Order Code RS21944
September 23, 2004

Clinical Trials Reporting and Publication

Erin Williams
Specialist in Bioethical Policy
Domestic Social Policy Division

Susan Thaul
Specialist in Social Legislation
Domestic Social Policy Division

Summary

The recent focus on public access to pediatric clinical trial data for certain selective serotonin reuptake inhibitors (SSRIs) and other antidepressants has highlighted the issues surrounding public access to clinical trial data generally. Clinical trials data are central to assessing drugs' effectiveness, yet there is no centralized system for reporting results. Due to medical journal practices and drug sponsor and researcher incentives to publicize positive results, many trials are never publically reported. Although Food and Drug Administration (FDA) regulations require applicants to register clinical trials at clinicaltrials.gov, not all trials are listed there. Several groups have called for public access to standardized clinical trials data, including notice trial launch and research results. Members of the House and Senate are pursuing legislative action and encouraging FDA regulation.

Announcements of new methods to standardize data submissions and trial identification to facilitate the sharing of research information were made by the World Health Organization in June 2004, and by FDA in July 2004. In September 2004, the International Committee of Medical Journal Editors announced that their journals would only publish the results of studies that had been reported in a public registry. With increased executive, judicial, and congressional interest in clinical trial results, the pharmaceutical industry moved to make some trial results available to the public. This report will be updated on a regular basis.

Introduction

The safety and effectiveness of approximately 10 antidepressants approved by the FDA for adult use have been increasingly questioned. Several of the drugs are SSRIs (selective serotonin reuptake inhibitors), such as Prozac, Zoloft and Paxil. Concerns have focused on the possibility that certain antidepressants are not effective for children and may cause an increased risk of self harm and suicidal thoughts. In September 2004, both Congress and the FDA held hearings on antidepressant use by children. Both hearings

reflected broader concerns that negative clinical trials data were not made available, and therefore not heeded by the public. A lawsuit on this topic was brought by New York State's Attorney General, Eliot Spitzer, against Glaxo Smith Kline (GSK), the manufacturer of the antidepressant Paxil, alleging that the company withheld negative information about the drug. The terms of the August 2004 lawsuit settlement required, among other things, that GSK release "both positive and negative studies about the safety and efficacy of its drugs."[1]

Randomized, double-blinded clinical trials are the gold standard for assessing drug effectiveness, yet a balanced presentation of results across varied trials can be difficult to find. There is no centralized system for reporting results, 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. Researchers have traditionally reported clinical trial results in the peer-reviewed medical literature. Such journals, however, historically have tended to favor for publication those clinical trials having favorable results; the results of unfavorable trials often go unpublished.[2] Other venues for the dissemination of research results are industry, government, or university press releases and presentations at medical conferences. The researcher — who may be affiliated with the 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 results. Some have expressed concern that the concealing of negative data could adversely affect medical decisionmaking.[3]

The FDA Modernization Act of 1997 (FDAMA)[4] required the Secretary of Health and Human Services (HHS) to establish a clinical trials registry, intending the availability of information to increase the access of disenfranchised individuals to cutting-edge medical care available only through research protocols. In response, the National Library of Medicine (NLM) established a clinical trials registry and made it available to the public in 2000 at a website, [http://www.clinicaltrials.gov].[5] However, as reported in the *Washington Post*, an "FDA analysis found that in 2002 only 48 percent 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 the sponsoring company or the drug being tested."[6] Recently, several national and international groups have recommended

---

[1] Office of New York State Attorney General Eliot Spitzer, "Settlement Sets New Standard for Release of Drug Information," press release, Aug. 26, 2004, at [http://www.oag.state.ny.us/press/2004/aug/aug26a_04.html].

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

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

[4] FDA Modernization Act of 1997, PL 105-115, Section 113, Information program on clinical trials for serious or life-threatening diseases.

[5] A.T. McCray and N.C. Ide. "Design and Implementation of a National Clinical Trials Registry," *J Am Med Inform. Ass'n* 7(3) (2000), 313-323, at [http://www.pubmedcentral.nih.gov/articlerender.fcgi?tool=pubmed&pubmedid=10833169];also [http://www.clinicaltrials.gov].

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

that clinical trial reporting be centralized and standardized, including the reporting of all results — both positive and negative.[7]

Recent Events

World Health Organization. On the international front, 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.[8] The system will assign an International Standard Randomised Controlled Trial Number (ISRCTN) to each randomized controlled trial the WHO ethics review board approves. The ISRCTN provides a means of identifying and unambiguously tracking a trial throughout its life cycle.[9] The company Current Controlled Trials will maintain a no-charge, online register of these numbered trials.[10] By posting information on trial starts and their results, the system will avoid problems of publication bias.

American Medical Association. In the United States, in June 2004, the American Medical Association (AMA) recommended to HHS that it should 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 approval."[11] Noting the AMA's position, U.S. Senators Tim Johnson and Christopher Dodd called for a national registry of clinical drug trials in a July 8, 2004 letter to National Institutes of Health (NIH) Director Elias Zerhouni and FDA acting Commissioner Lester Crawford.[12]

Food and Drug Administration. On July 24, 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.[13] According to the FDA, "[b]y providing a consistent framework and format for clinical trial information, this standard

---

[7] "Pressure Mounts for Clinical Trial Registry," *Medicine & Health* (June 21, 2004); see also Committee on Assessing the System for Protecting Human Research Participants, Institute of Medicine, *Responsible Research: A Systems Approach to Protecting Participants*, Washington, DC: National Academy Press, Oct. 2002, p. 14.

