

Recommendations From the STAIR V Meeting on Acute Stroke Trials, Technology and Outcomes

Marc Fisher, Daniel F. Hanley, George Howard, Edward C. Jauch and Steven Warach

Stroke. 2007;38:245-248; originally published online January 4, 2007;

doi: 10.1161/01.STR.0000255951.37434.aa

Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Copyright © 2007 American Heart Association, Inc. All rights reserved.

Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the World Wide Web at:

<http://stroke.ahajournals.org/content/38/2/245>

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in *Stroke* can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the [Permissions and Rights Question and Answer](#) document.

Reprints: Information about reprints can be found online at:
<http://www.lww.com/reprints>

Subscriptions: Information about subscribing to *Stroke* is online at:
<http://stroke.ahajournals.org/subscriptions/>

Recommendations From the STAIR V Meeting on Acute Stroke Trials, Technology and Outcomes

Marc Fisher, MD; Daniel F. Hanley, MD; George Howard, PhD;
Edward C. Jauch, MD; Steven Warach, MD, PhD; for the STAIR Group

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 four STAIR meetings generated publications with 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.¹⁻⁴ The impact of these recommendations from the prior STAIR meetings has been substantial, especially those related to preclinical assessment of purported stroke therapies.⁵ A fifth STAIR meeting was held on March 24 to 25, 2006 in Arlington, Virginia, and over 150 attendees discussed 3 main topics: considerations for measuring outcomes in acute stroke therapy trials, how to incorporate new technologies such as telemedicine and electronic databases into clinical trials, and how to best approach the development of multimodality approaches for acute stroke therapy. This report will summarize the discussions related to these 3 topics.

The recently reported SAINT-I trial has generated discussion regarding using the “shift analysis” to assess treatment efficacy in outcomes such as the modified Rankin Scale (mRS).⁶ This represented a novel approach because mRS data have previously been analyzed by dichotomization of the 7-point scale—for example, outcome of a Rankin score of 2 or less (slight or less disability) versus 3 or more (moderate handicap, severe handicap or death). It is well-known (at least among statisticians) that using such a dichotomization or categorization of data is likely to lose information—and thus make it harder to detect treatment differences (ie, lower statistical power to detect efficacy improvements). As such, the approaches used by the SAINT investigators likely produced a statistically more “powerful” measure of the treatment effect, allowing the hypotheses to be addressed with fewer subjects and over a shorter period of time than might otherwise be required. Future studies should consider using a similar approach.

The “shift analysis” approach, however, has not yet been widely accepted and there are arguments supporting other analytic methodologies. The dichotomous approach to the

analysis of the mRS has some substantial advantages. Specifically, there are virtually no restrictive assumptions underlying the analysis of a dichotomous outcome. In contrast, the most common approaches for analysis of ordinal scale data requires the “proportional odds” assumption in which the magnitude of the improved efficacy associated with the new treatment is assumed to be consistent across the ordinal spectrum of responses. If this assumption is “reasonably” met then ordinal analysis captures the shift in the distribution of outcomes and the statistical power that is lost in the categorical analysis will be captured. If, however, this assumption is not met, the ordinal analysis may have lower power and fail to detect differences that would have been found using a categorical approach. Hence, in an attempt to gain additional statistical power there is a risk of actually lowering statistical power. There are statistical tests to assess whether these assumptions are reasonable, but unfortunately these tests have notoriously low power to detect violations of the assumption. The trial design decisions to gain power can be further extended by considering the mRS as a continuous scale; however, this gain in power comes with even more stringent assumptions.

The naïve investigator might suggest that analyses be performed under categorical, ordinal, and even a continuous structure for the mRS with the final approach selected on the basis of the results. It is important that the analysis plan be specified before database-release to avoid incorrectly concluding a treatment effect by having “selected” the “best analysis”. Not only are more assumptions required as one moves from a categorical to an ordinal structure, or from an ordinal to a continuous structure, but it also becomes harder to interpret the results. The obvious implications of a 2-category outcome (for example, “12% more of the patients had a ‘good’ outcome with the new treatment”) give way to subtler interpretations of results from an ordinal analysis (for example, “the pooled odds across the seven mRS categories of better outcome were 1.4 times greater with the new treatment”) or continuous outcome (for example, “the mean mRS was 0.8 points better with the new treatment”) can become problematic, particularly to patients. Hence, the decision to evaluate outcome using an ordinal or continuous

Received and accepted December 1, 2006.

