Disclosure of Clinical Trial Results When Product Development Is Abandoned

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Currently, sponsors are not required to report the outcomes of clinical research on drugs or devices that do not lead to an approved product. Consequently, the public cannot benefit from scientific information derived from all failed or abandoned drugs and devices. Provisions in the U.S. Food and Drug Administration Amendments Act of 2007 provide an opportunity for the Department of Health and Human Services to rectify this situation. By reporting the results of clinical trials of abandoned products in a publicly accessible database and in the peer-reviewed journal literature, sponsors would satisfy a core ethical obligation of clinical research and enhance translational science.

Patients participate in clinical trials for many reasons, including the desire to contribute to medical knowledge and benefit humanity (1–3). In surveys that seek to determine why patients volunteer as research subjects, responses such as “to help develop new medicines,” “to help society,” and “to help the sick” are given more frequently than “to help my own health” (4, 5). Even healthy volunteers who participate in clinical trials that offer them no potential benefit cite the “desire to help others” as being nearly as important a motivating factor as financial considerations (6). Pharmaceutical company sponsors of clinical trials channel this altruism to encourage participation and compliance with clinical trials. This raises the question: Do industry sponsors have a responsibility to research subjects to ensure that medical science and society gain from the risk and discomfort that clinical trial participants endure, often for no personal gain? If sponsors diminish the opportunity for society to benefit from the altruism of research subjects, does this subvert an implicit moral contract between sponsors and study participants? (Fig. 1).

The current ethical framework that justifies medical experimentation with human subjects is grounded in the concept that exposure of subjects to the risk and burden of research is acceptable only if society will gain knowledge—a condition that requires the sharing of results, whether they are positive or negative (7, 8). This central concept represents a moral obligation that supersedes business considerations. Indeed, the World Medical Association’s Declaration of Helsinki states that “authors have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports. ... Negative and inconclusive as well as positive results should be published or otherwise made publicly available.”

**PUBLICATION BIAS**

In recent years, there has been increasing recognition that publication bias—the selective reporting of only clinical trials with positive results—may degrade the base of publicly available information on approved drugs (9, 10). Pharmaceutical company sponsors often do not submit the results of negative drug trials for publication (11–13) and may downplay adverse events (14, 15). Selective reporting of clinical trial results can yield flawed estimates of drug effectiveness and provide an erroneous impression of the risk-benefit ratio of treatments, leading physicians to make inappropriate prescribing decisions (16).

Mounting evidence of publication bias has led to calls for greater transparency with respect to the evidence that supports drug approval and for a requirement that all clinical trial data be open to public scrutiny (17). In response, a variety of organizations—including the American Medical Association and the International Committee of Medical Journal Editors—have advocated principles for disclosing trial results; furthermore, the U.S. enacted Section 113 of the U.S. Food and Drug Administration (FDA) Modernization Act (FDAMA) of 1997, which led to the establishment of the http://ClinicalTrials.gov registry, a database of federally and privately supported clinical trials. The original intent of ClinicalTrials.gov was to assist patients in finding clinical trials, but it also represents a tool for verifying the existence of trials so as to allow monitoring of selective reporting (18).

More recently, Congress enacted within the FDA Amendments Act (FDAAA) of 2007 a provision (Section 801) that mandates the inclusion of “basic results” data from all clinical trials of approved drugs, biologics (other than phase 1 investigations), and devices (other than small feasibility studies) in the ClinicalTrials.gov database (19). Today, ClinicalTrials.gov contains basic results data for some clinical trials completed after the enactment of FDAAA. In addition, since 1997, FDA has posted comprehensive “action packages” for newly ap-
proven drug products on its Web site, which consist of the full text of the FDA reviewers’ reports and associated administrative documents. These various initiatives represent important steps to address publication bias in the reporting of clinical trial results for approved drugs and devices.

**ABANDONED PRODUCTS**

A different type of failure to report occurs when pharmaceutical company sponsors do not make public the clinical trial results for drugs or devices for which development programs have been terminated. This situation has received much less public attention. Ordinarily, sponsors terminate a development program because of lack of efficacy or unacceptable adverse events. In some cases, however, development programs are discontinued because regulatory authorities require additional studies and the sponsor is unwilling to comply—or simply because of commercial considerations such as lack of resources or a reevaluation of the market opportunity.

Despite efforts by the FDA to enhance transparency (20), the agency does not make public data on rejected drugs (21). Currently, there is no legal requirement that sponsors disclose the results of clinical trials for unapproved products, and many sponsors consider the data proprietary (22). It is believed that companies sequester negative trial results so as to prevent competitors from gaining access to information of commercial value. In addition, because there is no commercial benefit to releasing negative clinical trial results for a drug whose development will not be pursued, sponsors are reluctant to devote resources, however minimal, to an activity that is not perceived as contributing to business goals. Finally, having invested heavily in product development and the creation of proprietary intellectual property rights, sponsors may determine that publication of negative results could constrain future development of the investigational agent, even for a different clinical indication.

