

Registration of Clinical Trials — Voluntary or Mandatory?

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Should the public registration of clinical trials be voluntary or mandatory, as bills introduced earlier this month in Congress would require? What trials should be included? Proposals for mandatory registration have gained support because of concerns about the effects on medical practice of concealing negative data, concerns about the protection of research subjects, particularly in studies of investigational products, and concerns about the availability of information to researchers, physicians, people seeking to enroll as subjects in trials, and the public.^{1,2} Critics argue that mandatory registration could reveal information that manufacturers consider proprietary, such as the results of small or exploratory studies, or impede the development of drugs or devices by forcing the release of research strategies to competitors. Proponents argue that these risks must be weighed against the benefits of registration and that registration will only be meaningful if all trials that should be registered are. They also doubt that voluntary efforts will work.

Pharmaceutical companies or other commercial entities may have business reasons to conceal certain trials or to disclose findings selectively. Recent proposals, however, require the registration of trials at inception, before subjects are enrolled, so that the existence and design of every trial is immediately part of the public record.² A clinical-trials registry may eventually include the results of a trial or a link to a report of the trial in a peer-reviewed journal. Posting on the Internet a summary of the results, as some companies have begun to do, is not registration. Despite the inherent interest in results, they are only meaningful in the context of the design and conduct of a study and the analysis of the data.

A comprehensive public trials registry, www.clinicaltrials.gov, already provides a mechanism for the voluntary registration of clinical trials. The registry, developed by the Food and Drug Administration (FDA) and the National Institutes of Health (NIH), through the National Library of Medicine,

includes studies of drugs for serious or life-threatening conditions, as required by the FDA Modernization Act of 1997. However, it accepts all research studies in human volunteers that are designed to answer specific health questions, regardless of study design or whether the studies are of drugs or other interventions. As a result of recent changes, it can also accept international trials. As of mid-October, www.clinicaltrials.gov listed 11,844 trials, including 3651 that have been completed and 4190 that are recruiting subjects. In September, more trials with commercial sponsors were registered than in prior months (see Figure).

In June, clinical-trial registration gained important support. The American Medical Association (AMA) endorsed the idea, and New York State Attorney General Eliot Spitzer sued GlaxoSmithKline for concealing negative information about the antidepressant medication par-

oxetine. In August, as part of the settlement of that lawsuit, GlaxoSmithKline agreed to post on its corporate Web site a summary of clinical-study reports for every company-sponsored trial of its medications completed after December 27, 2000. There is no requirement, however, that the studies be registered at inception. In September, as part of a separate agreement with Spitzer, Forest Laboratories, which manufactures the antidepressant medications citalopram and escitalopram, agreed to post on its corporate Web site summaries of the results of clinical studies of marketed drugs completed after January 1, 2000. Forest also agreed to post the number, title, starting date, and key objectives of each phase 3 and phase 4 trial when it is initiated.

In response to the concerns about concealed data, the Pharmaceutical Research and Manufacturers of America (PhRMA), the leading industry trade group, has established an electronic database of clinical-study results (www.clinicalstudyresults.org), which, according to a press release, “provides doctors and patients unprecedented access to clinical study information for marketed medicines.”



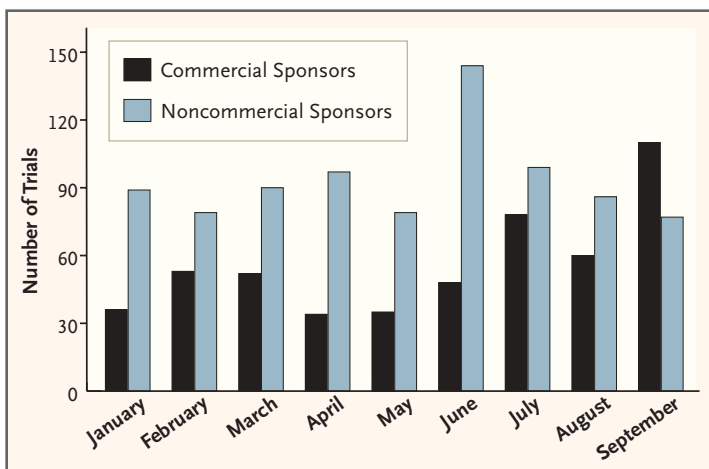


Figure. Trials Registered with www.clinicaltrials.gov between January and September 2004.

Data are from the National Library of Medicine.

Table. Proposed Information in the Clinical Trials Data Bank under the Fair Access to Clinical Trials Act.

Descriptive Information

Title and purpose, including the drug, biologic product or device being tested, the disease or condition, and the intervention or comparisons

The hypothesis, the primary and secondary clinical outcomes, the time at which they will be assessed, and the dates and details of any revisions

A description of the protocol to the extent necessary to evaluate the results

The total number of subjects

The estimated completion date, the actual completion date, and the reasons for any difference between them

For trials that are not completed, the termination date and the reasons for termination

Recruitment Information

Eligibility criteria

Location of trial sites, the starting date, and the enrollment status

Point of contact for those wanting to enroll, including the identity of each responsible person

Results

A summary of the results, including summary data tables, with respect to the primary and secondary outcomes, including information on statistical significance

Safety data, including the number and type of adverse events

Description of how the results were reviewed, including whether they were peer-reviewed by reviewers independent of the sponsors

Publications in peer-reviewed journals relating to the trial

Administrative Data

A unique trial identification number

Funding source or sources

Identification of a product as approved or unapproved, and whether a trial is investigating an approved or unapproved use

For trials of an unapproved use, information about the status of any application for approval of such use with the FDA, and the submission of data from the trial to the FDA

The database, which became available to the public on October 1, is a voluntary repository of the results of controlled trials of drug products that are marketed in the United States and that are sponsored by member companies. It is not a clinical-trials registry. As of October 12, the database listed studies from seven companies involving 10 medications; the numbers are expected to increase.

