

## Public Registration of Clinical Trials

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For many years, the registration in a public data bank of all clinical trials — from start to completion and reporting of results — has seemed a quixotic quest of some academic researchers, medical-journal editors, and librarians. Within the past two months, however, a constellation of events and developments has broadened this effort and captured the attention of the medical profession, the news media, and government officials. The events include a lawsuit against GlaxoSmithKline by New York State Attorney General Eliot Spitzer for concealing negative information about the antidepressant medication paroxetine and the endorsement of a comprehensive registry by the American Medical Association (AMA).<sup>1</sup> Other developments include the possibility of federal legislation and a potential requirement from the International Committee of Medical Journal Editors (ICMJE) for trials to be registered at inception as a condition for later consideration for publication.

In the United States, public registration is currently required for some trials, such as clinical gene-transfer trials registered with the National Institutes of Health (NIH) and studies of the effectiveness of treatments for serious or life-threatening conditions that are conducted under the investigational-new-drug regulations of the Food and Drug Administration (FDA).<sup>2</sup> But there is no system for comprehensive registration of trials or the public reporting of results. When companies seek approval to market a new medication or to market an existing drug for an additional indication, the FDA releases extensive information about the trials that support the approval — but it considers much of the other information it receives to be proprietary and never releases it.

The current situation has raised two types of concerns. The first is about the effects on medical practice of concealing negative data.<sup>1,3</sup> The lack of public information about the existence of trials allows unfavorable results to be hidden, even if the data show that a marketed medication, device, or other intervention is useless or harmful. Although some important negative studies are published in

prominent journals, many are not. Review articles and editorials, meta-analyses, and prescribing information may be misleading — or wrong — when they are based on only some of the relevant trials. When serious questions, such as those about the relation between selective serotonin-reuptake-inhibitor antidepressants and the risk of suicide in children, are raised, there is no substitute for getting all the data out and examining them critically.

The second concern is about investigational products and the protection of research subjects.<sup>3</sup> In most instances, research will not directly benefit participants and may expose them to risks. Thus, investigators and sponsors have a responsibility to the subjects to report the findings, including the adverse events, in a timely fashion. They also have a responsibility to inform physicians and prospective volunteers about ongoing trials in which they may wish to enroll.

Many of the criticisms have been directed at trials sponsored by pharmaceutical companies. Trials require human subjects, and companies stand to gain financially from favorable results. The medical goal is to find out what is safe and effective for patients, not to increase the financial returns for the sponsor. The company, however, often owns the study database and controls decisions about publication and release of data.<sup>4</sup> There is debate about whether some information about industry-sponsored trials, such as the results of small or exploratory studies, is legitimately proprietary or whether information about all trials should be made public routinely once volunteers are enrolled, regardless of the potential commercial consequences. In 2002, in a report on “responsible research,” the Institute of Medicine concluded that “The creation of a comprehensive clinical trials database that is soundly structured for public use would ensure that information about all clinical trials undertaken would be available to contribute to generalizable knowledge regardless of whether their results are viewed as positive or negative by investigators, sponsors, or publishers.”

Registering clinical trials was first proposed in the 1970s, both to speed President Richard Nixon's "War against Cancer" and to reduce bias in the reporting of trial results.<sup>3</sup> There are registries throughout the world, including those maintained by institutions and companies. There are also government registries, such as GenBank, the NIH's genetic-sequence database, and the Genetic Modification Clinical Research Information System ([www.genecris.od.nih.gov](http://www.genecris.od.nih.gov)), launched by the NIH and the FDA earlier this year to provide information about clinical gene-transfer trials and allow prompt reporting of adverse events.

ClinicalTrials.gov, a large searchable database, is often cited as a model for a comprehensive public trials registry or an international system encompassing multiple registries. It was developed by the FDA and the NIH, through the National Library of Medicine, and became operational in 2000.<sup>2</sup> It provides information on studies of drugs for serious or life-threatening conditions, as required by section 113 of the FDA Modernization Act of 1997. A clinical trial is defined as "a research study in human volunteers to answer specific health questions." Such a definition includes interventional and observational trials, preliminary trials, and trials with and without control groups. As of late June 2004, the registry listed 10,906 trials from about 90 countries; about 40 percent are still recruiting subjects. The NIH and other federal agencies, universities, and other organizations sponsor most of the studies listed. About 2230 are sponsored at least partially by industry, and about 425 companies have registered studies. Each study is assigned a unique registration number, regardless of the number of sites. The National Library of Medicine verifies the accuracy of the information (see Table) and provides quality control. The annual budget, including research and development, is about \$3.2 million.

ClinicalTrials.gov has limitations. It was established for studies of certain diseases and conditions, although it has accepted many other listings. Information about results is not required; however, links to relevant publications may be included. It includes only a small percentage of all clinical trials, and many studies that should be registered are not. One reason is that the FDA Modernization Act did not provide an enforcement mechanism. For example, a review by FDA staff showed that between January and September 2002, 91 percent of government-sponsored trials related to cancer that fall under section 113 had been registered, as compared

**Table. Information in the ClinicalTrials.gov Data Bank.<sup>2</sup>**

Descriptive information
Brief title (in layperson's language)
Brief summary (in layperson's language)
Study design, study phase, and study type
Condition or disease
Intervention
Availability for single-patient or expanded-access use
Recruitment information
Overall study status (e.g., recruiting vs. no longer recruiting)
Individual site status
Eligibility criteria, sex, age
Location and contact information
Administrative data
Unique protocol identification number
Study sponsor
Verification date

with 49 percent of industry-sponsored trials. The FDA has repeatedly provided detailed guidance to industry about the registration requirements. When asked about the missing studies at a congressional hearing in May, Dr. Richard Pazdur, the director of the Division of Oncology Drug Products at the FDA's Center for Drug Evaluation and Research, said that the agency is "greatly concerned about the low participation of industry in listing their trials."

