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Marc Fisher and for the Stroke Therapy Academic Industry Roundtable IV

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Enhancing the Development and Approval of Acute Stroke Therapies

Stroke Therapy Academic Industry Roundtable

Marc Fisher, MD; for the Stroke Therapy Academic Industry Roundtable IV

Background—Previous Stroke Therapy Academic Industry Roundtable (STAIR) meetings focused on preclinical evidence of drug efficacy and enhancing acute stroke trial design and performance. A fourth (STAIR-IV) was held to discuss relevant issues related to acute stroke drug development and regulatory approval.

Summary of Review—The STAIR-IV meeting had 3 main focus areas. The first topic was novel approaches to statistical design of acute stroke trials and appropriate outcome measures. The second focus was the need for better cooperation among participants in stroke therapy development that may be addressed through a national consortium of stroke trial centers in the United States and elsewhere. Lastly, regulatory issues related to the approval of novel mono and multiple acute stroke therapies were discussed.

Conclusions—The development of additional acute stroke therapies represents a large unmet need with many remaining challenges and also opportunities to incorporate novel approaches to clinical trial design that will lead to regulatory approval. The STAIR-IV meeting explored new concepts of trial methodology and data analysis, initiatives for implementing a US clinical trialist consortium, and pertinent regulatory issues to expedite approval of novel therapies. (*Stroke*. 2005;36:1808-1813.)

Key Words: ischemia ■ stroke, acute

The historic failure of neuroprotective ischemic stroke trials and the slow progress in the development of reperfusion drugs and techniques continue to stimulate debate focused on clinical trial design. This report builds on the discussions of the 3 previous STAIR conferences and focuses on further considerations related to clinical trial design and outcome assessment of treatment effects, on enhancement of cooperation among stroke trial participants, and on regulatory aspects related to the development of acute stroke therapies.¹⁻³ The unique requirements of device trials will be the topic of a future STAIR conference.

Recommendations for Improving Clinical Trial Design and Outcome Assessment

Several of the important issues concerning phase II and III trials that were addressed in STAIR-II need to be reconsidered in view of recent advances in the field.² These include pharmacokinetic evaluation and characterization of the dose response, the need to demonstrate adequate brain penetration of the drug being evaluated, enhancement of patient selection for phase II and III trials, and improvement of outcome assessment.

Phase III studies continue to be conducted despite limited pharmacokinetic data from animal and preliminary human studies. Helpful pharmacological data include the following: effec-

tive plasma levels, time window, and the delineation of a ED₉₅ (the minimal dose that achieves 95% of the maximal effect) of a drug. A previous STAIR meeting emphasized that lack of establishing the optimal dose, duration of therapy, and time window may have contributed to the failure of neuroprotection trials.² Better characterization of dose-response relationships and the determination of the optimal dose to be used in phase III trials should improve the chances for demonstrating efficacy. The use of an adaptive design with real-time learning of the dose-response relationship of a drug and continuous reassessment of futility could enhance the efficiency of phase IIB trials.^{4,5} This approach was successfully used in the Acute Stroke Therapy by Inhibition of Neutrophils (ASTIN) trial and led to early termination of the study because of futility.⁶ As compared with a traditional design where a fixed number of patients are allocated to a small number of doses,²⁻³ a larger number of treatment arms⁶⁻¹⁶ are used in a sequential design in which a Bayesian algorithm continuously models the dose-response on the basis of all outcome data collected across all treatment arms. Treatment allocation is adaptive in that the system is designed to optimize the integration of the dose-response data and the determination of the ED₉₅. Adaptive-design trials are associated with several features that can impose difficulties. The initial modeling necessary for designing an adaptive trial design is rigorous and time consuming, outcome data must be collected

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rapidly, necessitating cooperation from trial sites, and, lastly, the overall sample size with a large number of treatment arms will be substantially greater than traditional phase IIB trials with only 2 to 3 active treatment arms. The stopping rule in ASTIN was based on bounds of posterior probability. If the lower bound of the credible interval around the estimated ED₉₅ was more than a predefined minimal efficacy threshold, a recommendation by the Independent Data Monitoring Committee (IDMC) to stop the study would have been made because efficacy would have been demonstrated; a recommendation to stop the trial would have been made if the upper bound of the credible interval was less than a predefined threshold. The IDMC is critical in the conduct of trials using this design or another type of adaptive design and requires clinicians and statisticians to evaluate both safety-related issues and the performance of the algorithm.

