

CRS Report for Congress

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Clinical Trials Reporting and Publication

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Summary

In 2004, concerns arose that certain antidepressants, other medicines (e.g., Vioxx), and medical devices (e.g., coronary stents), had been marketed to consumers despite unresolved safety issues. Data from clinical trials conducted both before and after a product goes to market are central to assessing its safety and effectiveness, but there is currently no centralized system for reporting results. Due to medical journal practices and drug sponsor and researcher incentives to publicize positive results, many trials with inconclusive or negative results are not publically reported. Although Food and Drug Administration (FDA) regulations require sponsors of trials that test the effectiveness of new drugs for serious or life-threatening conditions to register with the Department of Health and Human Services (HHS) at clinicaltrials.gov, not all such trials are listed there. A voluntary registry of recent controlled trials results was created in October 2004 by the Pharmaceutical Research and Manufacturers of America (PhRMA).

Several groups have called for public access to standardized clinical trials data, including notice of trial launch and research results through a centralized system such as a registry. Proposals for registries for these purposes raise issues regarding the goals of public access, the appropriateness and presentation of information, the timing of a trial's inclusion, whether they will compromise intellectual property rights, whether reporting should be mandatory, potential conflicts of interest, and whether medical device trials should be included.

In October 2004, Representative Edward Markey and Senator Christopher Dodd introduced companion bills H.R. 5252 and S. 2933, the Fair Access to Clinical Trials Act, which would have required registration of clinical trials before the enrollment of human subjects, and the subsequent posting of results, at clinicaltrials.gov or a similar forum. Similar legislation is likely to be introduced in the 109th Congress. This report will be updated on a regular basis.

Introduction

In 2004, Congress and others raised questions about the safety and effectiveness of several FDA-approved biomedical products on the market. These included certain antidepressants, Merck's pain relief drug, Vioxx, Boston Scientific's cardiac stents, and other drugs and medical devices. Discussion about ways to help ensure safety and

effectiveness of biomedical products focused primarily on two questions: whether data from all clinical trials should be made publically available, and whether FDA's processes for product approval and post-market surveillance and study are adequate. This report focuses on the first of these questions.

Clinical trials, which are the gold standard for assessing drug and device safety and effectiveness both before and after they are marketed in the United States, are scientific studies that systematically test interventions on human beings. They may include behavioral studies or other biomedical investigations, such as those that test drugs and medical devices. As described by FDA, clinical trials are generally conducted in four phases following successful animal testing.¹ Phase I trials study a new drug or device in a small group of people (20-80) to evaluate its safety, determine a dosage range for drugs, and identify gross side effects. Phase II trials study the product in a larger group of people (100-300) to see if it is effective for a specific purpose and to further evaluate its safety. Phase III trials investigate the product in a large group of people (1,000-3,000), to confirm the product's effectiveness, monitor side effects, and collect information that will allow the drug, treatment or device to be used safely. Phase IV trials are usually large-scale studies, conducted after the FDA approves a product for marketing in order to demonstrate effectiveness in a broader clinical context and to watch for rare side effects that may not be identified until a significant number of people have used the product.

The federal government has historically regulated certain aspects of some clinical trials by attaching conditions to those conducted with federal research funds, and/or by creating requirements that must be met before a drug or device can be marketed in the United States. Most federal funding occurs through HHS' National Institutes of Health. Both pre-market approval and post-market monitoring of medical drugs and devices marketed in the US are the responsibility of HHS' FDA. Each FDA center that reviews and approves biomedical products for human use — the Center for Drug Evaluation and Research, the Center for Devices and Radiological Health, and the Center for Biologics Evaluation and Research — posts summaries of safety and effectiveness data from clinical trials that support *approved* applications for new products, or new uses of approved products; FDA does not otherwise post clinical trials data.

The FDA Modernization Act of 1997 (FDAMA, P.L. 105-115, Section 113) required the Secretary of HHS to establish a clinical trials registry, intending the availability of information to increase the access of individuals to cutting-edge medical care available only through research protocols. Sponsors of trials testing the effectiveness of life-threatening disease or condition treatments (drug and biological products, but not devices) that are either not yet on the market, or are new uses of treatments on the market, are required to register. In response to FDAMA, the National Library of Medicine (NLM) established a clinical trials registry and made it available to the public in 2000 [<http://www.clinicaltrials.gov>]. It was later reported that an FDA analysis found that in 2002 only 48% of trials of cancer drugs had been registered, and a preliminary review now indicates the listing rate for drugs for some other serious diseases is in the single digits. Some companies have listed no studies; some trials are listed without identifying

¹ For further information on the role of federal agencies in evaluating biomedical products, see CRS Report RS21962, *From Bench to Bedside*, by Michele Schoonmaker.

the sponsoring company or the drug being tested.² In March 2002, FDA issued a guidance document, instructing industry how and when to participate in the registry [<http://www.fda.gov/cder/guidance/4856fnl.htm>].

