

## Recommendations for Advancing Development of Acute Stroke Therapies

### Stroke Therapy Academic Industry Roundtable 3

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**Background**—The development of acute stroke therapy has proven to be a daunting task, with a few successful and many unsuccessful trials. New strategies need to be considered to enhance the chances for success in future trials.

**Summary of Review**—The third Stroke Therapy Academic Industry Roundtable (STAIR) conference focused on issues related to increasing the percentage of acute stroke patients who might be included in acute stroke therapy trials and ultimately treated with drugs proven to be effective. A second focus was directed at the need for implementing multimodality stroke trials and potential ways to organize such trials in the near future. Finally, concepts for organizing and implementing acute stroke trials that incorporate current, state of the art trial methodology were discussed.

**Conclusions**—It is hoped that these suggestions will enhance future stroke trials and the development of effective, new acute stroke treatments that are maximally effective and utilized. (*Stroke*. 2003;34:1539-1546.)

**Key Words:** clinical trials ■ drug therapy, combination ■ patient selection ■ stroke management

Unfortunately, there has been a lack of progress in acute stroke drug development since the efficacy of tissue plasminogen activator (tPA) was demonstrated on the basis of the pivotal National Institute of Neurological Disorders and Stroke trials in 1995.<sup>1</sup> Other drugs intended to facilitate reperfusion, such as intra-arterial thrombolysis with prourokinase and the defibrinogenating agent ancrod, given intravenously, have shown promise, but neither has been approved for marketing.<sup>2,3</sup> Despite numerous studies of neuroprotective compounds showing reduction of infarct volumes in animal stroke models and, in some cases, promising phase II results, none have been proven efficacious on the basis of a positive phase III trial.<sup>4,5</sup> The lack of efficacy can be related to many factors, including the following: testing of drugs that are not truly effective on the basis of preclinical data; underpowered phase III trials; inclusion of patients unlikely to respond to the drug being tested; and choice of a primary end point that may not have evaluated the total effects of the treatment. Given this past experience, it is clear that novel approaches will need to be considered and employed in future clinical trials. The focus of the third meeting of the Stroke Therapy Academic Industry Roundtable (STAIR) was to explore new concepts for expanding the therapeutic time window, to consider strategies for the development of combination acute stroke drug treatments, and to consider new paradigms for stroke trial design and organization.

### Potential Strategies to Increase the Proportion of Treatable Patients

The potential time window for therapeutic interventions aimed at reducing the amount of brain injured from acute ischemia is limited. Current proposed mechanisms of neuronal death due to hypoxic-ischemic injury involve several types of processes.<sup>6,7</sup> Experimental studies suggest that the time window for most interventions to prevent ischemic neuronal injury may be limited.<sup>8</sup> The limited time window for intervention is a major consideration in the development and use of acute stroke therapies. For example, intravenous tPA currently must be given within the first 3 hours of symptom onset, and delayed hospital presentation is one of the most common reasons precluding its administration. A study in Cleveland found that only 17% of patients with ischemic stroke were admitted within 3 hours of stroke onset.<sup>9</sup> This situation is widespread in more general practice, as the International Stroke Trial enrolled only 4% within 3 hours after symptoms began.<sup>10</sup>

Several strategies might be considered to increase the proportion of treatable acute stroke patients. These can be divided into 4 broad categories: (1) reducing delays between the onset of patients' symptoms and presentation for treatment; (2) using imaging or other laboratory measures to identify patients who might benefit from delayed interventions; (3) testing novel treatments that have a mechanism of

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A complete list of the members of the Stroke Therapy Academic Industry Roundtable 3 appears in the Appendix, which can be found online at <http://stroke.ahajournals.org>.

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action permitting delayed intervention; and (4) administering early temporizing treatments that can potentially prolong the time window for definitive interventions.

