Reports of Randomized Trials in Acute Stroke, 1955 to 1995
What Proportions Were Commercially Sponsored?

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Background and Purpose—Research in acute stroke has expanded rapidly. Many potentially important interventions lack commercial potential (eg, admission to a stroke unit). We therefore wished to examine the frequency of reports of randomized trials of interventions for acute stroke over the past 40 years, the source of support for such trials, the reporting of the commercial involvement, and whether the proportion of commercially supported trials had changed.

Methods—Eligible trials were identified from the Cochrane Stroke Group’s specialized register of controlled clinical trials. We included all randomized trials in patients with acute stroke which published a full text report, in English, between 1955 and 1995. Two reviewers independently extracted data on the involvement of the pharmaceutical industry in all eligible trials.

Results—There was a substantial increase in the number of acute stroke trials published per year between 1955 and 1995. The description of pharmaceutical industry involvement in each trial report was poor. Only a minority of supported trials made explicit statements about the role of the sponsoring company. The proportion of trials apparently supported by the pharmaceutical industry has increased substantially.

Conclusions—The increasingly important role of the pharmaceutical industry in evaluating new treatments gives substantial scope for bias and may not be in the interests of public health. Poor reporting of the sponsor’s involvement suggests that modifications to the guidelines for the reporting of randomized controlled trials to include more details of the sponsor’s involvement in the design, conduct, management, analysis, and reporting of the trial are justified. (Stroke. 1999;30:1995-1998.)

Key Words: controlled clinical trials ■ drug industry ■ research support ■ systematic review

Stroke is now regarded as a potentially treatable illness. There has been a very rapid expansion of research into new treatments for acute stroke, largely led by the pharmaceutical industry. While the development of new treatments for acute stroke is very welcome, it is possible that interventions with commercial potential may be evaluated in preference to equally promising interventions that have no commercial potential (eg, admission to a high-intensity acute stroke unit). The development of new drugs usually requires collaboration between independent clinicians and the pharmaceutical industry. This collaboration may take a variety of forms: at one end of the spectrum, the clinician has no scientific role, and the study is designed, conducted, analyzed, and reported by the pharmaceutical sponsor. At the other end of the spectrum, the sponsor may provide either funding or the drug (or both), but the trial is designed, conducted, analyzed, and reported independently—and without necessarily requiring the approval—of the sponsor. The relationship between the researcher and the commercial sponsor is important. Indeed, the International Committee of Medical Journal Editors has recently decided to ask authors to describe the role of sponsoring companies in study design, collection, analysis, and interpretation of data and the writing of the report.1 However, the proportion of trials supported by pharmaceutical companies and the reporting of the relationship between the sponsor and the scientific conduct of clinical trials has not been studied systematically.

There are many different aspects of a trial in which a company may be involved: the original concept and systematic review of any existing trial evidence, the design, the choice of investigators, the control of allocation schedule, the conduct of the trial, the collection and monitoring of data, and then the analysis, interpretation, and writing or approval of the report. We therefore performed a systematic review of the published reports of randomized controlled trials, taking as an example trials in patients with acute stroke, to examine the expansion in acute stroke research, the way in which any pharmaceutical company involvement was reported, and whether the proportion of trials that were commercially supported has changed.

Methods

All trials of interventions (drug and nondrug) in patients with acute stroke were considered for inclusion in the current study. The
original reports of these trials were identified from the Cochrane Stroke Review Group's specialized register of controlled clinical trials. This register has been assembled through a variety of search strategies, including computerized bibliographic searching of the MEDLINE database from 1966 to the present, with a validated strategy; systematic manual search of 21 English language and 5 Japanese journals and the proceedings of more than 40 conferences related to stroke; search of bibliographies of reviews, trials, book, and dissertations; and personal contact with trialists.

A trial was included if it fulfilled the following criteria: (1) it examined the effect of interventions within 14 days of onset of acute stroke using a randomized or quasi-randomized method of treatment allocation and (2) it published a completed full text (not abstract) trial report in the English language between 1955 and the end of 1995.