From the University of Massachusetts (M.F.), Worcester, Mass; Johns Hopkins (D.H.), Baltimore, Md; the University of Alabama at Birmingham (G.H.), Alabama; the University of Cincinnati (E.J.), Ohio; and the National Institutes of Health (S.W.), Bethesda, Md.

Correspondence to Marc Fisher, MD, UMASS/Memorial Healthcare, 119 Belmont St, Worcester, MA 01605-2982. E-mail fisherm@ummhc.org (*Stroke*. 2007;38:245-248).

© 2007 American Heart Association, Inc.

Stroke is available at <http://www.strokeaha.org>

DOI: 10.1161/01.STR.0000255951.37434.aa

measure runs the risk of losing power and obscuring a clear description of the treatment effects. Hence, before making this decision one needs to check the reasonableness of the assumptions by reviewing similar studies, and checking that both scientific and clinical audiences are comfortable with a subtler presentation of results. The global statistic, which often increases study power, is not accepted by the FDA Neuropharmacological Division as a primary end point analytic technique because it is difficult to interpret clinically. Shift analysis, in contrast, is accepted, as clinical interpretation is attainable.

The most commonly used end points for assessing treatment efficacy in phase III stroke trials are the mRS and the National Institutes of Health Stroke Scale (NIHSS). Regardless of the chosen end point, steps must be taken to reduce variability among personnel performing the assessments. Appropriate steps should be implemented to ensure that personnel performing the outcome scales receive adequate training and as appropriate have acceptable certification/documentation.⁷ Many acute stroke therapy trials have required such training and certification in the NIHSS via the viewing of a training tape and then completing an examination tape with centralized scoring for certification. The SAINT trial took such an approach with the mRS, and future trials that use the mRS should consider adopting similar procedures. If repeated assessments over time are required to evaluate temporal changes, having one individual perform each assessment eliminates inter-rater variability for that subject. Another approach to minimizing variability in the acquisition of outcome measures such as the mRS and the NIHSS could be to use centralized data collection. Both of these outcome measures can be performed reliably remotely and a qualified, blinded, centralized individual could gather the information needed to derive an outcome score.^{8,9} Such an approach is used in imaging-based trials in which centralized reading of images by one qualified reader is typical. In addition to using a functional outcome scale such as the mRS or a neurological deficit scale such as the NIHSS, consideration should be given to measuring cognitive outcome. The most appropriate scale to measure cognitive outcome remains contentious. A recent conference on vascular cognitive impairment harmonization standardization suggested a 5-minute protocol that could be readily adapted to the follow-up period of an acute stroke therapy trial once adequate validation of this protocol is available.¹⁰ The vascular cognitive impairment data could then be used as a secondary and perhaps primary outcome measure for an acute stroke therapy trial.

A variety of new information and other technologies are being used to improve or extend clinical practice. These technologies offer both opportunities and challenges for clinical trials. Three evolving information technologies that are potentially relevant for the design, implementation and performance of acute stroke therapy trials are telemedicine, electronic databases and electronic case report forms (CRF's). Several telemedicine networks are currently available in the United States and elsewhere.^{11,12} They are being used to extend stroke-care expertise into smaller hospitals without these resources and specifically to increase the use of intravenous tissue plasminogen activator (t-PA) within the

TABLE 1. Potential Challenges Posed by Telemedicine Use in Acute Stroke Trials

1. Is a local coinvestigator for the trial needed?
2. How can local responsibility and accountability for conducting the trial and source documentation be managed?
3. How can local pharmacy support be implemented?
4. Is IRB oversight the responsibility of the local hospital or the central hospital?
5. Is follow-up of the patient the responsibility of the local or central hospital?
6. What are the most appropriate mechanisms for financial compensation to the local and central hospitals?
7. Will there be regulatory concerns about data derived via telemedicine accrual of patients?