### Reducing Treatment Delays

Studies have now demonstrated a general lack of public knowledge regarding stroke and its risk factors, symptoms, and potential treatment modalities.<sup>11–14</sup> This is true even among high-risk patients (the elderly and blacks) residing in high-risk regions of the United States.<sup>11</sup> If symptoms are not appropriately recognized, patients or bystanders cannot act. A variety of programs were developed to improve public awareness and knowledge among stroke patients and their caregivers that show that knowledge can be improved with educational programs.<sup>15–17</sup> However, data clearly demonstrating a relationship between efforts to increase knowledge and appropriate patient action are limited. Studies aimed at altering behavior show that the use of multiple strategies is superior to any single strategy. A multimodal public/professional educational campaign, including television and radio interviews, newspaper articles, continuing education lectures to local and regional primary care and emergency department physicians, and targeted mailings to area physicians, led to an increase in the proportion of patients presenting to one facility within 24 hours of the onset of symptoms from 39% to 86%.<sup>18</sup> However, no clear data show that these programs increase the proportions of treatable patients.

Even if educational strategies effectively improve public knowledge, a discrepancy between knowledge and action may remain. One study found that patient knowledge of stroke symptoms was not associated with early presentation to an emergency department.<sup>12</sup> Even when patients recognized that they were having a stroke, the symptoms were often perceived as not being serious. Once symptoms are recognized and the healthcare system is activated, organizing emergency responders to recognize stroke and to rapidly transport the patient to an appropriate facility is critical.<sup>19</sup> Scales and screening instruments have been developed to facilitate accurate stroke diagnosis by emergency medical services personnel.<sup>20,21</sup> The hospital to which patients are transported should have the organization and staff available to provide immediate evaluation and treatment.<sup>22</sup> The American Stroke Association–sponsored Operation Stroke is aimed at organizing stroke care on a community-wide basis to reduce unnecessary prehospital and intrahospital delays.

### Identifying Subgroups That Can Be Treated Effectively With Longer Delays

Not every patient's time window for treatment is the same because acute ischemic stroke is a highly heterogeneous disease. Estimates of the maximal duration of the therapeutic window in acute human stroke are based on experimental animal data and human imaging studies. In animal models, a central core rapidly proceeds to infarction after the onset of focal ischemia with irreversible injury, then spreads out circumferentially.<sup>8</sup> Experimental studies in different animal models have found wide variations in time window for treatment efficacy, ranging from just a few minutes to as much as 24 hours.<sup>8</sup> Recent reviews of experimental studies

**TABLE 1. Potential Benefits of Imaging in Acute Stroke Trials**

1. Confirm that the patient is experiencing ischemic stroke and exclude symptoms that may mimic stroke
2. Identify contraindications to treatment (eg, presence of hemorrhage in a trial of fibrinolytics)
3. Determine that the lesion affects tissue responsive to the drug under trial and that there is an appropriate tissue target of therapy (eg, large, persisting penumbral zone)
4. Provide a more homogenous patient population (eg, inclusion of middle cerebral artery territory lesions only, or exclusion of brainstem lesions)
5. Determine whether there is an appropriate large vessel occlusion target for reperfusion therapy
6. Potentially identify tissue markers of increased risk of therapy (eg, a large necrotic core increasing the likelihood of hemorrhagic transformation with fibrinolytic or antithrombotic molecules)
7. Serve as a possible surrogate marker for clinical outcome and correlate imaging outcome with traditional clinical end points

suggest a treatment window of 6 hours<sup>23,24</sup> to as long as 8 to 12 hours.<sup>25</sup>

Imaging and biochemical studies in acute stroke patients similarly suggest that the window for efficacy may be prolonged in select individuals. There are several potential reasons for obtaining imaging studies in acute stroke clinical trials, as outlined in Table 1. Positron emission tomography studies implied persistence of a potentially salvageable ischemic penumbra in many patients with large-vessel occlusions at 9 hours after ischemic stroke onset.<sup>26,27</sup> Serial diffusion MRI studies demonstrated progression of ischemic lesion volume beyond 12 hours after onset.<sup>28</sup> Cerebrospinal fluid analyses have shown that the excitotoxic amino acid glutamate continues to increase for 24 hours after onset in patients with progressing ischemic stroke.<sup>29</sup>

A wide variety of imaging modalities are potentially useful to aid in patient selection.<sup>30</sup> The greatest promise and experience appear to lie with multimodal MRI and multimodal CT. Both MRI and CT can delineate the extent of ischemic core, the extent and severity of perfusion impairments, potentially the extent of the ischemic penumbra, and the presence of large-vessel occlusions.