Two reviewers (P.D. and C.C.) independently sought the following information on all eligible trials:

1. Year of publication
2. Number of patients randomized
3. Nature of the intervention (drug or nondrug)
4. For drug trials, the following data were also sought:
   a. Did the pharmaceutical company provide the drug?
   b. Was support (other than drug provision) from the pharmaceutical company acknowledged?
   c. Were pharmaceutical company employees involved in writing the report?
   d. Was the pharmaceutical company reported as being involved in the design of the study?
   e. Was the pharmaceutical company reported as being involved in the conduct of the study?
   f. Was the pharmaceutical company reported as being involved in the data management or analysis?
   g. Was approval required from a sponsoring organization before publication?

Pharmaceutical company involvement was coded as "yes" or "no" if the trial report included a specific statement of involvement; otherwise, it was coded as "not sure."

Disagreements between the 2 reviewers were resolved by discussion. The data were analyzed with a computer database (Microsoft Access 2.0) and spreadsheet (Microsoft Excel 5.0).

Results

Between 1955 and 1995, 154 trials in Cochrane Stroke Group Specialized Register fulfilled the inclusion criteria. Since the first controlled trial in patients with acute stroke published by Dyken and White in 1956, there has been a substantial increase in the number of trials (Figure) and in the number of patients included in acute stroke trials. The proportion of trials supported by the pharmaceutical industry has increased from zero in the 1950s to 25 of 46 (54%) of all trials published in the period 1991 to 1995 (Figure). We classified each trial according to its apparent degree of involvement with the pharmaceutical industry. Of the 154 eligible trials, only 18 (12%) tested nondrug interventions. Of the 136 trials that tested pharmacological interventions, 59 (43%) did not acknowledge any assistance from or involvement with the pharmaceutical industry; 48 (35%) trials only acknowledged either the provision of the drug or other financial support; and the remaining 29 trials included the names of company employees in their authorship (in 16 of these studies, the company employees were listed as members of a collaborative group). Trials that reported at least some commercial support accounted therefore for approximately half of all trials reported in the whole study period.

The reporting of the extent to which the pharmaceutical industry was involved in each trial was generally poor. For the 29 trials that included company employees as authors, we inferred that the company was involved in key areas of the study unless the trial report made explicit statements to the contrary: 6 of these trials explicitly reported industry involvement in data analysis, and only 2 studies indicated that the relevant company was not involved in this area. None of these trial reports included explicit statements on the company's role in the design, conduct, or reporting of the study. In the 48 commercially supported trials, in which the company provided either the drug or funding, the role of the company was even less clear. Very few trials in this category made explicit statements regarding the role of the supporting company in the trial (Table). No trials reported any details on the financial (or other) reimbursement of the clinical investigators.

Discussion

This study confirms our impression not only of a rapid expansion of research into treatments for acute stroke, but also in the proportion of apparently pharmaceutical industry-supported trials in the past 10 years. Pharmaceutical industry-supported trials now appear to account for approximately half of all acute stroke trials and for an even greater proportion of the total number of stroke patients enrolled in randomized controlled trials in the period 1985 to 1995. Commercial sponsorship is most likely to be acceptable if the trial has
been designed, conducted, analyzed, and reported independently of the sponsor; these steps minimize the potential for bias. However, in the reports of most trials in acute stroke, the contribution of sponsors to these key areas of research was not explicitly identified. This and the recognized underreporting of supported research indicates that it is likely we have substantially underestimated both the frequency of commercial sponsorship of trials and also the influence of the pharmaceutical industry on current stroke trials. Our findings are likely to be generalizable to other disease areas. The major limitation of the current study was that we could not clarify how many of the apparently independent trials were truly independent or determine the exact involvement of the company in supported trials. For example, we found that in several cases a company was cited as part of a collaborative group but may not have been involved in the design, conduct, analysis, or reporting of the study. However, one of our aims was to establish the adequacy of reporting, and we have shown this to be clearly deficient by current standards. We did not attempt to examine the relationship between pharmaceutical sponsorship and statistically positive results, given our uncertainty regarding the extent of the commercial involvement.