Despite the centrality of clinical trials in assessing biomedical products' safety, particularly phase III and IV studies, a presentation of all results related to a product can be difficult to find. Researchers have traditionally reported pre- and post-market trial results in peer-reviewed medical journals, which have historically tended to favor publication of clinical trials demonstrating successful intervention; the results of negative or inconclusive trials often go unpublished.³ Other venues for the dissemination of research results are industry, government, or university press releases and presentations at medical conferences. Researchers — who may be affiliated with a product's manufacturer, a university, the government, or an association established to find better treatments for a particular disease — may have various motives for publishing or not publishing results. Some observers have expressed concern that the concealment of negative data could adversely affect medical decision-making.⁴

Clinical trials reporting can mean public access to results after a trial's conclusion, to a proposed plan before a trial is begun, or both. There is no centralized system for either type of reporting, so different trials may have the same title, one trial may be reported in several places under different titles, and many trials are never reported. Discussions of clinical trials reporting have largely focused on post-market trials concerning drugs' and devices' long term effects, and their safety and effectiveness in specific sub-populations such as children or persons with heart conditions.

Recent Events

In 2004, a number of national and international groups recommended that clinical trial reporting be centralized, standardized, and/or include both positive and negative results. In April 2004, the World Health Organization (WHO), which supports and funds much of the international research on marginalized populations, announced a system designed to facilitate the sharing of research. The system will assign standardized numbers to each randomized controlled trial the WHO ethics review board approves. A London-based company will maintain a no-charge, online register of these numbered trials at [<http://www.controlled-trials.com>] to identify and track them throughout their life cycle. The system is designed to avoid the problem of publication bias by posting information on trial starts and their results.

In June 2004, the American Medical Association (AMA) recommended that HHS create a comprehensive, centralized clinical trials registry. The AMA further called on all institutional review boards to make registration in this database a condition of their

² Sharon Vedantam, "Drugmakers Prefer Silence on Test Data," *Washington Post*, July 6, 2004, p. A1.

³ "Pressure Mounts for Clinical Trial Registry," *Medicine & Health*, June 21, 2004.

⁴ Robert Steinbrook, "Public Registration of Clinical Trials," *JAMA*, vol. 351, no. 4, July 22, 2004, p. 315.

approval of the bioethical aspects of clinical trials.⁵ Noting the AMA's position, Senators Tim Johnson and Christopher Dodd called for a national clinical drug trial registry in a July 8, 2004, letter to the heads of NIH and FDA⁶

In July 2004, the FDA announced that clinical trial sponsors could use a standard format, the Study Data Tabulation Model (SDTM) developed by the nonprofit organization, Clinical Data Interchange Standards Consortium (CDISC), to submit data to the agency [<http://www.cdisc.org/index.html>]. According to the FDA, providing a consistent framework and format for clinical trial information is expected to enhance data integration opportunities and thereby reduce data management barriers for sharing the latest clinical trial data.⁷

In September 2004, the International Committee of Medical Journal Editors (ICMJE), which comprises the editors of 12 major journals including the *New England Journal of Medicine*, *The Lancet*, and the *Journal of the American Medical Association*, announced a new clinical trials publication policy. The policy requires, for publication of clinical trial results, that a sponsor have posted its trial in a public registry before enrolling patients.⁸ The policy is expected to go into effect on July 1, 2005. The ICMJE said it did not advocate any particular registry, but cited clinicaltrials.gov as the only database currently meeting its requirements.”

In an effort that dovetails with the ICMJE policy, NIH announced that as of May 2, 2005, it would request that investigators with manuscripts that are accepted for publication, and that are the result of research supported in whole or in part with direct costs from NIH, submit them voluntarily to NLM's PubMed Central.⁹ This effort would only enable free access to results published elsewhere and would not facilitate access to previously undisclosed results. The NIH announcement was preceded by a July 2004 House Committee recommendation that NIH provide free public access to the complete text of articles and supplemental materials generated by NIH-funded research.¹⁰

⁵ Joseph M. Heyman, “AMA Encouraged by Early Signs of Industry Support for National Clinical Trials Registry,” *American Medical Association*, press release, June 18, 2004, at [<http://www.ama-assn.org/ama/pub/category/13909.html>].

⁶ “Senators Call for National Registry of Clinical Drug Trials,” Senator Tim Johnson, press release, July 8, 2004, at [<http://johnson.senate.gov/~johnson/releases/200407/2004708B20.html>].

⁷ “FDA Announces Standard Format That Drug Sponsors Can Use to Submit Human Drug Clinical Trial Data,” *FDA News*, July 21, 2004, at [<http://www.fda.gov/bbs/topics/news/2004/NEW01095.html>].

⁸ Catherine De Angelis, et al., “Clinical Trial Registration: A Statement from the International Committee of Medical Journal Editors,” *New England Journal of Medicine*, vol. 351, no. 12 Sept. 16, 2004, p. 1250, at [<http://content.nejm.org/cgi/content/full/351/12/1250>].

⁹ Policy on Enhancing Public Access to Archived Publications Resulting from NIH-Funded Research,” *National Institutes of Health*, NOT-OD-05-022, Feb. 2, 2005, at [<http://grants2.nih.gov/grants/guide/notice-files/NOT-OD-05-022.html>].