IRB indicates Institutional Review Board.

currently approved 3-hour treatment window.¹² Several different platforms for stroke telemedicine are available, but they share commonalities such as high-speed secure access between participating central and remote hospitals, high-resolution video synchronized with a concomitant audio feed, and simultaneous DICOM access for viewing of images.¹³ These telestroke systems allow physicians at a remote site to directly interact with patients at the local hospital to provide clinical evaluations and decision-making support so that therapy can be given quickly, with or without subsequent transport to the hub hospital. Telestroke is, however, associated with a number of challenges and concerns. The system requirements for the best implementation and performance of stroke telemedicine have not been standardized. The safety and efficacy of stroke telemedicine consultations as compared with on-site evaluations is uncertain, although preliminary experience suggest that the 2 are comparable.¹⁴ Furthermore, telemedicine methods may not be more effective than telephone consultations. Administrative and legal hurdles such as how to best obtain appropriate credentialing at multiple hospitals and licensure in multiple states, how to provide adequate written or electronic documentation of service and adequate reimbursement remain unresolved issues. Despite these multiple hurdles to widespread implementation of telemedicine-based stroke networks and care delivery, it is likely that their availability and use will dramatically increase over the next few years. Stroke telemedicine can then be used in clinical trials for both on-site initiation of treatment or remote assessment of inclusion/exclusion criteria and then rapid transport of appropriate subjects to the central trial site. The number of potential trial sites and investigators could expand, leading to a larger and more diverse pool of subjects, and presumably more rapid completion of trials. The use of stroke telemedicine for acute therapy trials will, however, pose many challenges as outlined in Table 1.

The use of electronic databases for clinical stroke trials could provide several unique advantages but will also pose a number of challenges. An electronic database can be generated in conjunction with electronic data capture and an electronic CRF.¹⁵ Such an electronically derived and maintained database of trial participants could be used to improve the quality of data collection, provide standardization across

TABLE 2. Advantages and Disadvantages of Electronic CRFs**Advantages**

1. Provide real-time monitoring capability
2. Ease of data checking and enhanced data consistency
3. Common training and data elements
4. Interface with electronic data sources

Challenges

1. Regulatory concerns
2. Is double entry, paper and electronic going to be required
3. Electronic Security of the data base
4. Data security with computer failures, requiring extensive backup systems

trial sites, be linked ultimately to similar databases such as the VISTA collaboration and then be used collaboratively for trial simulations and determination of sample-size requirements. Among the challenges posed by electronic databases in clinical trials are costs, personnel recruitment and training, maintaining confidentiality, source documentation and site monitoring, and data validity/reliability. These challenges should be surmountable, and the acquisition and maintenance of electronic databases in future acute stroke trials were strongly encouraged. Electronic CRFs are now frequently used in stroke trials, and their use will likely become the standard. The use of electronic CRFs provides a number of advantages over paper CRFs but also several challenges (Table 2). The advantages appear to outweigh the limitations, and it is very likely that use of electronic CRFs in stroke trials will continue to expand.

The third topic discussed by the STAIR V group was the issue of combination stroke therapies, an important area for the future that was initially discussed at the STAIR III meeting. Targets for combined therapies should include vascular recanalization with complete restitution of flow and tissue protection either pre- or postrevascularization. The scientific issues involved in combination therapies focus on vascular patency and tissue preservation but does not always consider the practicalities of therapeutic development, regulatory approval and commercialization. Industry is concerned about regulatory requirements and the market environment that can affect the implementation and performance of a development program. Considering each perspective is important given the shared goal of enhancing the current treatment environment and the need for cooperation between academia and industry. Maintaining the integrity of the research program is of primary importance.

Because treatment with intravenous t-PA is established as appropriate for selected patients with ischemic stroke who can be treated within 3 hours of symptom onset, new interventions need to evaluate additional revascularization or tissue preservation techniques in comparison to this standard.¹⁹ Characterizing vascular and tissue abnormalities identified by diffusion/perfusion MRI and magnetic resonance angiography or perfusion CT and CT angiography may be used to select the subsets of patients who would be most likely to benefit from these approaches.¹⁶ Preliminary information from the initial desmoteplase trials and the DEFUSE study support the utility of MRI-based penumbral imaging for

patient selection beyond 3 hours.^{17,18} Preclinical safety and efficacy data should be available to support the testing of the combination in the specific clinical situation.

Because there remains no approved therapy of proven benefit given beyond 3 hours, trials including patients after 3 hours would use placebo controls. Equipoise with respect to the potential beneficial outcomes would be the major principle in trial design in this time frame. Specific localization of anatomic and vascular lesion locations and penumbral-imaging may be important for defining appropriate patients. It would be important to have evidence from preclinical studies supporting improved outcome using similar imaging characteristics as those to be used in the clinical trial with the proposed interventions would be useful to develop specific trial designs in this time frame. Trials of 2 drugs or a device+drug could also be considered. These could be evaluated in a classic factorial design in which each therapy is evaluated alone and compared with the combination arm and a placebo. In special circumstances, it can be envisioned that the combination might only be compared with a placebo arm.

