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Industry Funding of Clinical Trials: Benefit or Bias?

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CLINICAL TRIALS ARE THE PRIMARY MEANS TO EVALUATE THE efficacy and safety of new drugs and other medical technologies. When published in peer-reviewed journals, the results of these studies not only provide a scientific basis for treatment decisions but also enable governments and insurers to develop sound reimbursement policies. Most clinical trials, however, are funded by pharmaceutical companies with enormous financial stakes in the products being evaluated. Furthermore, the scientists who design, conduct, analyze, and report clinical trials often receive monetary compensation from drug companies, in the form of either salaries or consulting fees.

These arrangements raise several concerns. First, should individuals with a financial interest in the outcome of clinical trials be so closely involved in conducting them? Second, in what ways could industry sponsorship potentially bias these studies? Finally, how do medical journals ensure that the data in trial reports are accurate and unbiased? Understanding the advantages and drawbacks of industry's contributions to clinical trials may help to refine the policies that govern how industry-supported research influences medical practice.

The pharmaceutical industry plays a vital role in financing the research required to develop new drugs. While grants from the National Institutes of Health (NIH) fund most basic research in academic laboratories, it is largely industry that bears the cost of identifying new molecular entities and testing them in animal models and human subjects.[1] Clinical trials make up the largest portion of the $266 million[2] to $802 million[3] estimated total cost to industry for bringing each new drug to market. Furthermore, of all funding for clinical trials in the United States, nearly 75% currently comes from corporate sponsors.[1] In addition, scientists employed by pharmaceutical companies play an important role in evaluating the efficacy, safety, and cost-effectiveness of new drugs. Academic medical centers may be unable to perform all these tasks on their own. Gelijns and Thier comment, for instance, that "most lack the integrated infrastructure of people with expertise in statistics, clinical trial management, quality of life, and economics needed to tackle these roles."[4]

Unlike publicly funded studies, however, clinical trials supported by the pharmaceutical industry may be adversely affected by business interests. Numerous industry-sponsored trials, for example, are prematurely terminated for financial rather than for scientific or ethical reasons.[5,6] Evans and Pocock argue that this practice "dangerously implies that business needs can override both scientific intent and the ethical obligation to patients already randomized."[7] Psaty and Rennie further note that the inappropriate termination of a clinical trial diminishes its usefulness for testing the scientific hypothesis for which it was designed.[6] When a study's value is thus made questionable, Boyd asserts that "the risk [to patients] becomes unacceptable" and the "grounds on which both patient consent and ethical approval were given" are no longer valid.[8] Discontinuation of a clinical trial for financial reasons thus violates the Declaration of Helsinki, a covenant that safeguards the interests of human research subjects.[6,8,9]

Corporate financing of clinical research, which often includes incentives for academic investigators, may also create conflicts of interest that can bias study results. Some companies pay physicians for each patient they recruit into clinical trials.[10] In other cases, clinician-researchers serve as paid scientific consultants who speak on behalf of industry[11,12] or are offered shares, options, or paid positions on scientific advisory boards at the companies who fund their work.[11,13,14] A review of disclosures by faculty at one institution, for example, revealed that 7.6% (68/896) of principal investigators had direct financial ties to the companies sponsoring their research in 1999, a 3-fold increase from 1985.[11] Industry also provides individual physicians or entire academic departments with unrestricted funds that can be applied toward personal or institutional research initiatives.[13] These forms of compensation may undermine investigators' objectivity by rewarding those who produce results most favorable to the sponsor's interests.

Research supported by pharmaceutical companies may also be subject to methodological bias. Industry-funded clinical trials and cost-effectiveness analyses, for instance, yield positive results far more often than studies that are funded or conducted by other entities.[15-18] This may reflect bias caused by enrollment of relatively healthy patients, insufficient selection or dosage of comparator drug, inadequate sample size, or inappropriate length of patient follow-up. Other problems may include reliance on invalidated surrogate end points, inappropriate use of statistical analyses, or misleading presentation of data.[19,20] Djulbegovic et al [21] suggest that the overwhelmingly positive results of industry-funded studies are due to violations of the "uncertainty principle," an ethical guideline stating that a randomized controlled trial should be conducted only "if there is substantial uncertainty about which of the trial treatments would benefit a patient most." Industry-financed studies also more frequently compare novel treatments against a placebo than against drugs that are known to be effective.[21] Companies may simply avoid conducting head-to-head trials, particularly when they are unlikely to reveal the superiority of a new drug over available treatments.[1] Furthermore, although comparison against a placebo may be neither meaningful nor ethical, drug companies still use such "successful" trials to market their products.[22]

Bias may also occur in the reporting of industry-funded clinical trials. Withholding the publication of unfavorable results, for example, is not uncommon although the practice is considered scientific misconduct.[1,23] This situation poses a serious problem when new drugs are approved for marketing but the sponsors have failed to disclose all of their potential benefits or risks. In one example, a pharmaceutical company delayed for 7 years the publication of a study concluding that its widely prescribed preparation of levothyroxine was no more effective than less expensive generic formulations.[24,25] Bias in reporting may also arise when sponsors and investigators disagree about how trial data should be analyzed and interpreted. One company, for example, initiated arbitration proceedings against academic collaborators who published unfavorable data from a clinical trial of an experimental human immunodeficiency virus treatment.[26] In another case, a Canadian hematologist was sued by her sponsor for breach of contract when she reported her concerns over the safety of a drug she was evaluating.[27] Both cases illustrate that corporate sponsors may control the analysis and reporting of clinical trials to protect their interests.

As gatekeepers of the scientific literature, journal editors play a critical role in limiting bias in trial reporting. Most peer-reviewed journals mandate that reports of clinical studies conform to Consolidated Standards of Reporting Trials (CONSORT), a set of guidelines issued by physician-investigators to standardize descriptions of trial methods and to ensure inclusion of important details about the therapeutic regimen, adjunctive therapies, and patient enrollment and withdrawal.[28] With evidence that biased reporting may result from academic-industry relationships that compromise the intellectual freedom of clinical investigators, members of the International Committee of Medical Journal Editors (ICMJE) specifically condemn all contractual agreements that deny researchers the right to independently analyze clinical trial data and prepare and submit a manuscript for submission.[29] In addition, the ICMJE now mandates that authors disclose all details about their role and the role of the corporate sponsor in the clinical study.[29] Members of the ICMJE may also request lead authors to sign a statement accepting complete responsibility for the conduct, analysis, and reporting of the trial.[29]

Although industry sponsorship of clinical trials can lead to important therapeutic advances, the potential for bias in these studies may exist on multiple levels. Academic internal review boards, US Food and Drug Administration drug advisory committees, peer reviewers, and journal editors all play vital roles in recognizing bias in clinical research and ensuring that only drugs supported by unbiased, scientific evidence reach the market and clinic. To ensure objectivity in clinical research, some investigators have suggested that industry-academia collaborations continue only if academic medical centers assume sole responsibility for the design, conduct, analysis, and reporting of clinical trials.[1] Others have supported the creation of conflict-of-interest committees at academic institutions to monitor the financial interests of both clinician-investigators and institutional decision makers.[30] By establishing checks and balances for academic-industry partnerships, such proposals may help to mitigate the potential for bias in industry-sponsored research.

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