The Case for Modality-Specific Outcome Measures in Clinical Trials of Stroke Recovery-Promoting Agents

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Abstract—Clinical trials for acute stroke treatments have often used composite clinical rating scales as primary outcome measures of treatment efficacy. Recent preclinical and clinical studies highlight the opportunity to administer treatments in the subacute and chronic phase of stroke to promote neurological recovery. Because different neurological deficits recover to different extents at different rates after stroke, putative stroke recovery-promoting treatments may exert differential effects on various functional aspects of stroke recovery. For this reason, we propose that the use of modality-specific outcome measures may be best suited as primary end points in clinical trials of stroke recovery-promoting agents. The use of such end points may result in a more selective labeling of stroke recovery treatments.

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Key Words: clinical trials ▪ outcome measures ▪ stroke recovery

Most patients show spontaneous return of neurological function after a stroke. Because damaged brain tissue does not fully regenerate in adult humans, these functional gains most likely occur on the basis of reorganization or proliferation of surviving cellular elements in brain,1–6 processes that appear to be heavily dependent on age.7 Functional recovery is often incomplete, making stroke a leading cause of adult disability in the United States.8 Many ischemic stroke therapies currently undergoing development, including thrombolysis and neuroprotection, focus on the acute phase of stroke in an effort to reduce the volume of cerebral infarction. However, recent preclinical and clinical developments have also highlighted the potential for reducing poststroke disability via therapies that target the cellular and molecular processes underlying stroke recovery. Examples of such treatments include growth factors, cell-based therapies, stimulants and other small molecules, and electrical and magnetic brain stimulation.9–19 These are treatments specifically designed to enhance neurological recovery after stroke and, accordingly, are distinguished from preventative, thrombolytic, or acute cytoprotective therapies. These treatments might augment spontaneously occurring processes that contribute to recovery of neurological function after stroke, including new neuronal sprouting and synapse formation in undamaged regions of brain, and stimulation of progenitor cell proliferation, migration, and differentiation in brain.20,21 The importance of a stimulatory environment or “practice” has also been confirmed in preclinical studies, and corresponding practice-based therapy programs have been designed for stroke patients.20,21 Because stroke recovery in humans commonly occurs during weeks to months after stroke,22–25 it is conceivable that pharmacological, biological, or device-based treatments might be usefully applied during this period. By contrast, most acute stroke treatments currently undergoing development must be given within hours after stroke onset to reduce infarct size. This editorial addresses the specific contention that optimal clinical trial designs for stroke recovery treatments are likely to differ in several important respects from those for acute stroke therapies.

In terms of clinical symptomatology, stroke is a multimodal disease, ie, a single infarct often causes deficits in multiple domains of neurological functioning. The nature of stroke deficits is highly dependent on the size and location of cerebral infarcts.26,27 Such deficits include motor, sensory, cognitive, attention, language, visual, coordination, and gait disturbances, among others. Moreover, the extent and rate of recovery after stroke differs among these different functions.

These points are best illustrated by example. A common variety of clinical stroke is that caused by thromboembolic occlusion of the middle cerebral artery (MCA). The vascular territory of the MCA includes more of the cerebral cortex controlling arm than leg function. Thus, during recovery from MCA stroke, patients often regain the ability to walk, whereas recovery of contralateral arm function may remain minimal.28 Similarly, after a dominant hemisphere MCA stroke with aphasia, an auditory comprehension deficit may clear considerably, whereas spontaneous speech may remain severely dysarthric and nonfluent.29 A visual neglect may clear over time, whereas a dense field cut may not.24
These examples illustrate the point that different neurological functions recover to different extents after stroke.

Similarly, various neurological functions recover at varying rates after stroke. Motor function shows the most dramatic improvement in the first 30 days; gains in constructional apraxia may be seen up to 6 months after stroke; language deficits often show gains for months to years after stroke onset; recovery of visuospatial neglect and anosognosia is usually not complete until 5 months after stroke; motor impersistence and extinction often continue to improve for 9 to 12 months after stroke; gait generally improves over a 14-week period after stroke, although gains may be seen after this period in patients with accompanying sensory deficits; resolution of urinary incontinence is seen beyond 20 weeks after stroke; and cognitive functions often continue to improve for many months after stroke. The time course of recovery in one neurological domain can be independent of recovery in a second domain of neurological function.

