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Stroke Therapy Academic Industry Roundtable (STAIR) Recommendations for Extended Window Acute Stroke Therapy Trials

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Abstract—The Stroke Therapy Academic Industry Roundtable (STAIR) meetings focus on helping to advance the development of acute stroke therapies. Further extending the time window for acute stroke therapies is an important endeavor for increasing the number of stroke patients who might benefit from treatment. The STAIR group recommends that future extended time window trials initially should focus on selected patient groups most likely to respond to investigational therapies and that penumbral imaging is one tool that may identify such patients. The control group in these trials should receive best locally available medical care; if regulatory approval for intravenous (i.v.) tPA is extended to 4.5 hours, then tPA will become the most appropriate comparator in trials conducted within this time window. In future well-designed extended window clinical trials randomization is appropriate and should not be precluded by using unproven treatment with intraarterial (i.a.) thrombolysis or mechanical devices. For proof of concept, extended time window, phase II trials of i.v. thrombolysis, or mechanical devices in which early recanalization/reperfusion is the primary end point, rescue therapy/bailout treatment with i.a. thrombolysis or devices may be acceptable. Statistical considerations and definitions of successful recanalization/reperfusion are suggested for these trials. (*Stroke*. 2009;40:2594-2600.)

Key Words: stroke ■ therapy ■ clinical trials

The STAIR meetings bring together stroke neurologists and other physicians, industry representatives, and regulators to discuss issues related to the development of new stroke therapies. The first 5 STAIR meetings generated recommendations for the preclinical evaluation of stroke therapies, phase II and phase III trial design, enhancing trial implementation and completion, novel approaches to measuring outcome, and regulatory considerations. The impact of these recommendations from the prior STAIR meetings has been substantial, but successful development of new therapies remains highly challenging, necessitating reconsideration and refinement. This report, which is based on expert opinion from the meeting and consideration of information not available at the time of the meeting but subsequently released and of critical importance to this topic, provides recommendations for enhancing clinical trials using longer therapeutic time windows.

Selection of Patients for Entry in Clinical Trials

Whether to formulate the eligibility criteria for clinical trials of acute stroke therapies as broad versus selective has been a

controversial area in stroke trial design. Broad criteria are designed to include a wide variety of patients, whereas selective or “likely responder” criteria limit eligible patients to those with specific clinical, laboratory, or neuroimaging features. In general, the STAIR group recognizes the recent trend toward using more selective eligibility criteria, particularly for phase II proof of concept trials after 3 or 4.5 hours. The development of tPA demonstrates the advisability of initially focusing on selected patient groups most likely to respond to investigational therapies, having first explored 90- and 180-minute windows and subsequently exploring extended therapy further to 270 minutes.^{1–3} However, pooled trial data suggests that 4.5 hours likely represents the upper limit at which a strategy of lytic therapy for a relatively broad unselected group of patients will confer net benefit.⁴ There is strong evidence that treatment benefit diminishes in an unselected population as the time from stroke onset increases. The key advantage of an appropriately selective approach is that it is more likely to detect treatment effects by targeting patients who are most likely to benefit from the study agent. This potentially allows a clearer signal of benefit to be identified in a smaller patient sample. Potential disadvantages

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include excluding patients who may unexpectedly benefit from the therapy, substantial limits on generalizability, selection based on sophisticated technology that may not be widely or uniformly applied in community practice throughout the world, and slower recruitment. However, if marketing approval is obtained for a limited patient group, additional trials can be performed to delineate benefits and risks in expanded population groups to potentially broaden the approved indication. Another potential weakness of small focused trials is greater risk of baseline imbalances in prognostic factors attributable to smaller sample sizes, but this risk can be reduced by stratifying randomization based on key prognostic parameters.

The STAIR recommendation to consider the selective approach is based both on theoretical reasons as well as the repeated failures of trials with broad eligibility criteria in extended time windows over recent decades. Preclinical benefits of stroke therapies have up to now been primarily evaluated in homogeneous animal models with optimized physiological variables. These models use a uniform mechanism of injury and typically are designed to maximize the volume of salvageable cortical tissue. In contrast, clinical trials have usually included a wide variety of stroke subtypes and etiologies in patients with a multitude of comorbidities. Such heterogeneity may mask the treatment effect.