In June 2004, the AMA recommended that the Department of Health and Human Services (DHHS) "establish a comprehensive registry for all clinical trials conducted in the United States; every clinical trial should have a unique identifier; and all results from registered clinical trials should be made publicly available through either publication or an electronic data-repository."<sup>1</sup> The AMA also recommended that "Institutional Review Boards consider registration of clinical trials to an existing registry as condition of approval."

Implementing these recommendations would probably require federal legislation — which is being considered by Congress — as well as funding and enforcement mechanisms. An international system of registries would require coordination, including a system of assigning a universally recognized identification number resembling the ISBN, the unique machine-readable identification number that is used for books. Under the AMA proposal, investigators or sponsors might provide institutional review boards with a registration number when a trial was submitted for approval, allowing the trial to be tracked. For example, editors of medical journals could use registration numbers and

registries to prevent duplicate or partial publication of results, to learn of related studies, and to put them into context. “The important first step is to get all the trials registered,” said Alexa McCray, the director of the Lister Hill National Center for Biomedical Communications at the National Library of Medicine. “That would be a huge step toward transparency.” Dr. Greg Koski of Massachusetts General Hospital, the former director of the DHHS Office for Human Research Protections, said that registration is a “good idea but will be fought by some segments of the industry.”

In June it became known that the ICMJE (representing 11 general medical journals, including the *New England Journal of Medicine*) was planning a statement on registration and publication of trials, but no specific proposal has yet been released. Neither the DHHS nor the Pharmaceutical Research and Manufacturers of America (PhRMA), the leading industry trade group, had taken a position on the AMA recommendations. On June 30, in a related development, PhRMA updated its principles for the conduct of clinical trials and communication of the results.<sup>5</sup> Among other provisions, the principles provide that “There will be timely communication of meaningful study results, regardless of the outcome of the study. The results must be reported in an objective, accurate and complete manner, with a discussion of the limitations of the study. Study sponsors will not suppress or veto publications.” The principles — adherence to which is voluntary — are effective for trials begun after October 1, 2002, and are compatible with a clinical-trials registry.

Some pharmaceutical companies have endorsed a clinical-trials registry, but their positions

do not appear to be as comprehensive as the AMA proposal. Merck supports a data bank run by the government that would track all late-stage drug trials. GlaxoSmithKline plans to establish its own database, linked to its corporate Web site, to provide summaries of the protocols and results of the trials of marketed medicines that it has sponsored.

Even if Congress enacts legislation, DHHS could not implement it immediately. Many substantive issues would have to be resolved. For example, what clinical trials would be included? How much detail would be provided about the protocols? How would results be reported for studies that are not published in the peer-reviewed medical literature? How could the completeness of registration and the quality and accuracy of the information be ensured? Although uncertainties are ahead, there is a growing realization that the public registration of clinical trials is an idea whose time has come. In the long term, no one benefits from the selective release of information about trials and the selective reporting of results.

1. Council on Scientific Affairs, American Medical Association. Featured CSA report: influence of funding source on outcome, validity, and reliability of pharmaceutical research (A-04). June 2004. (Accessed July 2, 2004, at <http://www.ama-assn.org/ama/pub/article/print/2036-8608.html>.)
2. Food and Drug Administration. Guidance for industry information program on clinical trials for serious or life-threatening diseases and conditions. January 2004. (Accessed July 2, 2004, at <http://www.fda.gov/cber/gdlns/clintrial.pdf>.)
3. Dickersin K, Rennie D. Registering clinical trials. *JAMA* 2003; 290:516-23.
4. Davidoff F, DeAngelis CD, Drazen JM, et al. Sponsorship, authorship, and accountability. *N Engl J Med* 2001;345:825-6.
5. Pharmaceutical Research and Manufacturers of America. Updated principles for conduct of clinical trials and communication of clinical trial results. Washington, D.C., June 30, 2004. (Accessed July 6, 2004, at <http://www.phrma.org/mediaroom/press/releases/30.06.2004.427.cfm>.)

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## The Price Tag on Progress — Chemotherapy for Colorectal Cancer

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From the 1960s until the mid-1990s, fluorouracil was the primary chemotherapeutic agent available for the treatment of colorectal cancer. During the past decade, the Food and Drug Administration (FDA) has approved five new drugs for metastatic colorectal cancer. Irinotecan (approved in 1996) and oxaliplatin (2002) are cytotoxic agents that interfere

with DNA replication, and capecitabine (1998) is an oral formulation of fluorouracil. This spring, the monoclonal antibodies bevacizumab and cetuximab, targeting vascular endothelial growth factor and epithelial growth factor receptor, respectively, were approved by the FDA for use in conjunction with cytotoxic regimens.