Clinical trials of acute stroke therapies, including thrombolytic and neuroprotective agents, have generally relied on composite clinical rating scales as primary outcome measures. Examples of such composite measures include functional outcome scales, such as the modified Rankin scale and Barthel Index, and neurologic disability scales, such as the National Institutes of Health Stroke Scale. In this context, the term composite refers to scales that combine multiple aspects of neurological functioning, such that a single score can be applied to describe overall outcome after stroke. Analysis of such scales in clinical trials has often relied on dichotomization of “satisfactory” versus “unsatisfactory” outcome, or more recently on “shift analysis,” to examine differences in distribution of scores among treated versus untreated patients. The attraction of composite scales for clinicians, drug developers, and regulatory agencies is simplicity, because they appear to provide a single score that succinctly summarizes outcome. Scores on composite scales are presumed to correlate with quality of life, the most important, but most difficult to measure, outcome of a therapeutic intervention.

However, because symptoms of stroke are multimodal, and because different neurological functions recover to different degrees at different rates, it seems reasonable to assume that treatments designed to enhance stroke recovery may also affect different functions to different degrees at different rates. As a consequence, composite rating scales may not be the most appropriate primary outcome measures for clinical trials of stroke recovery treatments. In particular, with use of composite scales, a meaningful gain in one domain may be either obscured or overemphasized by little or no gain in another, especially if domains are unequally weighted. The composite scales in common use are weighted more heavily toward motor than cognitive function, often with special attention given to the ability to walk. Thus, use of a motor-weighted composite scale in patients with MCA stroke may obscure a remarkable recovery of aphasia or neglect, when meaningful recovery of motor function has not occurred. Similarly, a composite scale may overemphasize recovery of walking, which often occurs after MCA stroke, while arm function may remain severely impaired. Indeed, these two clinical patterns are common clinical experience after MCA stroke.

Because of these reasons, we propose that “modality-specific” outcome measures are the most appropriate primary end points for clinical trials of stroke recovery treatments. Specifically, well-validated and reproducible measures exist for the assessment of sensorimotor, gait, language, neglect, memory, frontal lobe, and neuropsychiatric function after stroke. Primary outcome measures for stroke recovery trials might separately address “motor recovery” or “cognitive recovery,” or, more specifically, might address recovery of arm function, gait, aphasia, etc. For example, to measure upper extremity motor function, several tests are available, including the Action Research Arm Test, Box and Blocks Test, and arm motor subscale of the Fugl-Meyer scale, among others. In phase II clinical trials, tests for several functional domains can be chosen as end points, and the ones providing the most promising results might be chosen as primary outcome measures in pivotal trials. Current preclinical models of stroke recovery emphasize sensorimotor over cognitive recovery. If such models are used in the development of stroke recovery treatments, then surely motor recovery scales should be included as stand-alone outcome measures in clinical trials. Major treatment-induced improvements on modality-specific outcome measures should be mirrored by improved quality of life, the ultimate standard of treatment efficacy. Recent early-stage trials of stroke recovery-promoting treatments have indeed adopted modality-specific scales as primary outcome measures.

Use of modality-specific outcome measures in clinical trials of stroke recovery drugs may, in turn, result in modality-specific “labeling” of treatments. Thus, for example, a stroke recovery treatment would be approved as an agent “to promote motor recovery,” “to promote cognitive recovery,” or, more specifically, “to promote recovery of arm function,” or “to promote recovery from aphasia” after stroke. These deficits are common occurrences after stroke, insuring a substantial market for such a product. In this regard, approval of stroke recovery drugs may prove similar to approval of Parkinson disease drugs, which are approved primarily for efficacy on motor symptoms, or to approval of Alzheimer disease drugs, which are approved primarily for cognitive symptoms.

In addition to reliance on different outcome measures, stroke recovery trials are likely to differ from acute stroke trials in other significant ways. First, because stroke recovery is a prolonged process occurring over weeks to months, the time window for recruitment into such studies is likely to be much longer than acute stroke trials, in which recruitment windows are typically 0 to 6 hours after stroke. Second, because of this longer time window to recruitment, patients can be carefully selected by rigorous inclusion and exclusion criteria, including demographic, imaging, and functional criteria to achieve more homogeneity within treatment and control groups. Third, because of the long time window to recruitment, detailed baseline functional assessments of patients can be undertaken, against which repeated measures of outcome assessments can be compared during the months.
after stroke. By relying on within-patient change scores as primary outcome assessments, rather than a single cross-sectional measurement taken at the end of the study period, variance and thus clinical trial sample size requirements may be substantially reduced. Because of considerable preclinical data showing that functional recovery from brain injury or stroke depends on repeated practice of the impaired functions, concomitant behavioral treatments, including physical, occupational, and speech therapies, will have to be controlled carefully (or, at a minimum, recorded as covariates) in clinical trials of stroke recovery-promoting agents.

In conclusion, because the clinical problem of stroke recovery is distinct from that of acute stroke, we propose that different strategies and designs are warranted for clinical trials of stroke recovery treatments. Such designs will benefit from the use of modality-specific outcome measures.

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