stroke therapy interacts with the processes of recovery. Scales with higher granularity might also be useful to identify the relative contributions that specific neural systems make towards improvement.

2. Greater insight into acute therapy effects on individual brain systems.

One approach to increasing measurement resolution is to assess the individual behavioral components that together constitute a global endpoint. Reperfusion therapies target clots and arteries to reverse ischemia in neural systems that support motor, sensory, coordination, cognitive, attention, vision, language, and other behaviors. Differences in infarct size and location determine which neural systems are injured and the severity of their involvement[25, 26]. Moreover, the *extent* and *rate* of recovery after stroke are not the same across these different neural systems[12]. For example, a patient might recover language function but not the ability to functionally use the hand. Neglect might resolve but the patient might remain fully hemianopic.

An effective acute stroke therapy improves recovery from treatment to the day-90 outcome. This enhanced recovery occurs variably in each of the neural systems involved by stroke, and so using domain-specific endpoints to measure recovery in key affected neural systems provides greater insight than using a single measure that collapses many neural systems' recovery into one global endpoint score. Because a global scale such as the NIHSS combines all of this neurologic information into a single score, it may be less sensitive and provide weaker insights compare to domain-specific endpoints that capture behavioral

recovery related to affected neural systems. For example, the overall NIHSS would be a comparatively weaker choice of endpoint than one or more domain-specific endpoints in a thrombectomy trial targeting patients with acute posterior cerebral artery occlusion because much of the NIHSS does not measure loss of function likely to occur when tissue is salvaged within the visual, memory, and sensory systems subserved by this artery. Using domain-specific endpoints to measure therapeutic effects on the individual neural systems involved in each patient (Braun R, Heitsch L, Cole J, Lindgren A, de Havenon A, Cramer S, and Worrall B, unpublished data, 2020) might also bolster personalized medicine approaches to care.

3. Foster a common language across all stroke trials.

Inclusion of domain-specific endpoints in acute stroke trials is rare[27]. Similarly, in trials of stroke recovery therapeutics, inclusion of the mRS is uncommon, although doing so has recently been recommended[18]. Adoption of a common language across different stages of stroke therapeutic investigations can enable a more cohesive system for understanding the benefit of stroke therapeutics, from the acute phase through recovery to the chronic phase[28], and extending to stroke prevention. Achieving this goal might require revision of educational goals in acute stroke, stroke recovery, and stroke prevention training programs. There are many domain-specific endpoints that might be used. Choosing among these can be based on expert consensus[18], available common data elements[29], matching preclinical endpoints[22], or relevance to underlying treatment mechanisms[30].

4. Better understanding of treatment mechanism.

Domain-specific endpoints can provide mechanistic insights into what is changing in the brain with treatment. Such endpoints can improve treatment-related insights into clinical-imaging relationships[31, 32]. For example, when trying to understand the impact of endovascular therapy targeting eloquent cortex, a language measure, such as naming, might be more sensitive to treatment effects than a global measure[33]. Many language-focused endpoints are available depending on the study's needs, ranging from the language subscore of the NIH Stroke Scale (quick but low granularity) to the Philadelphia Naming Test[34] (relatively brief with better granularity) to the bedside Western Aphasia Battery-Revised (longer with substantial granularity). Such insights enable the study of specific brain targets, modulation of which might provide further benefit[35]. The initial infarct and the pattern of resulting behavioral deficits vary tremendously across patients. Domain-specific endpoints enable an improved understanding of the relationship between specific cerebral pathologies and behavioral outcomes[36]. A related potential benefit is that domain-specific endpoints, whether measured serially from acute to chronic or just once in the chronic phase, can add information regarding the natural history of stroke and so allow for more informed planning for future trials.

5. Better understanding of what goes on in the brain from acute treatment to day-90.

Currently, many studies treat the time period between the acute intervention and the day-90 outcome as a black box, with little or no measurement of events or influences that might affect final status. However, many factors between acute stroke treatment and day-90 outcome scoring might influence patient outcomes[37], such as occupational therapy for arm

motor deficits or speech therapy for aphasia. Domain-specific endpoints therefore provide data that directly correspond to the output of neural systems targeted by standard-of-care interventions and so may provide useful insights into global outcomes. For example, intensive physical therapy enhances recovery of gait and balance after stroke[38]. If some patients in an acute stroke trial received intensive physical therapy and have superior improvement in gait, such knowledge could be used to better interpret how the experimental treatment affected a global outcome measure such as the mRS. Measuring stroke recovery, and its influences, through more frequent and more detailed assessments over a 90-day interval, can therefore provide insights useful for understanding the effects of an acute intervention. Furthermore, it may prove evident that domain-specific endpoints consistently demonstrate benefit sooner than 90 days. Such knowledge could inform trial design and reduce research costs.