It is also important to demonstrate that adequate drug concentrations can be achieved in the target organ. It is uncommon to have confirmation that a compound reaches the relevant brain areas at therapeutic concentrations in either animals or humans. Hence, studies should be performed to demonstrate that adequate target tissue levels can be achieved in both animal models and humans by direct cerebrospinal fluid or brain sampling. For some compounds, MRI or positron-emission computed tomography might provide useful information about central nervous system drug penetration and tissue levels.

Broad entry criteria should be used in phase IIA safety studies to evaluate unexpected risk at the extremes of age, comorbid conditions, and stroke severity. In subsequent phase IIB studies, more focused approaches with narrower entry criteria may reasonably be used. Narrowing selection criteria in phase IIB to target patients more likely to respond based on clinical and imaging characteristics may optimize the chances of detecting a biologically relevant drug effect.

Many reliable and validated outcome measures are available, but there is a need for further refinement and improvement. The Rankin score has been widely used but is suitable only when a large difference in outcome among treatment groups is expected.⁷ The development and validation of surrogate outcome measures, especially for phase IIB studies, may be helpful in establishing the biological plausibility of a new therapeutic approach and could be accomplished in a single trial with a split sample and cross-validation approach. Putative surrogates should have an established statistically documented relationship to validated clinical outcome measures or may become validated during the trial itself.⁸ The sensitivity and specificity of outcome measures may be improved by the following:

1. Reducing the variability of assessment by, for example, using a central assessment by a single person or panel or by standardized investigator training.
2. Improving precision and reducing respondent variability for assessing clinical outcome measures through computerized adaptive testing. One strategy to use is Item Response Theory statistical methodologies to create large item pools capable of precise measurement, from which only a small number of items are used to assess individual subjects. Computerized adaptive testing can be used to present only the most relevant items to the individual based on his or her ability level and store the responses for aggregate analysis.

3. Using more hypothesis-specific outcome measures. For example, if a clinical trial is directed toward improving mobility, outcome measures should be focused on gait rather than on more general parameters that may dilute the gait component. Using a combination of clinical and imaging measures could be more sensitive than either approach alone.

Similar recommendations apply to phase III trials, particularly the need to develop more sensitive and specific outcome measures. Sharing datasets by placing trial results in the public domain in databases such as Virtual International Stroke Trials Archive (VISTA) and MR STROKE would be helpful in advancing the development and testing of new outcome measures.

Although limitations in physical function following stroke have a major impact on quality of life and contribute to the economic burden of the disease,^{9,10} commonly used measurement instruments are not sensitive across the entire continuum of stroke severity.^{11–13} The most frequently used measure of stroke-related physical disability is the Barthel index.¹⁴ Ceiling effects limit its sensitivity to change because patients with the highest score can, nevertheless, have substantial disabilities.^{15,16} The physical domain of the Short Form 36 (SF-36) has also been used to measure physical function after stroke.^{17,18} In contrast to the Barthel index, the SF-36 has floor effects in which patients with the lowest score may have further clinical deterioration. Although different instruments could be used for patients at different levels of severity, there are benefits to having a single instrument. The Stroke Impact Scale (SIS) is a comprehensive and psychometrically robust stroke-specific outcome measure that was developed to extend the range of function measured by the Barthel index and the physical domain of the SF-36.^{19,20} The SIS was developed from the perspective of patients, caregivers, and health professionals with stroke expertise and includes items measuring 8 domains (strength, hand function, activities of daily living and instrumental activities of daily living, mobility, communication, emotion, memory and thinking, and participation). In addition to the full version of the SIS, an abbreviated version that focuses on the physical domain has been developed.¹² This shorter version, the SIS-16, is specifically designed to better capture the broad range of poststroke physical limitations. As such, it may be useful in monitoring improvement in function over time in this population.