The design requirements for combined studies for acute stroke therapy in which devices might be coupled with drugs raises concerns about the differences between the regulatory requirements for devices and pharmaceuticals.^{20,21} The evaluation of combined interventions should be appropriately tailored to nature of the combination, ie, drugs+devices. FDA assigns an agency component to lead the review and regulation of such combinations based on its determination of the "primary mode of action" of the combination product. For example, drug-eluting stents were assigned to the device branch of the FDA, not the cardiovascular/renal drug branch, although the drug branch consulted extensively in the review. The requirements for approval of drugs and devices differ.²² Harmonization of these differences as much as possible within the current statutory framework was strongly suggested to avoid perceived and apparent discrepancies in the rigorosity of the approval process between the regulatory approval process for these 2 vital therapeutic modalities. This harmonization will be especially relevant when drugs and devices are combined and it is unclear which component of the therapeutic combination is of primary or secondary importance.

The goals of the STAIR V meeting were to build on the foundation of recommendations provided by the prior STAIR meetings in a timely and innovative manner. The development of acute stroke therapies now encompasses both drugs and devices. It is important to recognize that the utility of either of these treatment approaches alone or in combination can only be evaluated with the use of appropriate outcome measures that are clinically meaningful and relevant. The mRS distribution shift used in SAINT-I represents a novel approach to trial data analysis. It is likely that new technologies such as telemedicine and electronic data forms will enhance trial implementation and expedite trial completion. The new era of combination stroke therapy development and implementation will be challenging for clinical trialists, industry sponsors and regulatory agencies. Most feel that combination therapies represent a future direction that will optimize patient outcomes and study design and regulatory

requirements must be carefully considered to avoid as many pitfalls as possible.

Appendix

STAIR V Contributors: Harold Adams, Gregory Albers, Harvey J. Altman, Timothy Ashwood, Christopher A. Assaid, Richard Atkinson, Lori Austin, Natan Bornstein, Joseph Broderick, Nikolai C. Brun, Stephen Davis, Hans-Christoph Diener, J. Donald Easton, Lori Enney, Paul F.C. Eng, Seth Finklestein, Anthony Furlan, Katherine Gallagher, Larry B. Goldstein, Philip Gorelick, Savion Gropper, Werner Hacke, Vladimir Hachinski, David C. Hess, Daniel B. Hier, Tony W. Ho, Gary Houser, George Howard, Sonja Illic, Markku Kaste, Kennedy Lees, David Levy, Robert Lew, Marie Luby, Patrick Lyden, Dexter L. Morris, Gerard O'Malley, Tomas Ordergren, Arthur Roach, Melissa C. Rosenberg, Allan Rozenberg, Marilyn M. Rymer, Wade Smith, Ralph L. Sacco, Laura R. Sauerbeck, Jeffrey L. Saver, Sean Savitz, Richard Scheyer, Julio J. Secades, Isaac E. Silverman, Walter Singleton, Brett Skolnick, Michael Sloan, Eric Smith, Wolfgang Söehngen, Mariola Söehngen, Nina J. Solenski, Jackson Streeter, Francisco Villar, Ajay K. Wakhloo, Michael Walker, Warren Wasiewski, Lawrence R. Wechsler, Margaret Zaleska, Justin Zivin.

Disclosures

None.