The anonymity of many of these commercial sponsors contrasts with current concerns over biomedical researchers claiming authorship despite having made little contribution to the study. This discrepancy may be a consequence of pharmaceutical companies’ understating their influence on major studies to gain marketing advantage. This is perhaps a reflection of the view that the credibility and importance of any study depends in part on who performed it, so that a trial published in the name of a group of well-known clinical researchers may attract less critical review than if published in the name of the sponsoring pharmaceutical company.

Alternatively, it may reflect that authorship is a goal less important than obtaining regulatory approval for the pharmaceutical industry, or simply that overall quality of trial reports (in all aspects, not just reporting of commercial involvement) has been poor over the past 40 years.

The increasing role of the pharmaceutical industry in evaluating new treatments for acute stroke (achieved with the active encouragement of central government research-funding agencies) is a concern for several reasons. First, drug development strategies adopted by the pharmaceutical industry are likely to address primarily commercial, regulatory, and marketing requirements rather than issues of public health. Indeed, these commercial needs may sometimes even be in direct conflict with the requirements of public health. For instance, the substantial reimbursements given by drug companies to collaborating doctors may make large (and therefore statistically reliable) trials prohibitively expensive, as well as damage recruitment in competing nonsponsored trials that cannot afford to offer investigators equivalent honoraria. Furthermore, empirical evidence suggests that these reimbursements provide an incentive for fraud, necessitating costly and complex systems to monitor and audit the conduct of trials. Close involvement of the company in the design, conduct, analysis, and reporting of a trial may evoke—rightly or wrongly—the suspicion of bias in favor of the company’s product. This allegation is difficult to substantiate, but there are certainly anecdotal examples, such as the suppression of commercially unfavorable data, the selective reporting of data only from centers with favorable results, or the use of dosage regimens that favor the company’s product. This view is further supported by the finding that articles which acknowledged the support of the pharmaceutical industry were more likely to favor the drug of interest than articles which did not acknowledge pharmaceutical industry support. Sponsored trials are also more prone to publication bias. Easterbrook and coworkers reported that commercially sponsored trials were published less often than other trials, and one of the reasons cited for lack of publication was that the sponsors had control of the data. Liebeskind and colleagues reported similar evidence for publication bias and time-lag bias (when speed of publication is dependent on trial results) in acute stroke trials. Furthermore, they also found that in acute stroke trials, corporate sponsorship appeared to accentuate both publication and time-lag bias. We believe that nonpublication of clinical trials is ethically unjustifiable. Indeed, one of the anonymous reviewers of this paper suggested that investigators participating in commercially sponsored trials should ask the sponsor to clearly state in the contract something to the effect that “the results of this trial (or the reasons for stopping) will be reported to the scientific community.” Goldstein and colleagues have recently made a similar suggestion in light of recent events at the 24th AHA International Joint Conference on Stroke and Cerebral Circulation, at which an investigator announced that he was prevented from presenting the results of a study (which had been selected for oral presentation) by the pharmaceutical company sponsor.

On the other hand, the increasing involvement of the pharmaceutical industry in acute stroke is also a positive development. Commercial sponsorship has led to a substantial number of trials (which would not otherwise have been performed), so in turn, greater numbers of doctors and hospitals are now involved in stroke research than ever before. Pharmacologically driven research has also furthered our understanding of the nature of ischemic brain lesions, at the level of molecular and cellular mechanisms, in both animal models and humans. However, the relatively small...
number (and proportion of the whole) of trials of nondrug interventions is a source of concern.

The CONSORT statement has provided a framework for the reporting of randomized controlled trials.13 Our data support the recent decision of the International Committee of Medical Journal Editors to ask authors to describe the exact role of the sponsor in the design, conduct, management, analysis, and reporting of the trial. This requirement might be criticized because authors of government-sponsored research have other potentially equivalent prejudices or conflicts of interest.8 However, these pressures are unlikely to be as powerful, because these trials are conceived with the aim of improving public health rather than generating profit for shareholders.

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References


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