Clinical Trial Data as a Public Good

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KNOWLEDGE OF THE BENEFITS AND RISKS OF PRESCRIPTION drugs is based mainly on published reports of clinical trials, yet the medical literature may present an incomplete and potentially biased sample of clinical trials.[1] Trials with positive results generally are published more frequently than studies that conclude that a new drug poses greater risks or is no more effective than standard therapy or a placebo. Furthermore, some articles may distort trial findings by omitting important data or by modifying prespecified outcome measures. Lack of access to detailed information about clinical trials can undermine the integrity of medical knowledge.

To increase transparency, the International Committee of Medical Journal Editors decided in 2004 that their journals would not publish results of a clinical trial unless the trial was registered prior to patient enrollment. The committee stated that registries should include data specified by the World Health Organization, although these data elements do not provide a complete picture of the clinical trials. Since 2007, US law has required researchers to register phase 2 and higher trials of drugs and biologicals on the ClinicalTrials.gov website if there is a trial site in the United States or if the trial is part of a US Food and Drug Administration (FDA) investigational new drug application. Researchers are typically required to post key results within a year of completing data collection, but studies of off-label drug uses (ie, uses other than those described in an FDA-approved drug label) are allowed 3 years to post trial results.

However, actual trial registration falls short of requirements. A review of 323 articles found that nearly 28% of the trials were unregistered. Among articles with adequately registered trials, 31% had discrepancies between outcomes reported in the registration and in the published report.[2] Moreover, no authority checks whether registration information is accurate. Even more important, current law does not require registration of sufficient information to ensure accuracy, completeness, or reasonable interpretation of the findings.

See also p 869.

The Standardized Clinical Study Report

Current policy does not consider a practical, inexpensive solution: mandatory disclosure of the standardized Clinical Study Report (CSR) for all clinical trials involving FDA-approved drugs. The FDA follows the International Conference on Harmonization Standards for Registration of Pharmaceuticals for Human Use, which requires submission of a CSR (with specified content and format) when reporting clinical trials to governmental authorities.[3] The CSR summarizes the trial, clinical end points, methods, key data, and data analysis. The CSR includes "statistical description, presentations . . . tables and figures . . . with appendices containing the protocol, sample case report forms, investigator related information, information related to the test drugs/investigational products including active control/comparators, technical statistical documentation, related publications, patient data listings, and technical statistical details such as derivations, computations, analyses, and computer output etc."[3]

A CSR includes the most pertinent information about a clinical trial in an easily analyzed format. Drug manufacturers already produce these reports to meet international and national regulatory requirements. Making CSRs publicly available would not be expensive, yet disclosure would promote research integrity, medical knowledge, and public health. Furthermore, CSRs are more likely to be reliable than other summaries. Drug manufacturers submit CSRs to public authorities when they seek marketing approval and cannot alter or delete data without potentially jeopardizing their relationships with regulatory agencies and risking criminal prosecution.

A review of the clinical trials that evaluated the efficacy of gabapentin for off-label use demonstrated the importance of disclosing CSRs.[4] In litigation involving illegal marketing, internal corporate documents for 20 clinical trials (including 18 CSRs) for off-label use of gabapentin were discovered. However, the results for only 9 of these studies were fully published and only 1 published report presented both primary outcome measures and *P* values consistent with the

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manufacturer's internal documents. None of the clinical trials for which the prespecified primary outcome measure failed to achieve statistical significance were published in full with the primary outcome unchanged. Even the most discerning readers of these reports could not have known that the manufacturer's clinical trials had not shown that gabapentin effectively treated pain (other than of postherpetic origin). Indeed, a 2005 Cochrane collaboration literature review erroneously concluded that gabapentin was effective for acute and chronic pain.[4]

Public Good or Proprietary Information?

Even though drug manufacturers fund most clinical trials, trial results constitute a public good. The FDA uses clinical trial data to ensure drug safety. Journal editors and peer reviewers need comprehensive clinical trial data to ensure that manuscripts accurately reflect trial findings. Experts require such data to develop practice guidelines. Physicians need access to such data to practice evidence-based medicine. Medical facilities and insurers need complete trial data to decide whether and under what terms to include a drug in their formularies. Medical schools need this scientific evidence to train physicians. The public needs the information to hold federal authorities accountable for regulatory decisions, and patients need access to the data to help make informed decisions.

Drug manufacturers have opposed disclosure of CSRs on the grounds that they are proprietary and constitute a trade secret, the release of which would aid their competitors.[5] However, the information in CSRs cannot help a competitor develop or manufacture a similar product or a generic version. Nor does testing information (such as the dose, duration of use, therapeutic goals, and profile of research participants) reveal how to develop similar drugs with lower risks or greater benefits. Furthermore, patent laws and exclusive marketing periods protect the sponsor's investment; in addition, manufacturers of generic drugs must wait 5 years to seek FDA approval when using an originator's test data. Cochrane reviewers note the importance of access to CSRs.[6] And in 2010, the European Medicines Agency changed its policy, making possible public disclosure of CSRs.[7]

Drug manufacturers overlook their large public subsidies when they claim that because they fund the clinical trials they own the data. Tax policy subsidizes drug manufacturers by allowing the deduction of research expenses on an accelerated basis and by granting research tax credits. Drug patents and exclusive marketing periods have contributed to the creation of sanctioned monopolies that have made the pharmaceutical industry one of the most profitable industries since the mid-20th century. Furthermore, public programs—Medicare, Medicaid, and the Veterans Administration—pay for more than half of drugs purchased, and by subsidizing private insurance premiums the public funds a major portion of most other drugs purchased.

CSRs: Necessary But Not Always Sufficient

Despite their value, CSRs are not a panacea. Patient-level data can reveal flaws in the CSR summary and conclusions. For example, the CSR for the VIGOR (Vioxx GI Outcomes Research) trial, which compared the gastrointestinal safety of rofecoxib with that of the nonspecific nonsteroidal anti-inflammatory drug naproxen, reported that rofecoxib was safer. However, reanalysis of patient-level data in the context of litigation demonstrated that among the patients not concurrently treated with corticosteroids, those treated with rofecoxib did not experience fewer serious upper gastrointestinal complications than those treated with naproxen (9 vs 10, respectively).[8]

Accordingly, some observers have suggested enabling limited access to masked patient-level data,[9] and others have suggested disclosure of all FDA reviews of clinical trials submitted in support of new drug applications.[10] To expand public access to clinical trial data, Congress could require the FDA to disclose all CSRs that drug manufacturers submit when seeking marketing approval and also could require drug firms to disclose CSRs for all clinical trials they conduct for drugs that they market in the United States. Those actions would go a long way toward making the knowledge derived from clinical trials truly a public good.

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