The AMA, the International Committee of Medical Journal Editors (ICMJE), and some Democratic lawmakers in Congress advocate mandatory registration of clinical trials. The AMA recommended that the federal government “establish a comprehensive registry for all clinical trials conducted in the United States.”^{1,3} In September, the ICMJE, which represents 11 general medical journals, including the *New England Journal of Medicine*, announced that “member journals will require, as condition of consideration for publication, registration in a public trials registry. Trials must register at or before the onset of patient enrollment.”² The policy takes effect in the summer of 2005. Although not advocating a particular registry, the ICMJE established specific requirements, which are currently met by www.clinicaltrials.gov and which may eventually be met by additional registries. Although other journals have voiced support for this approach, it is not known how many will actually adopt a similar policy.

In early October, Senators Christopher Dodd (D-Conn.), Edward Kennedy (D-Mass.), Tim Johnson (D-S.D.), and Ron Wyden (D-Oreg.) introduced the Fair Access to Clinical Trials Act in the Senate, and Congressmen Edward Markey (D-Mass.) and Henry Waxman (D-Calif.) introduced a companion bill in the House.^{4,5} The bills, which are similar but not identical, would build on www.clinicaltrials.gov to create a mandatory public electronic database of clinical trials that would be searchable without charge. It would be administered by the federal government and would meet the minimum criteria for a trial registry set by the ICMJE (see Table). The national registry would include “all publicly and privately funded clinical trials involving drugs, biological products, or devices regardless of the outcome of the trial.”⁵ An exception would be made for most trials conducted to test solely the safety of an unapproved product or to investigate pharmacokinetics.

The legislation would ensure the accuracy of the information supplied, through audits and the ability to correct inaccurate or false or misleading infor-

mation. Compliance would be ensured by overlapping mechanisms. Registration would be required before clinical trials could be approved by institutional review boards, a condition that is also supported by the AMA.³ Registration would also be required before the FDA could authorize the testing of an investigational product.⁴ For federally supported trials, it would be required as a condition of an individual or institution's receiving a federal grant, contract, or other award. The Department of Health and Human Services (DHHS) could impose fines of up to \$10,000 per day for noncompliance. In a related area, the Senate legislation would ban contracts involving researchers or their institutions that prohibit, limit, or unreasonably delay the discussion of the results of a clinical trial at a scientific meeting or the publication of such results.⁵

Despite the support for public registration of clinical trials, the prospects for mandatory registration are uncertain. Individual institutional review boards could decide on their own initiative that registration is ethically required as a condition of their

approval of trials, but they are unlikely to do so without national guidance. The DHHS, whose agencies include the FDA and the NIH, has not taken a position on mandatory registration, nor have other governments. The effective dates of the ICMJE proposal are months away. Although the Fair Access to Clinical Trials Act would mandate registration, it has no Republican cosponsors in either the House or the Senate, and it was introduced as Congress was about to adjourn. The legislative outcome in the United States may depend on the results of next week's elections.

1. Steinbrook R. Public registration of clinical trials. *N Engl J Med* 2004;351:315-7.
2. De Angelis C, Drazen JM, Frizelle FA, et al. Clinical trial registration: a statement from the International Committee of Medical Journal Editors. *N Engl J Med* 2004;351:1250-1.
3. Council of Scientific Affairs. Featured CSA report: influence of funding source on outcome, validity, and reliability of pharmaceutical research (A-04). Chicago: American Medical Association, June 2004.
4. Fair Access to Clinical Trials Act of 2004, H.R. 5252, 108th Cong., 2d Sess.
5. Fair Access to Clinical Trials Act of 2004, S. 2933, 108th Cong., 2d Sess.

BECOMING A PHYSICIAN

A Precarious Exchange

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Related articles, pages 1829 and 1838

If an anthropologist were to stumble into this room between 6 and 8 p.m. this evening, he might find the telltale signs of a ritual: a group of residents and interns huddled around a table, scribbling hieroglyphics on scraps of paper.

To a physician, this scenario is all too familiar — we call it “sign-out” — but in a way, the anthropologist would be right: it is a peculiar ritual, this daily transfer of patients from one medical team to another. As I write this, at the end of a frantic afternoon, 18 residents are simultaneously handing off patients to one another in the noisy emergency room. In the medical units of the hospital, hundreds of such exchanges happen every week. And yet, ubiquitous as the sign-out is, it remains one of the most poorly examined transactions in medicine. It is odd, then, that this rickety old liturgy may soon become the centerpiece of a complex debate on the future of medical education. But it is precisely at

this transitional moment — in the frenzied blurring out of information and instructions — that some of the most contentious ideas about the residency system become most starkly defined.

It was on a similarly frantic evening two years ago that I discovered the precariousness of these daily exchanges. In April 2002, a young woman I'll call Anna was admitted to my team's care. That morning, her sister had found her curled up on the floor of her apartment with dozens of pills scattered around her. Over a two-hour period, Anna had swallowed a small pharmacy of drugs: ibuprofen, lorazepam, pseudoephedrine, and perhaps most ominously, an unusual antidepressant, phenelzine (Nardil). In the emergency room, she had asked for a glass of water and wrapped herself in an impenetrable nest of sheets. When the doctor had passed her off from the ER to the admitting intern, he had referred to her simply as “lethargic.” The handoff