Recommendations for the Relationship Between Sponsors and Investigators in the Design and Conduct of Clinical Stroke Trials

Geoffrey A. Donnan, MD; Stephen M. Davis, MD; Markku Kaste, MD; for the International Trial Subcommittee of the International Stroke Liaison Committee, American Stroke Association

Background—As increasing numbers of clinical trials are being conducted worldwide, there has been concern about the relationship between the sponsors and investigators. Both parties need benchmarks or recommendations to act as a reference point when trials are initiated and conducted. These recommendations are designed to fulfill this role.

Summary of Comment—A series of meetings of the International Trial Subcommittee of the International Stroke Liaison Committee, American Stroke Association, were conducted to review a series of draft recommendations that were then modified on the basis of the experience of the committee in the conduct of clinical trials. Consensus was reached on all points of the final document. The recommendations represent the opinions of the authors and do not necessarily reflect the views of the American Stroke Association. The document contains sensible recommendations concerning required sponsor company qualities, trial management structure, protocol development, trial conduct, data management, blinding, data analyses, publication, remuneration, and conflict of interest issues.

Conclusions—The recommendations should provide a simple and practical benchmark for both investigators and sponsors in the conduct of clinical trials. Although designed for trials involving therapies for stroke, the framework allows generalization to other disciplines. (Stroke. 2003;34:1041-1045.)

Key Words: clinical trials ■ drug industry ■ health planning guidelines ■ research support

A n increasing number of trials are being conducted internationally to test hypotheses concerning the safety and effectiveness of therapies, devices, or surgical procedures in the area of acute stroke as well as primary and secondary prevention. Since many of these trials are being conducted by the pharmaceutical industry, either alone or in partnership with other funding bodies, there is a need for a minimum set of standards to be established concerning the relationship between companies and investigators. Issues of quality, independence of the investigators, and low publication rates of negative trials have raised levels of concern worldwide among physicians generally; those conducting stroke trials are no exception.1-3 Further concern has been expressed recently about conflict of interest in trial interpretation and writing of guidelines.4-6 Publication of trials with low credibility ratings as well as publication bias arising from failure to publish negative trials has been well documented.7-10 While there is an alleged hierarchy of trial credibility ranging from purely investigator-driven and national research body–funded trials to in-house industry trials (Table),11 a pragmatic interaction between investigators and industry may help to raise standards overall. This concept is embodied in the meeting of the Stroke Therapy Academic Industry Roundtable.12

There are a number of increasingly well-organized trial networks or consortia being developed worldwide, for example, the Canadian Stroke Consortium and the Australasian Stroke Trials Network. Collaboration among these groups while using recommendations such as those developed here will help to set benchmark standards of trial development and conduct. Pharmaceutical companies taking heed of these recommendations will be more assured of acceptance of their data by the international stroke community.

Methodology

The views expressed in this article are the result of a series of meetings of the International Trial Subcommittee Committee of the International Stroke Liaison Committee of the Amer-
Funding for Clinical Trials: Models of Relationships Between Academic and Commercial Groups*