Based on the widely accepted concept that the ischemic penumbra is the primary target for most acute therapeutic approaches in ischemic stroke patients and the increasing availability of imaging modalities that can approximate the extent of penumbral brain tissue, the STAIR group is particularly supportive of developing and implementing techniques that allow patient selection based on imaging-based penumbral identification. Direct evidence from multicenter trials supporting the feasibility and selection benefits of penumbral imaging is now available, for example from the EPITHET and DEFUSE trials.^{5,6} The most accurate approach for identifying penumbral tissue in stroke patients is positron emission tomography; however, this technique is not feasible for routine clinical use.⁷ Multimodal MRI and multimodal CT appear to be the most promising modalities that are feasible in multicenter clinical trials and in routine clinical practice.^{8,9} Advantages of MRI include more reliable and accurate detection of regions of severe ischemic injury using diffusion weighted imaging (DWI) and more extensive coverage of the brain with MR perfusion compared with CT perfusion techniques. Advantages of the CT approach include wider availability of emergency CT imaging, more rapid imaging, more open space and suitability for patients who may aspirate, and fewer contraindications to CT versus MR imaging. An important limitation of both MR perfusion and CT perfusion techniques is that the results of perfusion imaging can vary significantly depending on the acquisition or processing techniques chosen and there is no generally accepted methodology for these processes.¹⁰ Validation of penumbra identification techniques by independent study groups is also lacking. The international STroke Imaging Repository (STIR) group is currently addressing these issues for both MRI and CT, and the STAIR group supports their attempts to standardize imaging methodology, processing, and interpretation.

Another challenge is to determine whether the mere presence of “penumbral tissue” is sufficient or whether a minimum volume should be required. For example, 3 recent retrospective studies that used MRI penumbral identification techniques concluded that enrolling only patients with more extensive volumes of penumbral tissue than originally targeted would have produced clearer signals of efficacy.^{11–13} There is an urgent need to have more sophisticated processing of penumbral maps included in the programs provided on commercial MRI and CT machines to test the observation prospectively. At present, individual investigators or groups have designed automated and semiautomated software programs for these purposes. These programs have yet to be implemented by MRI or CT scan manufacturers and there is no validation between software packages, adding further variability to their potential use in clinical trials.

Limited imaging capability at many clinical sites and the great variability in methodology, processing, and interpretation in those that have imaging capability could impair recruitment into acute stroke clinical trials requiring penumbral imaging. Additionally, the presence or absence of such imaging capability in community hospitals uninformed in the conduct of the clinical trial may affect the ready applicability of study results that require these imaging protocols. The STAIR group recommends that a tiered system be developed by the stroke research community that stratifies clinical sites based on the ability to either simply obtain baseline imaging or to both obtain and interpret baseline imaging because some trials will require advanced imaging capability with rapid assessment and others will not. Such a system will enhance both clinical trial enrollment and the success of the translation of study results to the community setting.

Control Groups in Extended Time Window Trials

In the past, the control comparator universally used in acute stroke clinical trials in the greater than 3-hour window was supportive medical care, including antiplatelet therapy, deep venous thrombosis prophylaxis, prevention of aspiration pneumonia, and correction of derangements in physiological variables including oxygen, temperature, glucose, electrolytes, and acid base balance. The recently published ECASS III and SITS-ISTR data and ensuing changes in clinical practice guidelines in Europe and Canada indicate that this window will expand to 4.5 hours in some patients.^{14–17} The data available for endovascular recanalization interventions, however, such as intraarterial fibrinolysis and endovascular mechanical recanalization, as well as induced hypertension, are limited.