The debate concerning the advantages and disadvantages of large megatrials versus smaller focused phase III trials should be guided by the principles that sample sizes in trials are determined by the study hypothesis and the expected effect size of the intervention.²¹ For example, a trial for a neuroprotective agent with a purported action restricted to white matter, a large expected benefit (eg, >10%), and where the sample might consist of stroke patients with discrete lacunar syndromes demonstrated by imaging an appropriately powered trial might require a relatively small sample size. Another example would be thrombolytic or device recanalization of a specific vessel, such as the middle cerebral or basilar arteries. In such homogeneous stroke populations, an appropriately powered trial might also involve a relatively small sample size because a greater absolute treatment effect is possible in such reperfusion stud-

TABLE 1. Potential Approaches to Reduce Sample Sizes in Phase III Stroke Trials

1. More sensitive outcome measures.
2. Reducing variability of outcome assessment.
3. Developing new methods of analysis of outcome measures (see below).
4. Developing trial recruitment techniques to shorten time windows to increase likely absolute benefit, for example, ambulance-based therapies such as in the FAST-MAG trial.

ies.²² Although focused trials are useful for proof of concept, they may not be broadly generalizable. Conversely, a mechanistically heterogeneous patient population testing an intervention with a small absolute expected benefit would require a large sample size with outcomes measured by a relatively crude measure. However, investigators conducting previous neuroprotection trials expected absolute benefits that were likely too optimistic. This has likely resulted in “large,” but still underpowered, trials.²³ For example, realistic absolute effect sizes for a neuroprotection drug should be $\approx 5\%$ (range 2% to 8%) that would require substantially larger sample sizes (>4000 patients) than previous trials. To control expense and patient and investigator fatigue, sample sizes need to be as small as possible to test the hypothesis. Suggestions to accomplish this goal are outlined in Table 1.

Several other issues related to outcome assessment should be considered. Dependence on a single outcome measure may obscure a beneficial treatment effect, especially in a heterogeneous population. The use of a global test statistic to incorporate data from several measures is attractive and was used successfully in the National Institute of Neurological Disorders and Stroke recombinant tissue plasminogen activator trial (NINDS rt-PA). If a global test statistic of multiple end points is used, all of them must be prespecified and those specified used in the analysis. Heterogeneity among patients in terms of age, severity, and pathophysiology contributes to wide variability outcome. In the absence of highly restrictive selection criteria, a single threshold to determine success may be inappropriate. A “responder” analysis adjusted to baseline severity and other factors may be preferable. In its simplest form, a responder analysis stratifies patients at randomization into groups according to initial severity, predefines a different outcome measure indicative of a positive effect for each stratum, and presumes that all of the strata will be incorporated into the data analysis. For example, the Abciximab in Emergent Stroke Treatment Trial (AbESTT) assigned strata of National Institutes of Health Stroke Scale Score (NIHSS) of 4 to 7, 8 to 14, and ≥ 15 and specified thresholds for success based on the modified Rankin Scale of 0, ≤ 1 , and ≤ 2 , respectively.²⁴ More complicated approaches combine ≥ 2 baseline variables such as age and severity. For example, among patients with moderate initial stroke severity, older patients may be judged against a higher modified Rankin Scale outcome than younger patients; a young patient with a low NIHSS or an elderly patient with high NIHSS may be judged ineligible for a trial, although other patients with similar stroke severity remain eligible.²⁵ Assessing improvement across the entire range of an outcome scale, rather than losing outcome information by dichotomization or trichotomization, is another innovative approach to improving the sensitivity of trial end

TABLE 2. Approaches to Reducing Costs for Stroke Trials

1. Enhancing techniques to simplify recruitment and monitoring.
2. Maximizing productivity of individual centers and, thus, reduce the spread of monitoring costs across a larger number of centers.
3. Developing better relationships between study phases; for example, phase IIB studies may be rolled into phase III studies.
4. Using novel trial design approaches such as the adaptive design and imaging-guided patient selection.