<table>
<thead>
<tr>
<th>Model</th>
<th>Comments</th>
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<tr>
<td>1. Investigator-only–driven studies, either unfunded or funded from local sources.</td>
<td>• Samples sizes often small because investigators less experienced and funding levels low.</td>
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<td></td>
<td>• Modest peer review.</td>
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<td>• Level of monitoring may be low.</td>
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<td>• Trial results reasonably credible.</td>
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<tr>
<td>2. Investigator-driven with national research organization funding.</td>
<td>• Usually well-run studies with adequate sample size. Studies run to completion without external influence.</td>
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<td></td>
<td>• High-quality peer review.</td>
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<tr>
<td></td>
<td>• Trial results highly credible.</td>
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<tr>
<td>3. Partnership between academic investigators and pharmaceutical company. Funds provided by national research organization and pharmaceutical company. Trial conducted entirely by investigators.</td>
<td>• High-quality peer review.</td>
</tr>
<tr>
<td></td>
<td>• Very adequate sample sizes with credible results because of “hands-off” approach by the pharmaceutical companies.</td>
</tr>
<tr>
<td></td>
<td>• Trial results highly credible.</td>
</tr>
<tr>
<td>4. Investigator–pharmaceutical company partnership but pharmaceutical companies monitor trial, collect and analyze data in house. Independent steering and safety monitoring committees.</td>
<td>• Data not often able to be checked by investigators.</td>
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<td>• Trials sometimes not completed because of “futility analyses.”</td>
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<tr>
<td></td>
<td>• Modest or nonexistent peer review.</td>
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<tr>
<td></td>
<td>• Trial results reasonably credible.</td>
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<tr>
<td>5. Pharmaceutical company conducts trial entirely. No independent steering or monitoring committee.</td>
<td>• All analyses done “in house,” participants unable to check data.</td>
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<td></td>
<td>• Poor-quality peer review.</td>
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<td>• Negative trial results often not published.</td>
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<td>• Quality of study centers often less certain.</td>
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<tr>
<td></td>
<td>• Trials may not run to completion when “futility analyses” performed.</td>
</tr>
<tr>
<td></td>
<td>• Trial results least credible.</td>
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* From Reference 11.

American Stroke Association. The committee was selected and approved by the American Stroke Association on the basis of experience in clinical trial conduct. The recommendations refer primarily to phase II, III, and IV trials. Consensus was reached on all points of the report (at face-to-face meetings so that no member disagreed with the final stance taken), but the content does not necessarily reflect the opinion of the American Stroke Association. The list of participants is listed in the Acknowledgments section at the end of the article. All members are stroke physicians who have been involved in the conduct of clinical stroke trials. Literature concerning the role of sponsors in the conduct of clinical stroke trials was reviewed with the use of MEDLINE search strategies. Any existing guidelines or recommendations were also reviewed.

Recommendations

1. Pharmaceutical Company Qualities
   The pharmaceutical companies involved in clinical research should have a good track record of cooperation with experienced stroke investigators. In the case of new companies, emphasis on a good working relationship should be established early.

2. Management Structure
   As a minimum, the organizational structure of any trial should contain a Steering Committee and Safety Monitoring Committee or Data and Safety Monitoring Board.

   Steering Committee
   The Steering Committee should be independent of the sponsoring company but, on occasions, the company may have a minority number of members on the committee (preferably 1 or 2 members only). The Steering Committee should consist of experts in the area being investigated, and members should be of significant international standing. In trials in which a number of countries or continents are involved, a reasonable representation from each region should occur. The chairman of the committee should not be a member of the sponsoring company and should be selected by mutual consent of the Steering Committee.

   Safety Monitoring Committee
   The Safety Monitoring Committee will also be independent of the company and have no company representatives. Members should be experienced in the field of clinical trial conduct, and the committee should preferably contain representatives from clinical medicine and those with statistical expertise. Continuous safety monitoring to permit prompt assessment of individual and aggregate adverse experiences or adjudication of events should be possible.

   Relationship Between Steering and Safety Monitoring Committees
   Before commencement of the trial, the Steering Committee and Safety Monitoring Committee may meet to determine issues of data flow and cessation of trial rules. In general, recommendations from the Safety Monitoring Committee should be made to the Steering Committee concerning continuation or cessation of the trial. The final decision concerning the status of the trial will be taken by the Steering Committee.
Coordinating and Data Center

The Coordinating and Data Center should preferably be external to the company at a site designated by the Steering Committee. If the Coordinating and Data Center is within the company, the Steering Committee will have the right to influence its activities.

Randomization Center

Preferably the Randomization Center should be external to the Coordinating and Data Center so that the Randomization Center may hold the treatment allocation codes. This arrangement is not absolute, and other models of trial conduct may allow the randomization center to be collocated with the coordinating and/or data center. The Randomization Center should definitely be external to the company.

3. Trial Design and Protocol Development

A randomized, double-blinded, multicenter, controlled technique should be regarded as the gold standard for phase III trials. Modifications may be acceptable under some circumstances; for example, in trials of surgical procedures double blinding may not be possible. An initial draft of the protocol may be developed by members of the Steering Committee, the company, or investigators. The final protocol must be approved by the Steering Committee. It is highly desirable for the Steering Committee to make a meaningful and independent intellectual contribution to the final protocol.