IA Lysis

One small phase III trial has been completed. This trial evaluated prourokinase, an agent not available for clinical practice, and was marginally positive on the primary end point.¹⁸ This agent was not approved for registration, and U.S. practice guidelines appropriately judged this trial as providing only Grade B (single trial performed, additional trials needed) rather than definitive Grade A evidence in support of treatment.¹⁹ Another phase III trial, evaluating i.a.

urokinase, was halted early for reasons external to the trial, with findings trending toward evidence of benefit but not reaching statistical significance.^{20,21}

Endovascular Mechanical Recanalization

Three uncontrolled technical efficacy trials have demonstrated that 2 devices, the Merci Retriever and the Penumbra System, can frequently reopen occluded arteries with complication rates approximately equal to those encountered with intra-arterial fibrinolysis.^{22–24} However, no controlled trial has demonstrated that mechanical recanalization improves patient outcome. Based on these findings, international regulatory authorities permitted marketing of these devices under labeling indicating that they can reopen arteries, and the U.S. Center for Medical Services approved a higher reimbursement for hospitals when these devices are used.²⁵ However, U.S. practice guidelines recognize that controlled trial evidence supporting these devices is lacking and do not endorse their use as a treatment to improve patient outcome.¹⁹

Based on the current evidence, advanced practice centers in the United States frequently use i.a. fibrinolysis as an off-label treatment based on the limited guideline recommendations and endovascular mechanical recanalization as an on-label unproven treatment. Physicians at these sites are sometimes reluctant to participate in trials in which patients may be randomized to supportive medical care arms in which these interventions are prohibited. It is therefore increasingly difficult to conduct extended time window trials with only supportive medical care control arms in this environment in the US. Centers offering such off-label treatment should continue to prioritize clinical trial enrollment over off label treatments.

The STAIR participants recommend that the most appropriate control group to use in acute stroke trials in the greater than 3- to 4.5-hour window be patients treated with supportive medical care and specific additional approved therapies that are of proven benefit in improving the final clinical outcome of patients. National regulatory bodies, granting agencies, and institutional review boards should recognize that nonendovascular treatment is an ethical and appropriate control group in greater than 3- to 4.5-hour trials. Treatment may include intravenous tPA in the 3- to 4.5-hour window if this is local practice and supported by applicable national guidelines. Data supporting intraarterial fibrinolysis and endovascular mechanical recanalization therapies at later time points are suggestive and encouraging, but they are fragmentary and not definitive. Consequently, equipoise clearly continues to exist regarding whether intraarterial fibrinolysis or endovascular mechanical recanalization yield outcomes that are better, the same, or worse than supportive medical care.²⁶ Therefore, the STAIR group recommends that the stroke community refrain from offering treatments of unclear risk or efficacy, if clinical trial enrollment or standard proven therapy options are available. Attempts to alter current reimbursement mechanisms to allow denial of reimbursement for unproven therapy if clinical trial participation or alternative proven standard care options are available should be explored, as the only rigorous and ethical alternative to use of unproven therapies. We recommend that a guideline be developed by the Joint Commission and other regulatory agencies. This guideline should

embrace the above concepts and should support appropriate enrollment in clinical trials at certified Stroke Centers as a condition of certification, if clinical trials can be performed.

For proof of concept phase II trials, the use of historical controls is an occasionally tenable approach, though concurrent controls are generally preferred. The National Institutes of Health has made detailed individual patient-level data from the 2 pivotal NIH NINDS TPA trials available as a public resource, and historical controls from this dataset were used in the NIH EMS, IMS 1, IMS 2, and ALIAS pilot trials among others. A major new and more comprehensive resource is the Virtual International Stroke Trials Archive (VISTA),²⁷ which now has detailed individual patient-level data on more than 27 000 placebo patients enrolled in past stroke trials. New mathematical techniques, including generation of multi-dimensional prediction surfaces, allow estimation of what a hypothetical control group's outcome would have been, based on key group variables.^{28,29} However, the use of historical controls in stroke trials, even for proof of concept studies, may carry theoretical risk that improvements that have occurred in supportive medical care over time as well as other sources of variation, rendering historical observations outdated.^{30,31} Recent evidence does not support a major change in outcome over the past decade.³² Historical controls cannot be used in pivotal trials designed to support approval.

