Clinical Stroke Trials
Guarding Against Bias
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Attendees at the recent 24th AHA International Joint Conference on Stroke and Cerebral Circulation were startled when an investigator of an industry-funded clinical trial selected for presentation took the podium to announce that he was being prevented from presenting the results of the study by the pharmaceutical company sponsor. Although the data had apparently been held by the sponsor for an adequate period to allow careful review and analysis, permission to publicly disclose the results was withdrawn by the company’s senior management the evening prior to the abstract presentation, purportedly based on concerns about the accuracy of the information. Because of contractual agreements with the investigators, the industry sponsor maintained a right to block public disclosure. Although we are not privy to the details of the circumstances prompting this episode, it may represent one of the most blatant recent examples of the potential negative side of academic-industry cooperation in the conduct of patient-based clinical research and has important legal, ethical, and scientific implications.

A contract between the investigators and the pharmaceutical company sponsor was cited as the justification for blocking the presentation of the study results. However, the American Heart Association abstract submission document was also signed and indicates that if accepted, the presentation will occur (and implicitly that time on the program will not be granted to another presentation), that it presents original work, and that there is no apparent conflict of interest. In addition, informed consent documents signed by patients (or their legal representatives) participating in clinical trials generally include statements indicating the potential risks and benefits of participation and the potential for gaining further information about the treatment of stroke patients that may be used to help others. The patients and their families have agreed to participate in an activity with risk and have the right to be assured that the results of the study will be transmitted to the scientific community in a timely fashion. We maintain that these other documents (and the informed consent in particular) may also have legal standing as contracts and that inappropriate delays or limitations in the scope of presentations may represent breaches of these contracts.

Regardless of the legal issues, investigators are ethically obligated to present both unfavorable and favorable results to the medical community. Negative or inconclusive studies are as important contributions to medical knowledge as trials demonstrating therapeutic benefits. The conduct of medical conferences and the activities of research and academic institutions are predicated on the premise that new information will be disseminated rapidly and accurately to permit appropriate peer review and discussion. The results of both positive and negative trials impact investigators as they design future trials. For example, knowledge of a decisively negative trial might lead to the abandonment or alteration of a specific treatment strategy being considered by others for clinical testing. Thus, patients consenting to participate in new clinical research would not be needlessly exposed to a treatment from which they would be unlikely to benefit but could instead be considered for studies of other novel treatments. This also reduces wasted time and resources and might lead to the more speedy development of new therapeutic approaches.

Investigators also have an ethical obligation to inform both potential patients and referring physicians about the most current available data concerning an experimental treatment. If investigators do not have access to these data because publication has been delayed, they are inadvertently violating this basic precept. Finally, knowledge of the results of negative trials is important to practicing clinicians as they weigh the relative risks and benefits of competing therapies.

From a scientific standpoint, bias in the design, conduct, and reporting of clinical trials may take several forms. Many of these problems are innocent but can lead to misperceptions about a given form of therapy. For example, Rothwell and colleagues carried out a systematic review studies assessing the risk of carotid endarterectomy. The risk of stroke and/or death was highest in studies in which the patient was assessed by a neurologist after surgery (7.7%) and lowest in studies with a single author affiliated with a surgery department (2.3%). In addition to these types of differences based on study methodology, there is likely also a publication bias, because centers or surgeons with high complication rates would be less likely to seek publication of their results in the medical literature.

Other biases may be introduced when a quasi-random means of treatment allocation are used, when selective censoring occurs, and when the report gives misleading
emphasis on an analysis that yields a positive result. At times, the latter problem has led investigators with differing views of data analysis to withdraw their names from the publication and write a dissenting opinion to accompany the main article. This occurred when two members of the coordinating committee of the Multicenter Acute Stroke Trial–Italy declined to be listed in the study’s primary publication and wrote an article providing an alternative interpretation of the trial results. Although differing views of data analysis are ordinarily included in a paper’s discussion section, this illustrates that even when profound disagreements occur, academic discourse need not be stifled. The same option is available when investigators and sponsors differ in their interpretations of the results of a study.

Another, somewhat more insidious, form of bias occurs when the results of negative clinical trials are withheld from publication or delayed. In another presentation at the AHA conference, Liebeskind and colleagues reported on a systematic analysis of all controlled clinical acute stroke trials reported in English from 1957 to 1997. There was an underreporting of clinical trials showing potentially harmful effects of experimental agents and a shorter delay between enrollment initiation and publication for positive studies. As discussed above, underreporting of negative trials is particularly dangerous in that it may allow trials of similar agents to continue, potentially exposing other patients to unnecessary risks.

Open review and debate is at the core of academic inquiry. When this is subverted to other agendas, we all suffer the consequences. Decisions regarding the publication of trial results must reside with the investigators. As a practical recommendation, principal investigators should include a statement in all consent forms informing the patient that, “It is the intent of the investigators and sponsors to submit the primary results of the trial for publication in a timely fashion so that the information gained by my participation can also be used to help others.” This statement would serve to both inform the study subject and make explicit the obligations of both the investigator and sponsor to seek publication. In clinical research, as in clinical care, our responsibilities to our patients override any other considerations.

References


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