4. Trial Conduct

The trials should be supervised according to Good Clinical Practice guidelines. An independent Clinical Research Organization may be employed to monitor the trial. Sites and investigators may be selected by a variety of means, but final approval based on quality of the sites must be given by the Steering Committee. These investigators should have experience in clinical stroke research so that the trial has credibility and Good Clinical Practice guidelines are more likely to be followed.

5. Data Management

Crude data will be held at the Coordinating and Data Center. Collations of these data will be supplied to the Safety Monitoring Committee at predetermined times requested by this committee or at any other time the committee may so determine. If the Coordinating Center is within the company, copies of the data shall be held by the Steering Committee at the completion of the trial to allow access by the investigators.

6. Blinding Issues

In the case of blinded trials, sponsors and all members of the Steering Committee shall remain blinded throughout the conduct of the trial. Blinded data will be reviewed by the Safety Monitoring Committee at predetermined times (see above) and unblinded data at the discretion of the same committee. Restricted members of the Data Center will be unblinded when data are forwarded or requested by the Safety Monitoring Committee.

Unblinding will occur at the completion of the trial or at its early termination. The unblinding sequence should be from the Randomization Center to the Coordinating and Data Center so that analysis according to treatment effect can occur. The Steering Committee should then receive the unblinded analysis for review.

7. Data Analysis

Data analysis will be undertaken at the Coordinating and Data Center or at a site approved by the Steering Committee. Full analysis will occur when the data have been cleaned and the database has been locked. The results of the data analysis will be given first to the Steering Committee. Initial access to this information by the company will be usually via its Steering Committee representative(s) so that early and inappropriate access to this information by the company may be avoided. By prior agreement, the data analysis results may be given simultaneously to the Steering Committee and sponsors. Futility analyses should be kept to a minimum, because early termination of a trial may be biased by commercial considerations, before an adequate sample size is examined. Stopping rules should be based on safety and efficacy. These rules should be established by the Steering Committee in conjunction with the Safety Monitoring Committee before trial commencement.

8. Publication

The results of the trial must be submitted for publication regardless of its outcome. The Steering Committee should approve a publication policy before trial commencement. A Publication Committee may be established that may have one or more representatives of the company as members, but they would be in the minority. Publication regarding further analyses performed on the data will be by mutual agreement between the Steering Committee and the company.

9. Remuneration

Investigator Sites

In general, remuneration provided for patient recruitment to individual sites shall be standardized to each country depending on infrastructure costs. Individual variation in site remuneration should be avoided.

Committees

Remuneration for time spent, travel, and accommodations may be made to committee members at a rate agreed to by all parties.

10. Conflict of Interest

Individuals who are aware of a potential or existing conflict of interest that may preclude them from committee involvement or investigator participation must make this known to the Steering Committee so that appropriate action may be taken.

11. Responsibilities of Researchers

All researchers have a responsibility to patients, their institutions, and the regulatory agencies to ensure that the trial is conducted to the highest ethical and scientific standards.

Discussion

As in other areas of medicine, the conduct of clinical trials in stroke is a continuously evolving process. Trial design is becoming more sophisticated, as is the relationship between
investigators and sponsors. This is necessary in view of the escalating costs of bringing a new compound into the market place, estimated to be as much as US $500 million in 1999. The failure of numerous trials of neuroprotection in acute ischemic stroke raises the stakes for investigators and industry, both anxious for success. In the context of these pressures, there is a need for recommendations concerning the relationship between investigators and sponsors to which both parties can refer when initiating a trial.