In trials testing neuroprotective therapies, it often may be acceptable to allow as background therapy in both the active treatment and control group concomitant treatment with other approved interventions that maximize recanalization in extended time windows. This approach is currently being used in the NIH ALIAS and FAST-MAG neuroprotective phase III trials, which permit use of endovascular mechanical embolectomy up to 8 hours after onset as concomitant treatment. This approach extends the already established and accepted incorporation of concomitant intravenous thrombolytic therapy in the under 3-hour window that has been used in several large-scale neuroprotective trials, including GAIN Americas and mRECT.³³ The mechanism of action of neuroprotective agents is complementary to, rather than coterminous with, recanalization. Consequently, clinical trial design issues arising from having 2 unproven interventions applied in the same patient may be manageable in neuroprotective trials in which concomitant recanalization therapy is permitted with appropriate stratification and statistical adjustment. This type of design, however, introduces greater variability and potential confounding. It is also possible that effective competing therapies could obscure a treatment effect, and it may be challenging to determine whether the neuroprotective investigational drug or the recanalization therapy or both caused serious adverse events. Additionally, interactions between the 2 interventions must be considered. To minimize the risk of imbalance in the rate of concomitant recanalization therapy between treatment and control arms, whenever possible, randomization should be stratified by intended concomitant therapy.

In phase II trials testing intravenous recanalization therapies in the extended time window, it may be acceptable to permit rescue/bailout intervention with approved endovascu-

lar recanalization methods as background therapy in both the lytic and the control arms. In phase II trials, the recanalization rate achieved at 1 hour is a key biomarker of potential efficacy, and these data are available before the application of rescue therapies thus providing proof of concept and guiding safety assessments, feasibility assessments, and dose optimization. In phase III trials, in which final clinical outcome end points are paramount, permitting bailout mechanical therapies poses substantial risks to trial interpretability and generalizability and is not recommended.

For trials of endovascular recanalization therapies in the extended time window, it may be acceptable to permit rescue/bailout intervention with approved endovascular recanalization devices in proof of concept and technical development trials, in which novel devices are first tested and refined to optimize their recanalization yield. The recanalization rate before application of bailout therapy is generally an adequately informative biomarker for these developmental trials. It is crucial to note that additional information on safety or clinical efficacy would not be available in such a design.

Before endovascular recanalization can be recognized as an efficacious treatment for acute ischemic stroke and endorsed as standard care in practice guidelines, a convincing randomized comparative clinical trial or trials showing superiority over supportive medical care must be completed. It is essential that ongoing trials comparing intraarterial fibrinolysis or endovascular mechanical recanalization against supportive medical, including the NIH IMS 3 and MR RESCUE trials, be completed. Additionally, it is essential that the stroke research community understand the importance of participating in these and other clinical trials to advance our knowledge of stroke care. Designs may be considered that render randomized trials more acceptable to therapeutic enthusiasts among practitioners, who have a high level of belief in the efficacy of their treatment, without substantially compromising study integrity and power. Two approaches that may be considered are:

- Trial statistical analysis plans may incorporate an aggressive alpha spending function, permitting an early interim analysis to detect an extremely persuasive treatment effect. This approach permits early trial termination and public adoption of the proven therapy if there is an early “win” in the data. This would reassure therapeutic enthusiasts that, if their hypotheses regarding large treatment effects were correct, the trial would be stopped early and avoid the ethical issue of randomizing many patients to a treatment arm that they suspect is inferior. However, if the interim analysis does not show an extremely persuasive treatment effect, clinical equipoise would persist and randomization should continue.
- Weighted randomization, such as assigning 2 patients to active recanalization intervention for every 1 patient assigned to control medical therapy, which can increase participation in a clinical trial by therapeutic enthusiasts and can increase the amount of safety data accumulated about a novel intervention. This approach substantially reduces study power to detect a treatment effect and therefore increases the required sample size, but only modestly as long as the weighting is 2:1 or less.