¹⁰ Report of the House Committee on Appropriations, H.Rept. 108-636, *Departments of Labor, Health and Human Services, and Education and Related Agencies Appropriations Bill, 2005*, Sept. 7, 2004.

The pharmaceutical industry's reaction to clinical trials reporting has been mixed, although as litigation and FDA and congressional interest have increased, some individual manufacturers and groups have volunteered to make some of their clinical trials data public. How the industry defines the types of trials to include (e.g., hypothesis-testing or late-phase only) could affect a registry's utility. Initially skeptical, PhRMA introduced its own clinical trials database in October 2004 at [<http://www.clinicalstudyresults.org>]. Companies that market drugs in the United States can voluntarily post the positive and negative results of controlled trials (mainly Phase III and IV studies) completed after October 2002 on the PhRMA database. As of January 10, 2005, 13 companies had posted results for 27 drugs. According to FDA, more than 10,000 drugs are approved for marketing in the United States. In January 2005, PhRMA additionally called for its members to voluntarily post all hypothesis-testing clinical trials on the NLM site.

Legislation Introduced in the 108th Congress

In October 2004, Representative Edward Markey and Senator Christopher Dodd introduced companion bills H.R. 5252 and S. 2933, the Fair Access to Clinical Trials Act (FACT). The FACT bills would have required the registration of clinical trials in a publically accessible HHS database prior to their enrollment of human subjects, with results to be added within a year of a trial's conclusion. They would have applied to all clinical trials conducted in the United States, as well as to foreign trials used in requesting FDA approvals. They would have also established enforcement mechanisms with monetary penalties for clinical trial sponsors who did not comply. Similar legislation is likely to be introduced in the 109th Congress.

Issues

Issues surrounding the possibility of clinical trials reporting and publication have focused on a range of topics:

Goals. Proponents of public access to clinical trials data cite the need to provide information to members of the general public, health care workers, and researchers, both to help inform treatment decisions, and to help eliminate abuses. Industry advocates have also cited the potential benefits of public awareness of the resources necessary to get a drug approved, and the elimination of duplicated failed efforts. PhRMA cites making clinical trial results for U.S.-marketed pharmaceuticals more transparent, and providing information to practicing physicians and their patients.

Appropriateness/Presentation. Some have questioned whether clinical trials publication is the best mechanism for ensuring patient safety, both because the language may be too technical for lay audiences, and because numerous trials may need to be viewed together in order to draw meaningful conclusions — an analysis that would be difficult for many doctors as well. (A single clinical trial may generate thousands of pages of documentation.) These questions have led some to focus on how information might be presented in an audience-appropriate way. PhRMA's registry contains a link to drug labels, a bibliography, and a summary of results in a format developed by industry

consensus.¹¹ The registry proposed in the FACT bills would have included among other things, trial descriptions, result summaries, and FDA actions.

Timing. Some have argued that only clinical study results are important to judging effectiveness, so publication of a trial's inception is not necessary. Others have argued that some registration at inception is necessary to avoid abuse, and is helpful for connecting potential subjects with various trials. FDAMA requires that notice of a qualifying trial be submitted to clinicaltrials.gov no later than 21 days after the trial is open for enrollment. PhRMA's database only accepts results from completed trials. Those in the FACT bills would have required registration at a trial's inception, before human subjects testing could have begun.

Intellectual Property. Some have expressed concern that publication of information about clinical trials will lead to problems protecting both trade secrets and copyright. Others maintain that the information needed to protect public safety is not the type protected by trade secret or copyright law. PhRMA's registry is voluntary, giving companies control over what information is released. Although the FACT bills would have required reporting, they would have allowed manufacturers to strip their submissions of trade secret information.

Voluntary or Mandatory/Penalties. Concerns about the potential regulatory burden on smaller drug and device manufacturers, and about the potential for intellectual property problems have led some to call for voluntary publication. The desire to protect public safety and to reduce abuse have led others to back mandatory reporting. PhRMA's registry is voluntary. The ones that were proposed in FACT would have been mandatory and would have carried penalties for noncompliance.

Conflicts of Interest. Some commentators have focused on the need for public disclosure of financial and other arrangements between researchers and sponsors in order to demonstrate potential conflicts of interest that may affect clinical trial design, interpretation of data, and presentation of results. The PhRMA database does not include information about funding relationships, though products there are identifiable by company, which may also be the trial funding source. The FACT bills would have required the disclosure of funding source(s), among other things.

Devices. Some have questioned whether information about clinical trials related to medical devices should be included in the registry. The medical device advocacy group, Avamed, points out that FDA regulation of devices is different from its regulation of drugs. Devices are often approved based upon analytical comparisons to existing products rather than the conduct of new clinical trials. Devices as compared to drugs also tend to present a lower risk to patients, tend to be manufactured by smaller companies, tend to have a short market life due to frequent, incremental refinements rather than major breakthroughs, and tend to require more financial incentives to test. PhRMA's database only contains information related to drug trials. Those proposed in the FACT bills would have included information about device trials.

¹¹ Structure and Content of Clinical Study Reports; Guideline approved by the International Conference on Harmonization; July 1996 at [<http://www.fda.gov/cder/guidance/iche3.pdf>].