Combined diffusion-perfusion imaging is the most widely studied MR approach for identifying patients who might be candidates for late acute stroke interventions. Diffusion-weighted imaging visualizes regions of advanced bioenergetic failure within minutes of the onset of ischemia<sup>31</sup> and is sensitive to decreased free water diffusion in brain tissue related to early cytotoxic edema. Some regions of diffusion abnormality can be reversed with early reperfusion,<sup>32</sup> but the region of diffusion abnormality provides an approximation of the core region of irreversible infarction. Perfusion-weighted MRI using rapid serial image acquisition to track the temporal passage of a paramagnetic contrast agent through brain tissue is the most commonly employed clinical perfusion imaging method. Perfusion MRI currently affords a relative, rather than absolute, quantitative measure of cerebral tissue perfusion. Regions of diffusion-perfusion mismatch provide a rough index of the ischemic penumbra, representing ischemic tissue that has not yet advanced to bioenergetic failure.<sup>33</sup>

Multiparametric analyses of tissue status combining information from several MR variables promise even more precise delineation of core and penumbra.<sup>34–36</sup>

Perfusion CT imaging provides a relative measure of cerebral blood flow more easily than can be acquired with preexisting xenon-enhanced CT techniques.<sup>37,38</sup> The perfusion CT technique employs repeated helical CT scanning of one or a few brain levels to track the passage of an intravenous bolus of iodinated contrast material. Perfusion CT allows rapid data acquisition and postprocessing and can be performed in conjunction with baseline standard CT and CT angiography. With perfusion CT, the infarcted core may be identified as regions of dramatically reduced cerebral blood volume, and the ischemic penumbra may be identified as regions with reduced cerebral perfusion but normal or increased cerebral blood volume. Xenon-enhanced CT measures cerebral blood flow quantitatively in 10 to 15 minutes with additional equipment added to a clinical CT scanner. In the setting of acute stroke, xenon-enhanced CT can be used to identify the severity and distribution of cerebral ischemia.<sup>39</sup>

The first clinical trials employing imaging to expand the therapeutic time window are now in progress. These include the DWI Evaluation for Understanding Stroke Evolution (DEFUSE) and Echo Planar Imaging Thrombolytic Evaluation Trial (EPITHET) trials seeking MR diffusion-perfusion signatures that identify treatment responders to intravenous tPA in the 3- to 6-hour window as well as the Desmoteplase in Acute Stroke (DIAS) trial and the Stroke Evaluation for Late Endovascular Cerebral Thrombolysis With MR (SELECT MR) trial, which are identifying patients with a diffusion-perfusion MRI mismatch for enrollment in the 3- to 9-hour window for intravenous desmoteplase (DIAS) or the 6- to 12-hour window for intra-arterial tPA (SELECT MR). These studies will provide critical information regarding the feasibility and practicality of large-scale, imaging-based patient selection trials. A critical issue these trials will address is how frequently patients presenting beyond 3 hours after symptom onset have an extensive, treatment-responsive salvageable penumbra.

### Agents That Permit Late Intervention

Several drug categories may offer some potential benefit even when started well beyond the first few hours after symptom onset.<sup>40</sup> Therapeutic approaches such as stem cell transplants, nerve growth factor administration, anti-leukocyte interventions, and modulation of apoptotic pathways show great promise and may be of some benefit when delivered >6 hours after stroke onset; however, on the basis of the trials conducted to date, they are likely to have at best modest effects when employed as monotherapy. These therapies may be tested in conjunction with very early thrombolysis or neuroprotection. If newer-generation fibrinolytic and thrombolysis-inhibiting drugs such as tenecteplase and glycoprotein IIb/IIIa agents are less likely to produce hemorrhagic complications than tPA, they could be tested in the 3- to 6-hour window with expectations that a somewhat diminished benefit with a lower risk of complications would yield a worthwhile therapy.<sup>41,42</sup>