In contrast, there are 2 approaches that are unlikely to be helpful and should generally be avoided:

- Adaptive randomization in phase II trials includes simple “play the winner” and more sophisticated allocation algorithms, but generally does not strongly influence the willingness to participate of therapeutic enthusiasts, and tends to reduce study power.
- Randomization based on the uncertainty principle of patient selection, relying on individual investigator, patient-specific equipoise, allows practitioners to only enroll patients for whom they are individually uncertain as to benefit and risk of therapy. However, an uncertainty principle entry criterion carries a high risk of biased selection and may yield misleading results when the intervention is dependent on the skills of operators and institutions, as are most endovascular treatments, and is not yet widely disseminated. A genuinely efficacious therapy may appear nonbeneficial if highly expert practitioners only enroll patients unlikely to respond to the intervention while unskilled practitioners enroll a broader population.

Recommendations to Clarify Trial Outcome Measures

Trials of intravenous and endovascular recanalization therapies are currently hampered by wide variations among trials in the timing and operational criteria for applying reperfusion and recanalization outcome measures. Previous efforts to bring clarity and uniformity to these assessments have helped substantially, but several difficulties remain that could be addressed by consensus group recommendations.

First, the conceptual framework for outcome assessment must clearly distinguish among (1) recanalization, (2) antegrade reperfusion, and (3) collateral perfusion. Recanalization refers to the achievement of structural patency in the initially occluded target vessel. Antegrade reperfusion reflects the volume of flow through previously occluded vessel. Collateral perfusion delineates the volume of flow via collateral channels, around and not through the initially occluded vessel, to the ischemic territory.³⁴ Although recanalization and reperfusion often improve in a parallel manner, they can be dissociated. A target artery can be completely recanalized, but flow may remain severely diminished because of multiple distal emboli. Conversely, a target artery may be only minimally recanalized but may be sufficient to permit perfusion to all of the threatened territory.

When to Measure Reperfusion/Recanalization in IV Thrombolytic Trials

To interpret the results of trials using intravenous thrombolytic agents optimally, assessments of reperfusion and recanalization are desirable to clarify how often the therapeutic effect is achieved in the overall population as well as in specific patient subgroups. The choice of timing for these assessments as well as the methodology used has varied among studies. Immediate detection of recanalization can be provided by continuous transcranial Doppler ultrasound (TCD) monitoring. However, this approach requires technical expertise that is available at only a limited number of centers and has the

potential to itself influence recanalization rates by ultrasound enhancement of thrombolysis. More widely available approaches are MR angiography/MR perfusion and CT angiography/CT perfusion. There is evidence from TCD studies that the benefits of recanalization are the most pronounced if it occurs rapidly after tPA administration.^{35,36} Therefore, if multimodal CT or MR techniques can be performed at baseline, a repeat study within a few hours after administration of thrombolytic therapy is the most clinically relevant time frame. However, obtaining an early scan can be challenging, particularly in unstable patients. In addition, the administration of a second dose of CT contrast material within a short time frame may increase the risk of renal toxicity. Therefore, some studies have chosen to obtain the follow-up scan at 24 hours, which fits easily with routine clinical practice and can also serve as the “safety scan” to evaluate for evidence of intracranial hemorrhage. However, this approach increases variability in the data by precluding distinction among nutritive reperfusion in the first hours and nonnutritive reperfusion occurring at later time points. Another option is to wait until 3 to 5 days to assess recanalization and then measure infarct volume at 30 days, a time that correlates well with infarct volume at 90 days.³⁷ The drawback is that the additional delay may lead to obscuring of early beneficial reperfusion by later nonbeneficial reperfusion. The STAIR group recommends that for both phase II (middle phase) and initial phase III trials, 2 follow-up imaging assessments should be obtained if possible; 1 early (either 3 to 6 hours or 24 hours) for assessment of recanalization/reperfusion and an additional scan at day 30 to determine infarct size. These scans should be correlated with clinical outcome measures such as the NIHSS.