References

- Fisher M; Stroke therapy academic industry roundtable. Recommendations for standards regarding preclinical neuroprotective and restorative drug development. *Stroke*. 1999;30:2752–2758.
- Fisher M; Stroke Therapy Academic Industry Roundtable. Recommendations for Clinical Trial Evaluation of Acute Stroke Therapies. *Stroke*. 2001;32:1598–1606.
- Fisher M; for the Stroke Therapy Academic Industry Roundtable. Recommendations for advancing development of acute stroke therapies. *Stroke*. 2003;34:1539–1546.
- Stroke Therapy Academic Industry Roundtable. Enhancing the Development and Approval of Acute Stroke Therapies: Stroke Therapy Academic Industry Roundtable (STAIR)-IV. *Stroke*. 2005;36:1808–1813.
- O'Collins VE, Macleod MR, Donnan GA, Horky LL, van der Worp BH, Howells DW. 1,026 experimental treatments in acute stroke. *Ann Neurol*. 2006;59:467–477.
- Lees KR, Zivin JA, Ashwood T, Davalos A, Davis SM, Diener HC, Grotta J, Lyden P, Shuaib A, Hardemark HG, Wasiewski WW. NXY-059 for acute ischemic stroke. *N Engl J Med*. 2006;354:588–600.
- Krams M, Lees KR, Hacke, Grieve AP, Orgogozo JM, Ford GA; for the ASTIN Study Investigators. Acute stroke therapy by inhibition of neutrophils (ASTIN): an adaptive dose-response study of UK-279,276 in acute ischemic stroke. *Stroke*. 2003;34:2453–2548.
- Wang S, Lee SB, Pardue C, Nichols FT, Adams RJ, Hess DC. Remote evaluation of acute ischemic stroke: reliability of National Institute of Health Stroke Scale via telestroke. *Stroke*. 2003;34:e188–e182.
- Merino JG, Lattimore Su, Warach S. Telephone assessment of stroke outcome is reliable. *Stroke*. 2005;36:232–233.
- Hachinski V, Iadecola C, Petersen RC, Breteler MM, Nyenhuis DL, Black SE, Powers WJ, DeCarli C, Merino JG, Kalaria RN, Vinters HV, Holtzman DM, Rosenberg GA, Dichgans M, Marler JR, Leblanc GG. National Institute of Neurological Disorders and Stroke-Canadian Stroke Network Vascular Cognitive Impairment Harmonization Standards. *Stroke*. 2006;37:2220–2241.
- Wang S, Hartmut G, Lee SB, Pardue C, Waller J, Nichols FT, Adams RJ, Hess DC. Remote evaluation of acute ischemic stroke in rural community hospitals in Georgia. *Stroke*. 2004;35:1735–1738.
- Audebert HJ, Kukla C, von Claranau SC, Kuhn J, Vatankeh B, Schenkel J, Ickenstein GW, Haberl RL, Horn M. Telemedicine for safe and extended use of thrombolysis in stroke: The Telemed Pilot Project for Intergrative Stroke Care (TEMPIS) in Bavaria. *Stroke*. 2005;36:287–291.
- Fisher M. Developing and implementing future stroke therapies: The potential of telemedicine. *Ann Neurol*. 2005;58:666–671.
- Mayer BC, Lyden PD, Al-Khoury L, Cheng Y, Raman R, Fellman R, Beer J, Rao R, Zivin J. Prospective reliability of the STROKE DCO wireless/site independent telemedicine system. *Neurology*. 2005; 1058–1060.
- Haux R. Health information systems-past, present and future. *Int J of Medical Informatics*. 2006;75:268–281.
- Donnan GA, Davis SM. Neuroimaging, the ischaemic penumbra, and selection of patients for acute stroke therapy. *Lancet Neurology*. 2002;1: 417–425.
- Hacke W, Albers GW, Al-Rawi Y, Bogousslavsky J, Davalos A, Eliasziw M, Fischer M, Furlan A, Kaste M, Lees KR, Soehngen M, Warach S; DIAS Study Group. The Desmoteplase in Acute Ischemic Stroke Trial (DIAS): a phase II MRI-based 9-hour window acute stroke thrombolysis trial with intravenous desmoteplase. *Stroke*. 2005;36:66–73.
- Albers GW, Thijs VN, Wechsler L, Kemp S, Schlaug G, Skalabrini E, Bammer R, Kakuda W, Lansberg M, Shuaib A, Coplin W, Hamilton S, Moseley M, Marks MP; for the DEFUSE Investigators. MRI profiles predict clinical response to early reperfusion: The DEFUSE study. *Ann Neurol*. 2006;23:508–517.
- The National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group. Tissue PA for acute ischemic stroke. *N Engl J Med*. 1995;333:1581.
- Felten RP, Ogden NRP, Pena C, Provost MC, Schlosser MJ, Witten CM. The Food and Drug Administration Medical Device Review Process: Clearance of a clot retriever for use in ischemic stroke. *Stroke*. 2005;36: 404–406.
- Katz R. Evidentiary standards for drug development and approval. *NeuroRx*. 2004;1:307–316.
- Furlan A, Fisher M. Devices, drugs and the Food and Drug Administration: increasing implications for ischemic stroke. *Stroke*. 2005; 36:398–399.

KEY WORDS: ischemia ■ telemedicine ■ therapy ■ stroke trials