[8] "International Coordination of Clinical Research WHO," *Medical News Today*, Apr. 3, 2004, at [http://www.medicalnewstoday.com/index.php?newsid=6986], visited Apr. 4, 2004.

[9] "International Standard Randomised Controlled Trial Number (ISRCTN) Scheme," *Current Controlled Trials* website, at [http://www.controlled-trials.com/isrctn/introduction.asp], visited Aug. 5, 2004.

[10] Current Controlled Trials Ltd is part of the Current Science Group of companies, headquartered in Tokyo and London. "About Us," *Current Controlled Trials* website, at [http://www.controlled-trials.com/information/]; information about Current Science Group available at [http://sciencenow.com/].

[11] 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/article/1617-8653.html], visited June 21, 2004.

[12] "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].

[13] Information about CDISC is available at [http://www.cdisc.org/index.html].

is expected to enhance data integration opportunities and thereby help to reduce data management barriers for sharing the latest clinical trial data."[14]

Medical Journals. 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 policy, to go into effect on July 1, 2005, that, for publication of clinical trial results in their journals, the sponsor (manufacturer, research entity) must have reported the trial in a public registry before it began to enroll patients.[15] The ICMJE "said it did not advocate any particular registry, but cited clinicaltrials.gov as the only database currently meeting its requirements." Following discussions with the ICMJE, the NLM Director announced that clinicaltrials.gov was "the right place" to list all clinical trials.[16] However, he also cautioned that studies conducted outside the purview of a US regulatory agency (such as FDA or NIH) may prove difficult to authenticate and/or validate: "For instance, how [would] we know that the description is a proper description of a trial and that the trial exists."[17]

National Institutes of Health. In an effort that dovetails with the ICMJE policy, in September 2004, NIH announced that it would establish a searchable public resource of all NIH-funded research results, making them freely available to the public six months after their publication in other journals.[18] 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 all research that it funds.[19]

Pharmaceutical Industry. Reaction from the pharmaceutical industry to clinical trials reporting has been mixed, although as litigation and FDA and congressional interest have increased, some individual manufacturers and Pharmaceutical Research and Manufacturers of America (PhRMA) have volunteered to make some of their clinical trials data public. One drug manufacturer, Eli Lilly, has announced it will disclose on a public registry all clinical trial results for the drugs its sells, beginning the fourth quarter

---

[14] "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].

[15] 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].

[16] Janet Coleman, "ClinicalTrials.gov Is "Right Place" to List All Initiated Clinical Trials, National Library of Medicine Says," *Washington FAX*, Sept. 22, 2004.

[17] Ibid.

[18] "Notice: Enhanced Public Access to NOH Research Information," *National Institutes of Health*, NOT-OD-04-064 (Sept. 3, 2004), at [http://grants1.nih.gov/grants/guide/notice-files/NOT-OD-04-064.html].

[19] Alison Cook "Open Access to US Govt Work Urged," *The Scientist* (July 21, 2004), at [http://www.biomedcentral.com/news/20040721/01].

of this year.[20] A spokesperson for another drug company, Merck, was supportive of the concept, recommending "expanding an existing National Institutes of Health database to include all Phase III and Phase IV — or post marketing — trials."[21] A spokesperson from PhRMA, Jeff Trewhitt, was more skeptical. Mr. Trewhitt expressed concerns about how proprietary information could be protected in a reporting system. He also stressed the need to avoid misleading people with the results of any single trial when usually "anywhere from a dozen to twenty clinical trials" are conducted to support a potential new medicine.[22] However, in September 2004, PhRMA announced that in the following month, it would introduce a clinical trials database of its own (at [http://www.clinicalstudyresults.org]) that "will contain the results of all controlled clinical trials (mainly Phase III and IV studies), both positive and negative, completed since October 2002 for PhRMA-member company drug products approved in the United States."[23]

Issues. Proponents of public access to all clinical trials data cite the need to help members of the general public, health care workers, and researchers. Industry advocates have also cited the potential benefits of "increased public awareness of the time and resources that are necessary to get a drug approved," and the elimination of "duplicated failed efforts."[24] However, some have urged caution in efforts to make all clinical trials data available to the public. For example, a former editor of the *New England Journal of Medicine* specified that a public registry would help to eliminate abuses only if it contained all clinical trials; registered trials at their inception and as a prerequisite to human subject enrollment; was administered by a publicly accountable entity; included specific elements of the trial design such as criteria for subject selection, drugs and doses to be used, and endpoints to be measured; and identified the main researchers and potential conflicts of interest.[25] Another commentator questioned whether such a technical resource would be meaningful to a person "without an MD or PhD," and whether the creation and maintenance of a clinical trials registry would be an appropriate in a system "already strained by limited resources to maintain drug pipelines."[26]

---

[20] Eli Lilly's drug trial registry is accessible online at [http://www.lillytrials.com/].

[21] "PhRMA Cautious, but Merck More Receptive," *Medicine & Health*, June 21, 2004.

[22] Ibid.

[23] "New Database Provides Doctors and Patients Unprecedented Access to Clinical Study Information for Marketed Medicines," Pharmaceutical Research and Manufacturers of America press release, Sept. 7, 2004, at [http://www.phrma.org/mediaroom/press/releases/07.09.2004.1063.cfm].

[24] Ibid.

[25] Marcia Angell, "Time for a Drug Test Registry," *Washington Post*, Aug. 13, 2004, p. A25.

[26] Kristen Hunter, "How Will the Publication of a Clinical Trial Registry Change the Design and Conduct of Future Trials?" *Clinical Inquirer: Kristen's Korner*, Sept. 10, 2004, at [http://www.iirusa.com/clinical/index.cfm/link=83/newsection=yes/brochurekeycode=E2700XXES9].