6. Optimizing therapeutic translation.

Domain-specific endpoints may also be useful for optimizing T1 (from preclinical to initial human) translation by better matching preclinical measures with clinical trial endpoints[39]. Preclinical studies often evaluate the translational potential of a stroke therapy using domain-specific endpoints, especially those related to motor function, but acute stroke clinical trials often rely on global endpoints of function, such as the mRS[40, 41]. Inclusion of domain-specific endpoints could improve the clarity with which candidate acute stroke therapeutics are translated from animals to humans. For example, let's say that a preclinical study suggests efficacy based on motor testing in animals, but the human translational study fails to show a benefit using a global endpoint, such as the mRS. The question is whether the study was negative because (a) the treatment improved motor outcomes (as in preclinical studies) without affecting mRS or (b) the treatment simply did not improve motor outcomes[41]. In addition, mechanistic insights into how brain function and behavior are enhanced by reperfusion or neuroprotection therapies can inform therapy development as well as T2-T4 (efficacy trials, implementation investigations, and population studies) translation.

7. Support therapeutic targeting of individual neural systems acutely.

Several therapeutic developments suggest potential utility for understanding acute stroke therapies in relation to the specific neural system affected. Some acute therapies target specific penumbral areas, e.g., via brain stimulation[42, 43]. Endovascular therapy can in some instances preferentially target elegant or eloquent cortex[44], an approach that can be guided by weighting affected brain voxels according to the functional consequences of infarction[45]. For these approaches to acute stroke therapy, measuring the behavioral output of target neural system(s) using domain-specific endpoints, as compared to global endpoints, would likely improve detection of efficacy. For example, if an endovascular therapy targeted voxels in motor cortex and in corticospinal tract that meet mismatch criteria, a measure of motor behavior might provide greater insights into treatment effects than a global measure. A similar approach could be adopted for aphasia and neglect. Domain-specific measures, acquired at the time of enrollment, might also serve as stratifying variables[46].

In addition, certain recovery-based therapies that target individual neural systems are also initiated during the acute stroke admission–the unfolding of acute injury effects and the initiation of neural repair are intertwined[47]. As with acute reperfusion therapies, such recovery therapies introduced during the acute phase might also benefit from the information provided by domain-specific endpoints[36, 48–50].

8. Capture improved outcomes in additional, patient-centered dimensions.

Treatment-related gains in outcomes beyond the mRS might also be important. For example, a treatment that substantially reduced depression or increased gait endurance might be perceived as clinically important, independent of whether mRS scores showed a treatment-related difference[51]. This is particularly important for patients within the common mRS categories of 2 and 3, where there are very wide ranges of functional ability and quality of life within each score level. As an example, in the BETAS trial of growth factors administered 24 to 48 hours after onset of ischemic stroke[36], domain-specific measures provided improved resolution of treatment-related change over time, e.g., one patient had modest improvement in NIHSS score, going from a baseline score of 10 to a day-90 score of 5, but tremendous gains in arm motor status measured as a gain in Fugl-Meyer score of 40 points on this 66 point scale. In many cases these likely represent meaningful differences for patients, caregivers, society, and health care payers. Further direct comparisons are needed modeling domain-specific endpoints in relation to global endpoints.

Domain-specific measures can provide information deemed valuable from a number of perspectives. The World Health Organization International Classification of Function divides endpoints into three constructs: loss of body structure/function (previously referred to as *impairment*), activities limitations (previously *disability*), and participation restrictions (previously *handicap*). Global endpoints generally capture activities or participation. Domain-specific endpoints often capture impairment (e.g., the Fugl-Meyer score), but can also measure activities limitations (e.g., the Wolf Motor Function Test).

Analogous issues with neuroimaging endpoints in acute stroke trials.

The clinical reasoning described above can also be applied to neuroimaging endpoints. The imaging counterpart of the mRS is the final infarct volume, which has been used in phase I and phase II trials as a surrogate endpoint for clinical outcome[52, 53]. The final infarct volume fails to capture many clinically relevant aspects of stroke injury that can be assessed by domain-specific neuroimaging endpoints. Examples include atlas-based approaches that weigh the infarct volume by the eloquence of stroke-affected brain regions[54, 55], measurement of injury to specific neural systems[56, 57], and measures of connectivity within and between neural networks that have been correlated with stroke recovery[58, 59]. Domain-specific neuroimaging endpoints, as compared to total infarct volume, can increase resolution of measurement, provide greater insights into injury and function of individual neural systems, and help optimize translation from preclinical models to clinical trials[57, 60]. Many of the same benefits thus exist for domain-specific neuroimaging endpoints as those listed above for clinical endpoints.