points and is the preferred approach to clinical trial design. When it is expected that the study intervention is likely to yield clinical benefits across all levels of stroke severity, the use of all of the data within a categorical scale will improve study power.²⁶ This potentially more sensitive approach is being used in the Field Administration of Stroke Therapy—Magnesium (FAST-MAG) trial.²⁷ The issue of trial expense is important for sponsors and investigators. The majority of trial costs are incurred in patient recruitment and monitoring. Suggested approaches for reducing cost are outlined in Table 2. By adopting flexible and innovative approaches, the efficiency of translational research in acute stroke trials can be maximized.²⁸

Enhancing Government, Industry, and Academic Cooperation in Acute Stroke Drug/Device Development

Successful clinical trials depend on excellent collaboration and cooperation between government regulatory bodies such as the US Food and Drug Administration (FDA), industry, the trial leadership, and the individual study sites.²⁹ Stroke studies that include combinations of therapies (drug–drug, drug–device, etc) will also involve multiple interested parties. Given this reality, it is important to examine current barriers, as well as suggested solutions, for the development of organized stroke trial networks to facilitate study design and implementation.

Studies with multiple stakeholders present unique challenges and communication can be particularly complex. Many of the communication problems may manifest themselves at study sites where employees of 1 or more companies, coordinating center personnel, and government representatives can all potentially interact with local administrative and clinical personnel. To minimize these local issues, experienced leadership from experienced study physicians and the overall study coordinator is necessary.

The funding source has implications for investigators. Advantages of NIH-sponsored clinical trials include greater investigator control of study design and conduct, a perception of objectivity by peers, prestige for academic centers, and relatively consistent long-term financial support for study cores. However, the NIH peer-review process can take several years from idea generation to awarding of funding. Pharmaceutical-sponsored trials can begin more quickly but often entail less investigator control. When studies combine NIH funding with industry-sponsored activities (device, drug, or other), the administration of the study becomes more complex, although this merger could combine advantages from each type of sponsorship.

There are several important issues to consider related to ethical review boards, which can be centralized, community or

institutionally based (ie, institutional review boards [IRBs]). One important topic of concern for IRBs is indemnification that can be particularly complex if a study involves multiple sponsors. If a study involves both drugs and a device produced by different sponsors, the device company may provide indemnification related to device failure, and the pharmaceutical company may indemnify only issues related to manufacturing defects or side effects of the study drug. For NIH-sponsored trials, the NIH cannot provide direct indemnification. As a result, local hospitals and treating physicians may be left with significant medicolegal risk and be reluctant to participate in trials. The indemnified legal entity (eg, universities versus hospitals) may not be clear. Early agreement by the sponsoring parties can help facilitate dialogue with local IRBs and resolve some of these issues.

A second major contractual issue is the assignment of intellectual property rights. Industry sponsors and lead investigators need to agree on intellectual property issues before trial sites are contacted. The most contentious issues often develop between academic institutions and the device or pharmaceutical sponsors. Negotiations around issues of intellectual property require knowledgeable clinicians and clinical researchers to help resolve institution–industry conflicts.

Despite the completion of more than 129 phase II and 60 phase III stroke trials, few effective treatments for stroke have been identified.^{30,31} There is an urgent need for rapid and efficient completion of additional trials of promising therapies. Progress in developing effective stroke therapies has been hampered by the lack of a large stroke clinical trial network in the United States. Efforts including site identification, hiring research personnel, developing case report forms, and developing data management systems often need to be redone for each new trial. Recreating this complex infrastructure is inefficient and costly. A more effective approach to facilitate rapid implementation and completion of clinical trials could be to develop a nonprofit, academic, stroke clinical trial network or consortium in the United States (that could potentially be expanded internationally). The primary mission of the network would be to efficiently execute high-quality stroke clinical trials.

A stroke clinical trial network could offer a number of important advantages for both industry- and investigator-initiated trials. By maintaining an ongoing infrastructure, supported by a steady stream of projects, clinical trials could be performed more rapidly and efficiently and at a lower cost. A steering committee could identify the most scientifically sound and promising studies and help ensure that trial design and sample size are appropriate. An established network could increase the likelihood that the participating sites and investigators have the necessary expertise, patient volume, and experience to successfully conduct the proposed trials. The network approach could provide the stroke community with an opportunity for education and training, facilitate rapid dissemination of successful therapies into the community, and provide several other advantages as outlined in Table 3.