Catheter Angiographic Outcome Measures in Endovascular Treatment Trials

A major obstacle to progress in acute stroke trials is the lack of a unified approach to measuring angiographic outcomes. Multiple rating scales have been proposed and applied. The most common method has been to adapt to the cerebral circulation the Thrombolysis in Myocardial Infarction (TIMI) scale, created in 1985 using conventional angiography to report the effect of myocardial reperfusion therapy.³⁸ However, different investigators have applied the TIMI scale in different ways to the cerebral circulation. The original TIMI scale was a perfusion not a patency measure, evaluating the wash-in and wash-out of contrast from the distal coronary capillary bed and not the degree of patency of the primary occlusive lesion. Several stroke trials, however, have treated the TIMI scale as a patency measure. Moreover, the cervicocephalic arterial tree is much more complex than the coronary system, with more branches and divisions, variation between deep and superficial territories, and multiple levels of collateral interconnections. Even when used as a perfusion measure as originally intended, the TIMI scale cannot be applied to common stroke lesions without the creation of additional operational rules. In M1 MCA occlusions, when the M1 is completely reopened but there is a small M3 residual embolus, some trials score the result as TIMI 2, others as TIMI 3. When the M1 clot burden is reduced, opening up flow to a few lenticulostriate penetrators but not through the length of

the M1 to the bifurcation, some trials score the result as TIMI 1, others as TIMI 2. In a recent review, among 9 clinical trial development programs in which the TIMI scale was the primary technical efficacy end point being reviewed by FDA, 7 different versions of the TIMI were used.³⁹ Currently, stroke investigation is divided, not united, by the use of a common rating instrument. All groups report that they are using the TIMI scale, but in fact under the same rubric they are using operationally very different measures.

We recommend that every trial reporting angiographic outcome measures should report separate clearly defined and operationalized measures of (1) target artery patency, (2) distal vessel filling, and (3) capillary phase perfusion. The Arterial Occlusive Lesion (AOL) Scale provides a good model for rating target artery patency.⁴⁰ The Thrombolysis in Cerebral Ischemia (TICI) scale assesses opacification of distal arteries in the target field and is the most appropriate instrument to rate distal vessel filling.⁴¹ Measurement of capillary level perfusion in the target field is often assessed by indicator imaging techniques, such as perfusion MRI and perfusion CT. However, tissue level perfusion can be assessed at catheter angiography, during the capillary phase. Rating scales for assessing perfusion at angiography are at an earlier stage of development, but hold promise, and include the Recanalization in Brain Ischemia (RBI) Scale perfusion item and the Cerebral Blush Grade (CBG) Scale.^{41,42} Because of the confusion they have engendered and continue to provoke and because they are not directly applicable to the cerebral circulation, we recommend against the use of the multiple versions of the TIMI scale that have been deployed in prior stroke studies.

Informed Consent Issues

The complicated nature of the informed consent process as well as the variability of regulatory requirements stemming from a range of state and federal statutes have long been recognized by stroke investigators. The additional complexity of informed consent in the acute stroke population resulting from the frequency of communication impairment, the inability of stroke patients to appreciate the extent of their deficits, and other cognitive limitations, has hampered the ability of clinical trials to provide treatment options in some situations. Surrogate consent, exception from consent, prespecified consent, and community consent are all mechanisms that have been considered acceptable in some, but not all, clinical environments.

The STAIR group recommends that standardization of acute stroke patient consent requirements occur in such a way that the patient is respected and protected while rapid participation in clinical investigations in appropriate situations is allowed. We see a need for the development of a tool kit for clinical investigators to guide the informed consent process as well as in communication with local Institutional Review Boards (IRB) and regulatory agencies. The development of documents that are concise as well as rapidly understood and considered by patients (as opposed to lengthy documents burdened by legal jargon) should be pursued. Standardized policies must consider the unique nature of the acute stroke population

including those evaluated by telemedicine or in the field and any additional necessary policies for these situations.

Appendix

Contributors

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