The typical interval from the initiation of an intra-arterial infusion of a fibrinolytic drug to completion of recanalization is 90 to 120 minutes. Therefore, the 6-hour treatment window in Prolyse in Acute Cerebral Thromboembolism (PROACT) II may be viewed as an 8-hour recanalization window.<sup>2</sup> On this basis, trials of mechanical embolectomy devices that have the potential of recanalizing an occluded vessel within minutes rather than hours of starting treatment might be designed with time windows for treatment initiation up to 2 hours longer than the intra-arterial fibrinolysis trials.<sup>43</sup>

### Temporizing Treatments

Certain acute stroke therapies such as endovascular interventions are generally available only at specialized centers, often requiring the transfer of patients from a hospital lacking this capability and an inherent delay in initiation. A brain imaging study is required to exclude intracerebral hemorrhage before fibrinolytic and antithrombotic agents may be administered safely. In contrast, many neuroprotective agents theoretically could be safe and might even be efficacious when given to patients with intracerebral hemorrhages. Therefore, another strategy for expanding the therapeutic window for recanalization is to administer neuroprotective therapies immediately on hospital arrival or even by paramedics in the field.<sup>44,45</sup> Such an agent or combination of agents could delay ischemic brain from progressing to infarction, potentially expanding the time window for delivery of recanalization therapies.<sup>46,47</sup> Pioneering multicenter trials have been conducted of combined neuroprotective and fibrinolytic therapy, but neuroprotective agents were usually given only after the start of fibrinolysis.<sup>48,49</sup> Trials of hyperacute neuroprotective agents preceding fibrinolysis are a promising strategy for expanding the therapeutic window.

### Rationale for Multiple Therapy and Multimodality Trials

Many potential reasons exist for the failure of neuroprotective drugs in clinical efficacy trials.<sup>50,51</sup> These include the excessively long time windows used in nearly all clinical trials to date (often far longer than should have been anticipated on the basis of animal models), inappropriate dosing or lack of drug in adequate concentrations in the ischemic penumbra (little knowledge of drug concentrations in ischemic brain), drug toxicity, lack of efficacy in white matter with some compounds, animal model deficiencies (often young, healthy rats with a markedly different cerebral circulation than that of atherosclerotic humans), lack of longer-term behavioral measures, lack of proof of concept trials before pivotal phase III studies (haste to progress to pivotal trials), and poor trial design, particularly in regard to inadequate sample sizes and inadequate measures of efficacy that could lead to the inability to detect small treatment effects.<sup>52</sup> The most important reasons for the negative neuroprotective trials probably are the lack of preclinical data to support the time window chosen for the efficacy trial and rapid movement to a pivotal trial without in-depth understanding of side effect profiles and the subtypes of stroke patients most likely to be benefited by the drug being tested. These issues were discussed in detail in the prior STAIR reports.<sup>50,53</sup>

Two other important reasons may explain the lack of efficacy of tested neuroprotective agents. First, neuroprotective strategies could have failed because of a lack of concurrent effective reperfusion.<sup>54–56</sup> There have been only a few trials of combining thrombolysis with neuroprotective agents. This approach was shown to be effective in animal stroke models.<sup>55</sup> Substudies using tPA in phase III neuroprotective trials have been underpowered. Second, the ischemic cascade is exceedingly complex and involves many different pathways.<sup>4</sup> Most neuroprotective compounds target only a fraction of these diverse processes, underscoring the concept that combinations of agents are likely to be more effective than single interventions. Single agents that target multiple aspects of the ischemic cascade are available for evaluation, and using a single agent with multiple effects would avoid many of the problems inherent in testing drug combinations. Drugs with multiple effects on the ischemic cascade include nicotinamide, adenosine, cannabinoids, tacrolimus (FK506), and iron chelators such as desferrioxamine.<sup>57–60</sup> A potentially novel agent is microplasmin, a thrombolytic with apparent neuroprotective effects.<sup>61</sup> In addition, physiological determinants such as blood pressure, temperature, and glycemic status also substantially affect ischemic lesion evolution and have received only limited attention. Drugs given to treat neurological side effects of neuroprotective drugs might also negatively affect functional outcome.<sup>62</sup> Given this background, there are compelling reasons that current trial design should include single agents or combinations of neuroprotective agents to target multiple aspects of the ischemic cascade as well as physiological manipulation such as hypothermia in addition to reperfusion strategies.<sup>63,64</sup> The likelihood of success may be enhanced by more extensively evaluating compounds in animal models or possibly by initially using surrogate end points such as diffusion/perfusion MRI and perfusion CT for proof of concept phase II studies.<sup>65–68</sup>