Regulatory Considerations

The approval of acute stroke therapies requires adequate safety and efficacy data that meet the current regulatory standards.³² The FDA has recognized that stroke is a serious and life-threatening condition, making it eligible for the

TABLE 3. Other Potential Benefits of Trial Consortia

1. Enhancing the efficiency of member centers for performing trials.
2. Enabling centers to more easily perform multiple, simultaneous trials.
3. Having a steering committee to provide expert leadership and opinions about the scientific validity of proposed trials.
4. Providing additional opportunities for investigator education and training.
5. Providing the opportunity to perform trials related to relatively uncommon clinical conditions, eg, carotid dissection or venous thrombosis.

fast-track approval process. However, because tissue plasminogen activator (tPA) remains the only approved drug for acute ischemic stroke, there is limited experience with the regulatory process in this therapeutic area. Lessons and examples regarding the regulatory process from other neurological and non-neurological serious and life-threatening disorders can be extrapolated to acute stroke. Four broad topics concerning the regulatory process for acute stroke therapies were discussed: pre–phase III data, clinical trial outcomes, novel approaches to regulatory approval, and multiple therapies.

Much of the information and opinions regarding pre–phase III data generation were reviewed in the STAIR-II report.² Several issues that are relevant for the regulatory process need amplification and discussion. The importance of a dose-escalation study before phase III is apparent, as the phase II study would provide valuable safety information and could provide confirmatory evidence of efficacy. Although the traditional approach to determine a maximally tolerated dose is conducting phase II studies, this may not be necessary in all situations, particularly if a validated surrogate measure or clinical outcome measure detected a biologically relevant effect at a dose less than the maximally tolerated one.

The difficulties in detecting a clinical “signal” of efficacy are apparent from previous phase II acute stroke studies.³⁰ However, there are several potential ways to try to increase the chances of detecting a valid signal in phase II acute stroke studies. One mechanism would be to enrich the population entered into a phase II trial with those individuals most likely to respond, for example, by only including subjects having a certain stroke subtype or level of severity, strokes restricted to 1 vascular territory, or patients with imaging study results that suggest the presence of an ischemic penumbra, the presumed target of acute stroke therapy.³³ Also, assessing outcome measures at several hours or days in phase II may also be easier and certainly more economical than the traditional 90-day outcome time point. As discussed, clinical outcome measures evaluating different domains such as stroke severity, disability, cognitive status, or quality of life might also be used to detect a signal in 1 of these domains before proceeding to phase III.

Surrogate outcome measures for acute stroke trials may be useful, but remain to be fully validated, in relationship to accepted clinical outcomes. Biomarkers reflecting disease activity are currently available for use in phase II acute stroke studies to provide evidence of drug activity on potentially relevant targets related to this disorder.³⁴ Preclinically, acute stroke therapies are designed to reduce ultimate infarct size with the assumption that clinical and functional outcome will be improved on average if ischemic lesion size is smaller. Thrombo-