Limitations and challenges.

While the above sections outline potential advantages of adding domain-specific endpoints to acute stroke trials, there are also potential limitations and challenges (Table 2). Some domain-specific endpoints have properties that can at times limit their application, such as time to administer, need for specific testing equipment, or the requirement for specific training or personnel. For some domain-specific endpoints, further data are needed, for example, to understand the natural history of scores (e.g., across the first 90 days post-stroke), as such knowledge is critical to properly powering future trials[12]. Moreover, experience remains limited for many endpoints. Other scales would benefit from further characterization, for example, of psychometric qualities such as validity, tendency towards floor/ceiling effects, and distribution of variance. Domain-specific endpoints could be advanced as a primary endpoint, added as secondary outcomes, or in certain cases be considered as a co-primary endpoint. Some of these approaches might require adjustment for multiplicity, and statistical strategies might need to be developed to deal with multiple streams of information, especially if results across endpoints are conflicting. Reliance on a domain-specific endpoint might increase or decrease sample size requirements, depending on study details and the number of endpoints employed. Studying the behavioral output of different brain systems does add complexity compared to scoring the single-digit ordinal mRS, but measuring behavioral data is crucial to achieving a better understanding of brain function[61] and its modulation by therapeutic interventions.

Summary.

Domain-specific endpoints and global endpoints are not mutually exclusive, and regulatory authorities are urged to incorporate elements of both as they relate to meaningful clinical benefits to patients[62], for both acute stroke trials and stroke recovery trials. Each type of endpoint has unique potential to contribute to interpreting research findings. Studies can measure both types of endpoint in parallel, depending upon a study's goals and desired balance, e.g., between granularity and time constraints. Strategies regarding choice of domain-specific endpoints must consider a number of factors, including allocating resources for patient testing, facilitating comparisons across trials, relevance to treatment mechanism, aligning with preclinical endpoints, feasibility of testing, cost, trial priorities, and burden of testing on patients and research teams. Domain-specific endpoints, many of which provide high-resolution measurements that are linked with treatment mechanism and preclinical endpoints, may be particularly valuable in phase II trials. Global endpoints, many of which capture broad effects of therapy on function, may be most valuable in phase III trials. However, these distinctions are not absolute, as domain-specific endpoints have been the basis for FDA approval[20, 21], and global endpoints provide useful insights in phase II trials.

Domain-specific endpoints complement global endpoints and warrant evaluation in acute stroke trials. In the current environment of EVT and fibrinolytics demonstrating substantial efficacy, with combination acute therapies or expanded indications likely to be tested with much greater frequency, with the development of numerous promising restorative therapies, and with the growing efficacy of preventative therapies, incorporating a broader set of

outcome assessments in stroke trials, including both global and domain-specific endpoints, is warranted.

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Appendix

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Non-standard Abbreviations and Acronyms

mRS	modified Rankin Scale
EVT	endovascular therapy

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Table 1.

Examples of domain-specific endpoints

Domain-specific endpoint	Behavioral domain assessed
Fugl-Meyer Arm Motor Scale	Upper extremity motor deficits
Gait Velocity	Functional walking ability
Western Aphasia Battery-Revised (bedside)	Aphasia
Line Cancellation Test	Hemineglect
Functional Oral Intake Scale	Dysphagia
Patient Health Questionnaire-9	Depression

Table 2.

Potential advantages and disadvantages of using domain-specific endpoints in acute stroke trials

Advantages	
1	Increased resolution of measurement
2	Greater insight into acute therapy effects on individual brain systems
3	Foster a common language across all stroke trials
4	Better understanding of treatment mechanism
5	Better understanding of what goes on in the brain from acute treatment to day-90
6	Optimizing therapeutic translation
7	Support therapeutic targeting of individual neural systems acutely
8	Capture improved outcomes in additional, patient-centered dimensions
Disadvantages	
1	Can require longer times to administer
2	Some domain-specific endpoints require specific testing equipment
3	Some domain-specific endpoints require specially trained personnel
4	Incomplete knowledge exists for the natural history of some domain-specific endpoints
5	Some domain-specific endpoints require further study of psychometric qualities such as validity
6	Experience remains limited for some domain-specific endpoints
7	Incorporating multiple domain-specific endpoints can increase risk of a type I error