For stroke, multimodal approaches include combined reperfusion and neuroprotective strategies, combinations of intravenous and intra-arterial thrombolytics, combinations of reperfusion strategies targeting different aspects of the hemostatic system, combinations of neuroprotective agents targeting differing portions of the cascade, and the incorporation of physiological strategies such as hypothermia.<sup>64</sup> Neuroprotective strategies targeting multiple sites in the ischemic cascade and some form of reperfusion (thrombolysis, mechanical devices) are probably needed to better deliver neuroprotective therapies to the target brain region. Both pharmaceutical companies and investigators need to consider differing modes of neuroprotective actions and reperfusion in their drug development plan. Considerations should include the risk versus benefit of each agent, individual toxicities, and stroke severity.

### **Multimodal Approaches: Thrombolysis Plus Neuroprotection**

The dose response for each agent should be tested initially, and drug interactions and toxicity should be evaluated. An example of a trial design would be to test intravenous tPA combined with neuroprotection versus tPA plus placebo. The timing of the neuroprotective drug could be given during the

tPA infusion, after tPA, or before hospital arrival, as in the Field Administration of Stroke Therapy–Magnesium (FAST-MAG) trial,<sup>45</sup> followed by thrombolysis, after expert assessment and imaging. Although neuroprotection might extend the therapeutic window for thrombolysis, protocols should not delay tPA administration. As previously indicated, an experimental neuroprotective compound could be tested with tPA in a phase III design, after acceptable phase II safety data are obtained. Such an approach could be considered with various time windows.

### **Multimodal Reperfusion**

Reperfusion strategies that might be tested would include mechanical reperfusion techniques, thrombolytic agents given intravenously and intra-arterially, glycoprotein IIb/IIIa agents, and thrombin inhibitors alone or in combination. Recent experience from large trials in cardiovascular disorders suggests that these multimodal pharmacological strategies may be applicable to carefully selected ischemic stroke populations.<sup>69,70</sup> An example of multimodal reperfusion is the combined intravenous and intra-arterial tPA preliminary trial. In this study patients with more severe strokes received a less than standard intravenous dose of tPA followed by angiography and then additional intra-arterial tPA and manual clot manipulation, if persistent vascular occlusion was present.<sup>71</sup>

Hemorrhagic transformation of brain infarcts after pharmacological or mechanical reperfusion remains a concern. There are limited data concerning this risk with mechanical reperfusion. Recently, the use of a metalloproteinase inhibitor was shown to reduce the risk of hemorrhage in tPA-treated animals.<sup>72</sup> The development of pharmacological methods to protect cerebral blood vessels could be useful for reducing hemorrhagic risk associated with reperfusion.

### **Recommendations and Strategies to Facilitate Multimodal Trials**

There appears to be a need for better coordination and integration between the various Food and Drug Administration divisions (drugs, devices, biologics) to streamline and facilitate the regulatory processes for multimodal trials of unapproved agents. From a regulatory perspective, it would be helpful if stroke were considered a “serious and life-threatening disease” such as cancer and AIDS. An International Conference on Harmonization should be convened to standardize regulatory requirements in this area. Additional trial consortia, as exemplified by the Canadian Stroke Consortium and the Australasian Stroke Trials Network, should be more fully developed to facilitate the conduct of stroke trials. International standardization is important. Stroke subtypes might be regarded as an “orphan disease.” Investigators need to confront the reluctant views of the pharmaceutical industry regarding the logistics and regulatory hurdles of testing multiple unproven agents in acute ischemic stroke. However, the problem of testing multiple proprietary drugs through intercompany collaborations is not trivial. Factorial designs and well-organized trial consortia might help to surmount these barriers. Cardiologists have organized extremely large and effective trial consortia, and the lessons for future stroke trials are obvious. Stroke trial design could be

facilitated via the newly established Virtual International Stroke Trials Archive (VISTA), allowing integration of very large acute stroke databases to optimize end point selection and other trial conduct issues.