lytic agents are presumed to achieve this effect by early initiation of nourishing reperfusion and reducing infarct size, whereas neuroprotective agents are presumed to reduce infarct size by interfering with aspects of the cellular cascade of tissue injury.³³ A potentially relevant biomarker for a thrombolytic agent would be vascular recanalization or an enhancement of reperfusion within the initial few hours after stroke onset. This type of biomarker approach was used in the initial tPA studies in acute myocardial infarction. A recanalization/reperfusion effect in acute ischemic stroke patients could be measured by imaging modalities including traditional catheter-based angiography, CT angiography, magnetic resonance angiography, perfusion CT, perfusion MRI, or ultrasonography. A combination of these modalities could also be used, as several of them provide complementary information. A recent phase II study with the novel thrombolytic desmoteplase suggested that the combination of magnetic resonance angiography and perfusion MRI can provide useful information concerning reperfusion efficacy.³⁵ For both thrombolytics and neuroprotective drugs, the effect of treatment on ischemic lesion evolution or salvage of the imaging-identified penumbra may be potentially relevant biomarkers. MRI is most applicable for this approach by using diffusion MRI pretreatment and T2-weighted or fluid-attenuated inversion recovery imaging at the more chronic time point. One preliminary study suggests that a lack of lesion growth over time is associated with much higher likelihood of reduced clinical severity.³⁶ Demonstrating recanalization/reperfusion effects with thrombolytics and inhibition of lesion growth with thrombolytics or neuroprotectants would be useful in confirming relevant effects on stroke pathophysiology and potentially provide causal confirmation of drug activity.³³ Not only might this information be useful in reassuring sponsors that the candidate agent has relevant activity in the target population, but the information could also be used to provide confirmatory evidence required for approval by the FDA based on the FDA Modernization Act of 1997.³⁷ This assumes that treatment with the agent also leads to a statistically significant beneficial effect in an adequately powered, well-conducted phase III study with a clinically relevant outcome. A report discussing these FDA Modernization Act provisions has emphasized that the confirmatory evidence must be scientifically sound.³⁸ Adequate confirmatory evidence, given that the mechanism of the drug is known, would establish some measure of biological activity, ie, would establish that the drug elicits the expected pharmacological action. In this regard, a dose-response pilot study demonstrating a dose-related effect on relevant biologic activity such as recanalization/reperfusion or ischemic lesion growth would be strong evidence that confirms an empirical, phase III randomized clinical trial with a clinical end point.

Finally, in pre-phase III studies, the issue of including patients with hemorrhage and stroke mimics should be considered. If hemorrhage patients and stroke mimics are to be included in the marketing package, then such patients should be included in the investigational design to ensure safety in this patient population.

Because of the poor record of neuroprotective monotherapy for acute ischemic stroke, combination therapies are the most likely way to markedly enhance the potential for improving outcome.² For combination drug trials in acute ischemic stroke,

it would appear, based on current FDA recommendations, that it is necessary to study each component individually along with the combination, unless there was evidence that 1 of the components by itself would be harmful. Studying each drug in the combination as monotherapy is necessary to confirm that all or most of the benefit of the combination is not derived from 1 component of the combination or that side effects are not entirely related to 1 drug in the combination. A factorial design would be the most efficient approach to a combination therapy trial. FDA attitudes on this issue are changing, as such combinational approaches are used in other therapeutic areas. In particular, if there is reasonable preclinical evidence that the individual components of the combination are either inactive or have a low likelihood of efficacy, then the FDA should be approached to help in understanding how such a combination might be most efficiently tested.

A second approach to multiple therapy trials is adding a new therapy onto an existing therapy such as tPA. For 3-hour time-window studies that include subjects who qualify for IV tPA, it is no longer acceptable to have a placebo arm in countries where tPA is currently approved. Therefore, a novel drug given in combination with tPA would have to be compared with tPA alone. In subjects who do not qualify for tPA, the drug would be compared with placebo. A stratified randomization scheme would be appropriate in this situation. Despite the use of intraarterial therapy up to 6 hours after stroke onset, there is no approved therapy 3 hours. Therefore, a placebo arm is still ethically justified in studies beyond 3 hours.

Conclusions

The development and approval of additional pharmacological therapies for acute ischemic stroke remains complex and challenging. Efforts to develop additional stroke treatments will require adapting and improving clinical trial design and implementation, increasing cooperation among the relevant participating parties and being cognizant of regulatory requirements and changes in the regulatory process. The traditional approach to acute stroke clinical trial design has been problematic at multiple levels. Research questions must be prioritized. Novel approaches to trial design are needed. The stroke research community must address slow recruitment into clinical trials and multiple competing trials. Surrogate markers, especially imaging, must be validated and combination therapies developed. Finally, licensing agencies should work with the stroke community and must recognize the unique challenges of acute stroke trial design that may warrant a different regulatory approach from other disease processes. The requirements of device trials are now impacting on trial methodology and will be the topic of a future STAIR conference.

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