This practice has important implications. It means that scientific information on the efficacy (or lack of efficacy) and safety (or lack of safety) of certain investigational agents is not available to the research community, and the opportunity to learn from unsuccessful clinical trials is eliminated. In addition, the ability of institutional review boards to safeguard the rights, safety, and well-being of study participants is undermined. As an example, consider the development of antiepileptic drugs, which is based on screening of molecules in animal models. Because sponsors often do not release the results of clinical trials for drugs for which development has been terminated, there is incomplete knowledge as to the predictive validity of the screening models. Because every approved antiepileptic drug has demonstrated activity in the screening models, it is assumed that the models have high predictive value. However, this assumption could be erroneous because we do not know if there are drugs that were effective in the models but did not exhibit efficacy or that had unacceptable side effects in clinical trials and were therefore terminated by their sponsors. Similar concerns have been identified in psychiatric drug research, leading to the conclusion that “translational medicine cannot approach its full potential if negative drug developments are unpublished” (23).

A second important implication of the failure of pharmaceutical company sponsors to release data on negative trials for abandoned products is that futile treatment strategies may be pursued unnecessarily by other entities. A sponsor may attempt to develop a drug for a molecular target that, unbeknownst to it, has already been demonstrated in one or more clinical trials to be inappropriate for treating the disease. This leads to the squandering of resources that could be applied to the development of potentially useful therapies. In addition, research subjects may be exposed unnecessarily to the risks of futile “treatments.” Ultimately, the industry may become discouraged and discontinue drug development for an indication based on an erroneous perception of the risk.

Although the basic results reporting requirement of FDAAA Section 801 will mean enhanced public access to the base of clinical data on drugs and devices, the law only applies to agents approved by the FDA. Moreover, for a drug or device that is approved, delayed submission is available if the sponsor is seeking approval of a new use for the entity. Thus, under the current rules, the Department of Health and Human Services (HHS) exempts sponsors from reporting the results of clinical trials for products that are still in development. If the product is not initially approved because of insufficient evidence of efficacy, safety concerns, or simply because the sponsor does not choose to file a new drug application, the results will never be made available on ClinicalTrials.gov.

Congress has provided an opportunity to close this loophole. FDAAA Section 801 has provisions that permit HHS to require results-reporting for clinical trials of drugs and devices not approved by the FDA (24, 25). NIH—the component of HHS responsible for implementation of ClinicalTrials.gov and for the provision of the database to satisfy the results-reporting requirements of FDAAA—is currently formulating a set of proposed regulations. The regulations are expected to be published by the end of the year (26). A public comment period will then begin. It is hoped that HHS will use its authority under FDAAA 801 to require sponsors to report results for any trial registered in ClinicalTrials.gov, even if product development is abandoned. Data from even a single subject could contribute to knowledge with respect to safety, if not efficacy. Every subject has a right to have his or her participation count.

**JOURNALS REMAIN RELEVANT**

The reporting of all trial results in ClinicalTrials.gov is an important step forward, but it is not sufficient. According to current requirements, the basic results mandated by FDAAA are organized into self-explanatory tables of demographic information, efficacy results for primary and secondary outcome measures (with statistical analyses), and adverse events (27). There is no provision for the presentation of detailed analysis or interpretation as in a journal publication, and there is minimal review. Therefore, the peer-reviewed journal article, if no longer the primary repository of clinical trial results data, remains essential to the adequate reporting of clinical research, including studies of products for which development is not pursued (18, 28). Such reports need to be carefully crafted to avoid the “spin” (distorted presentation) that has been found in reports of trials with statistically nonsignificant results (29).

It has been estimated that more than half of the clinical trials that support FDA approval of drugs are not published in medical journals (30). Recent efforts to address this issue by the scientific, clinical, and regulatory communities will improve the base of medical knowledge and are vital to preserving the public interest in participating in clinical investigation (31). Transparency in data sharing of trial results for products for which development has been abandoned will further improve translational science, engender trust among study par-
participants, and optimize resource allocations for the pursuit of the most promising new therapeutics.

REFERENCES AND NOTES


5. E. L. Andresen, K. A. Wilson, A. Castilho, C. Koopman, Participants, and optimize resource allocations for the pursuit of the most promising new therapeutics.


9. E. L. Andresen, K. A. Wilson, A. Castilho, C. Koopman, Participants, and optimize resource allocations for the pursuit of the most promising new therapeutics.


25. Pharmaceutical Research and Manufacturers of America, a trade association representing some U.S. firms, supports the posting of summary results of clinical trials of investigational products whose development programs are discontinued, regardless of outcome, within one year of discontinuation and also journal publication if the information is felt to be of significant medical importance. Principles on Conduct of Clinical Trials and Communication of Clinical Trial Results (revised April 2009). http://www.phrma.org/about/principles-guidelines/clinical-trials.


28. FDAAA 801 requires ClinicalTrials.gov to link to Medline citations of any publications “focused on the results of an applicable clinical trial.” Inclusion of the ClinicalTrials.gov unique identifier in journal publications will allow readers access to the basic results data, which may be more detailed than those reported in the journal article. It will also permit the National Library of Medicine to fulfill its legal mandate to provide applicable Medline links. The International Committee of Medical Journal Editors recommends that a clinical trial registration number be included at the end of the article’s abstract. http://www.icmje.org/publishing_10register.html.


32. Acknowledgments: The authors thank B. Lo for suggestions, T. Tse for advice and review of the manuscript, and E. D. Pellegrino for comments. Competing interests: M.A.R. is a special government employee of the U.S. Food and Drug Administration. The authors declare no other relevant competing interests. 10.1126/scitranslmed.3002939