### Planning for Future Acute Stroke Trials

To increase efficiency and accelerate progress, trials of acute stroke therapies must evolve to incorporate new technologies and research tools. Trials also must respond to changes in regulations, in healthcare systems, and in the population primarily affected by stroke. By incorporating advances in study design and performance, the ideal future acute stroke trial will produce reliable results more rapidly and cost-effectively.

There are randomized trial designs that may improve efficiency of acute stroke studies, but many are underutilized. Factorial designs should be considered when there is interest in studying more than a single treatment or when the interaction between treatments is of particular interest.<sup>73</sup> Compared with separate series of studies involving individual treatments, these designs may reduce sample size when treatment effects are independent. However, the possibility that an interaction may occur should be incorporated into sample size estimates. In addition, factorial designs as they relate to the investigation of interactions will require acceptance by regulatory authorities. Sequential or adaptive randomization is an acceptable, efficient alternative for studying multiple doses or agents.<sup>74</sup> Large, simple trials are appropriate for studying interventions with limited expected absolute benefit<sup>75</sup> but limit generation of new hypotheses and may be inadequate for regulatory agency approval for new indications.

Advances in health services research have led to improvements in outcome measures, and these new measures should be considered for use in acute stroke trials. Outcome measures should incorporate the entire range of possible outcomes that are important to patients and should encompass the major potential effects of the intervention.<sup>76</sup> Factors that influence the condition of a patient but that are unrelated to the studied intervention produce noise that may obscure important treatment effects. Therefore, outcome measures and their timing should be defined carefully to exclude extraneous variability.

Selecting an appropriate study population is paramount and requires attaining the correct balance between generalizability and homogeneity.<sup>77</sup> The patient population studied should reflect the changing broader population affected by stroke. As the world population has aged, the total number of strokes has increased, and those affected are generally older. Acute stroke studies have included too few nonwhites, and special efforts should be made to increase enrollment of generally underserved populations. Selecting a more homogeneous population by narrowing entry criteria may increase power<sup>78</sup> but should be considered carefully since it could affect the generalizability of results. In general, clinical trials should attempt to include patients representative of major stroke subtypes. Results of imaging studies and other biomarkers may be useful tools for identifying populations more likely to

**TABLE 2. Potential Benefits of Organized Consortia for Performing Stroke Trials**

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1. Provide a scientific forum for reviewing trial proposals and providing feedback on feasibility and trial performance
  2. Establish better and more direct links with industry sponsors
  3. Initiate a system to help develop and endorse standards of design, safety, and reporting of trials
  4. Provide a mechanism to help streamline the administrative infrastructure of trials
  5. Identify in a timely manner high-quality centers capable of delivering the needed number of patients in a timely manner
  6. Provide an efficient means to maintain quality standards and certification of investigators
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benefit from an intervention and should be more fully developed for use as inclusion criteria in trials.

Specific considerations will have to be made to improve the efficiency of the performance of future acute stroke trials. Stroke trials will need to capitalize on the lessons learned from cardiology and oncology, including the formation of trial consortia. Consortia may have to include international, national, and regional collaborations. These consortia need to include both academic and community sites. The Canadian Stroke Consortium is an example of a system that has been able to negotiate contracts with a lower-cost overhead and to efficiently perform multicenter trials. The potential benefits of such organized systems to perform acute stroke trials are outlined in Table 2.

Innovations will be needed to reduce delays between data collection and analysis through the use of electronic records, Internet systems with standard platforms, and audit trails. Institutional review board (IRB) efficiency needs to be improved, with a greater reliance on acceptance of centralized decisions applicable to a broader group of centers that may participate in the consortia. Given the severity of stroke, waiver of consent and the use of next-of-kin consent may be required, as in studies of cardiac arrest,<sup>79</sup> and this will require community boards to be involved in these decisions. Any means of streamlining the system of updating IRBs on serious adverse events will help to decrease the paperwork burden for investigators and to improve efficiency of common regulator-driven activities.