Adherence to these recommendations will overcome such thorny issues as access to data by investigators, timeliness of publication, and success in having submitted manuscripts accepted by credible journals. The majority of quality general medical journals (JAMA, New England Journal of Medicine, Canadian Medical Association Journal, Journal of the Danish Medical Association, Lancet, MEDLINE/Index Medicus, New Zealand Medical Journal, Journal of the Norwegian Medical Association, Dutch Journal of Medicine, Annals of Internal Medicine, Medical Journal of Australia, and Western Journal of Medicine) now require disclosure of the role of the sponsor and a written assurance that the investigators accept full responsibility for the conduct of the study, have had access to all the data, and had the authority to publish it. This requirement has now been endorsed by the leading neurology journals (Archives of Neurology, Muscle and Nerve, European Journal of Neurology, Neurology, Clinical Neurophysiology, Stroke, Annals of Neurology, Journal of Neurology, Neurosurgery and Psychiatry, Movement Disorders, Journal of the Neurological Sciences, and Brain). Adherence to other frameworks for trial reporting, such as the CONSORT agreement between leading journals, would also be facilitated.

Although focused mainly on issues relating to Data Monitoring Committees, a recently produced Food and Drug Administration draft document also provides helpful recommendations for sponsors and investigators in the conduct of clinical trials. Generally, the recommendations are in accord with our own; their presence also reflects the need for such documents in other countries as well as a global view. The UK Medical Research Council has produced “Guidelines for Good Clinical Practice in Clinical Trials,” in which the procedures for clinical trial organization and conduct are well addressed, but no real attempt to address the difficult issue of the relationship with sponsors is made. The European Agency for the Evaluation of Medical Products has produced a more specific document concerning treatments for acute stroke. In this document, study objectives, methods to assess efficacy, selection of patients, trial design, statistical issues, and safety assessment are discussed, but again, no reference to the relationship with sponsors is made.

The issue of publication of the results of clinical trials, regardless of outcome, is a particularly important one. In our recommendations (point 8, Publication), the results should be submitted for publication as a minimum requirement. If a manuscript is rejected, repeated submission may be necessary, particularly if trial results are negative. There is an ethical imperative to publish such results, and there is a view that research ethics committees may have an important role in this process. The publication of trial results in abstract form only is not an acceptable form of public dissemination of information.

We emphasize that our recommendations are provided to assist rather than to hinder the clinical trial process. As clinical trialists, the authors have been involved in many cooperative studies with industry and other sponsors that have been a positive experience and some that have been less so. We suggest that by both parties adhering to these recommendations, the experience is more likely to be uniformly positive. As one of the first of its type, modifications are certain to be needed to accommodate changing practices with time. Although designed primarily for trials involving therapies for stroke, the framework of the document allows generalization to other disciplines. We hope that publication of these recommendations may stimulate organizations to develop similar documents. Ideally, broadly based guidelines with representation from a range of stakeholders, including industry and consumers, need to be developed.

Definitions

The Company: Refers to pharmaceutical or other companies (eg, providing devices) that may be engaged in the need to conduct clinical trials and their financial sponsorship.

Good Clinical Practice (GCP): As per published guidelines.

Clinical Research Organization (CRO): Any commercial organization with expertise in the monitoring of clinical trials.

Steering Committee: Committee overseeing the development and conduct of the trial and in whom ultimate responsibility for this activity rests.

Safety Monitoring Committee: Otherwise known as Data and Safety Monitoring Board (DSMB). The independent committee to whom aspects of data monitoring and safety concerns have been entrusted.

Data Center: Location at which all data are collated and stored.

Coordinating Center: Location at which the main organization structure of the trial is located.

Randomization Center: Location at which the randomization process occurs if trial design includes central randomization.

Acknowledgments

The authors have received grants and/or consulted for numerous pharmaceutical companies involved in the conduct of stroke trials. The International Trial Subcommittee of the International Stroke Liaison Committee, American Stroke Association, includes the following participants: Markku Kaste (Chair), Geoffrey Donnan, Gregory del Zoppo, Jae Kyu Roh, Jean Marc Orgogozo, Julien Bogousslavskiy, Meng Cheong Wong, Nils-Gunnar Wahlgren, Richard Kay, Stephen M. Davis, Takehiko Yanagihara, Werner Hacke, Zhen Qin.

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Stroke. 2003;34:1041-1045; originally published online March 20, 2003;
doi: 10.1161/01.STR.0000063142.39828.67
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2003 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/34/4/1041

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