Despite the lack of positive neuroprotective trials, some very successful academic-industrial collaborations developed that could serve as models for future endeavors. The earlier the interaction between academics and industrial research and development teams, the better is the chance of mutually agreed on protocols. Such collaboratively designed protocols will benefit from the early input of experienced preclinical and clinical academic investigators and will fulfill the goals of industry to design the most cost-effective trial with the greatest chance of proving the efficacy of their drug. Inclusion of academic and clinical investigators as well as industry members on steering committees may be the best way to achieve more effective collaborations in the design, execution, and reporting of trials. The implementation of acute stroke trials will benefit from these collaborations and should avoid excessive reliance on commercial research organiza-

**TABLE 3. Recommendations for Future Stroke Trials**

1. Incorporate advances in trial design methodology, including sequential designs, factorial designs, and appropriate application of simple and complex designs
2. Optimize stroke trial target populations and expand to larger, more heterogeneous populations where appropriate and account for changing stroke profiles (older, race-ethnicity, other comorbidities, stroke subtypes)
3. Incorporate measures of bioactivity and innovative diagnostic modalities (ie, imaging, serum markers) in the design of trials
4. Include collaborations with prehospital and ER systems to enhance entry and reduce randomization delays
5. Refine stroke outcome assessments, including the judicious use of continuous outcomes and development of more sensitive scales, and encourage the use of adjusted outcomes (eg, by adjusting for baseline stroke severity)
6. Incorporate lessons from cardiology and oncology trials and form cost-efficient regional, national, and international trial consortia consisting of academic and community sites
7. Reduce delays between data collection and analysis through the use of electronic records, Internet systems with standard platforms, and audit trails
8. Improve IRB efficiency including wider acceptance of centralized decisions, waiver of consent and use of next-of-kin consent, and streamlining the system of updating IRBs on serious adverse events
9. Strongly encourage early academic-industrial collaborations at all levels from design to execution to reporting of trials
10. Improve funding for clinical trials by increasing NIH support for trials, reducing time delays in funding, and encouraging NIH-industrial collaborations
11. Support establishing a centralized stroke trial database (eg, VISTA)

tions. The reliance on external adjudication panels for outcome determinations, clinical coordinating centers to help in the identification and administrative management of trial sites, and the use of independent statistical coordinating centers to perform interim as well as final data analyses will undoubtedly improve validity as well as the collaborative structure of future trials. Another approach to trial implementation could be the assignment of promising new therapies by industry to academic consortia or government agencies for clinical evaluation. With this approach, trials would be more investigator driven but would have appropriate industrial input to allow for ultimate commercialization. Data and Safety Monitoring Board standards will need to be maintained, and trials will need to have early and timely terminations for safety, efficacy, or futility. When trial results are reported, the Consolidated Standards of Reporting Trials (CONSORT) recommendations should be followed,<sup>80</sup> with results published in a timely manner and findings widely disseminated. As trials grow in complexity and size, costs will need to be addressed. Funding for trials needs to be increased. The National Institutes of Health (NIH) and other, non-US-based public funding sources need to be enhanced, and public health-industrial collaborations should be encouraged as a method of sharing the fiscal burden of clinical trials. This will require a more rapid system of NIH and public health institutional review. A summary of recommendations for future trials is provided in Table 3.

## Conclusions

The development of acute stroke therapies has proven to be a daunting and difficult task, with rare successes and many failures. Many important and valuable lessons have been learned from both the successful and unsuccessful prior acute stroke trials. Currently, it appears to be appropriate to move forward into a new era of acute stroke treatment trials, employing new technologies and novel approaches to stroke trial design and implementation. It is hoped that this third set of suggestions from the STAIR group will provide investigators and industry sponsors with novel ideas and help to restore the momentum of acute stroke therapy development. Additional therapies are desperately needed, and it is hoped that carefully conceived, scientifically valid, and well-executed clinical trials will lead to the development of new acute stroke therapies.

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