

SPECIAL REPORT

Progress and Deficiencies in the Registration of Clinical Trials

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Clinical trials are essential to understanding the efficacy of medical interventions. The ethical underpinnings of this type of research involving human subjects, codified in the Belmont Report¹ and the Declaration of Helsinki,² require that the results be publicly available to inform medical practice as well as future research. In addition, basic principles of evidence-based practice require the analysis of all data on a given topic; the practice of publishing only some results, but not others,^{3,4} undermines our collective ability to make rational decisions about medical care.

In Section 801 of the Food and Drug Administration (FDA) Amendments Act,⁵ enacted in September 2007, Congress expanded the requirements for sponsors and investigators to post information about clinical trials, including selected aspects of trial results, on the U.S. government Web site ClinicalTrials.gov. These expanded requirements^{6,7} apply to all investigators and sponsors, whatever their source of funding. Section 801 also includes, for the first time, considerable penalties for non-compliance, including possible loss of grant monies from the National Institutes of Health (NIH) and civil monetary penalties of up to \$10,000 per day. This mandate for registration and results reporting (Table 1) has important ethical, practical, and scientific implications for all who are involved in clinical research, as well as for all who rely on research results to guide their decisions on clinical care.

REGISTRATION REQUIREMENTS

Section 801 of the FDA Amendments Act requires the registration and public posting of all applicable trials of drugs (including biologics) and devices subject to FDA regulation (generally, this means having at least one trial site in the United States). Section 801 excludes phase 1 drug trials and “early feasibility device trials,” but it is important to note that the International Committee of Medical Journal Editors (ICMJE) and the World

Health Organization (WHO) require the registration of all trials regardless of phase. In addition to broadening the scope of the trials that must be registered, the Act now mandates the posting of a number of data elements that had previously been optional on ClinicalTrials.gov but were required by the ICMJE⁷ and the WHO (Table 1). The law handles registration of device trials differently from drug trials, and device trials will not be discussed in detail in this article.

The requirements to submit registration data took effect on December 26, 2007, and ClinicalTrials.gov has been modified to accommodate compliance. However, the precise specification of mandatory data elements and delineation of compliance and enforcement provisions remain a work in progress and will be finalized at a later date by promulgating regulations. Sponsors and investigators are responsible for compliance with Section 801 even before the promulgation of formal regulations.

RESULTS-REPORTING REQUIREMENTS

A novel aspect of Section 801 is the mandated incremental expansion of ClinicalTrials.gov to include information about results. This is being implemented by linking existing databases and creating a new results database at the National Library of Medicine (NLM). First, ClinicalTrials.gov registration records for trials of FDA-regulated drugs and devices will be linked to existing results information available on the FDA, NLM, and NIH Web sites. Examples include electronic drug labels, FDA public health advisories and drug-approval packages, and peer-reviewed publications indexed in Medline. Early versions of these links are now functional on ClinicalTrials.gov. Second, the NLM has created a “basic results” database to collect data elements specified by the law and display them on ClinicalTrials.gov. The creation of this database was completed on September 24, 2008, and it is now available for inves-

Table 1. Registration and Reporting Requirements of the FDA Amendments Act, Section 801.*

Type of Requirement	Type of Trial	Deadline for Reporting	Type of Data	Effective Date
Registration	Applicable clinical trials of drugs or biologics and devices regulated by the FDA†	No later than 21 days after enrollment of first participant	Summary protocol: population, study design, outcome measures Recruitment information Location and contact information	Dec. 26, 2007
Basic results reporting	Applicable clinical trials of approved drugs or biologics and cleared or approved devices regulated by the FDA†	No later than 1 yr after completion date; delayed submission is permitted in some cases‡	Demographic and baseline characteristics of participant sample Participant flow Primary and secondary outcomes Certain agreements regarding dissemination of results information	Sept. 27, 2008
Adverse-events reporting			Serious events Frequent events	Sept. 27, 2009
Future expanded results reporting to be required by the FDA Amendments Act	Examples include applicable clinical trials of unapproved drugs or biologics regulated by the FDA†	Examples include extension of submission date, up to 18 mo after completion date, and reconsideration of timing and requirements for submitting updates‡	Examples include technical or lay summaries and complete protocol or other information necessary to evaluate results	Sept. 27, 2010

* Information on trial registration, basic results reporting, and adverse-events reporting is available at <http://prsinfo.clinicaltrials.gov/definitions.html> and at <http://prsinfo.clinicaltrials.gov/fdaaa.html>. The requirements for expanded results have not yet been defined.

† According to the FDA Amendments Act, an “applicable clinical trial” is generally one that has at least one trial site in the United States. Section 801 excludes phase 1 drug trials and “early feasibility device trials.” All applicable clinical trials of devices must be submitted, but only trials of devices previously cleared or approved are posted. Note that the ICMJE and the WHO require registration of all clinical trials for drugs and devices, regardless of phase.

‡ According to the FDA Amendments Act, “completion date” refers to “the date that the final subject was examined or received an intervention for the purposes of final collection of data for the primary outcome, whether the clinical trial concluded according to the prespecified protocol or was terminated.”

tigators to populate with data. Third, summary information on adverse events must be added by September 27, 2009, although a version of this information is now available for use by investigators. Finally, a more comprehensive results database — referred to in Section 801 as an “enhanced results” database — will be created after a public meeting is held and a rule-making process of up to 3 years has been completed.

Creating a comprehensive clinical trials database is very challenging because of the wide variety of trial designs that must be registered. Because the submitted data will not be peer-reviewed and will not be interpreted, qualified, or explained, the results reported at ClinicalTrials.gov will complement rather than replace the thoughtful presentation and discussion of results characteristic of the best peer-reviewed publications; journals represented on the ICMJE (www.icmje.org) do not consider the posting of results in this fashion in

the database where the trial was registered as prior publication.

The reporting requirements are summarized in Tables 1 and 2. The results of all drug trials — other than phase 1 — that were ongoing on or after September 27, 2007 (the date of enactment), must be reported at ClinicalTrials.gov if the products under study have already been approved by the FDA. The results for drugs not yet approved by the FDA do not have to be posted until the drug receives such approval. In general, trial results should be reported no later than a year after the date on which the last measurement concerning the primary outcome has been completed. For trials of approved drugs in which a new, unapproved indication is being studied, reporting can be delayed by up to 2 additional years regardless of the ultimate regulatory decision made by the FDA on the indication. A deficiency of the current law is that the results of older tri-

Table 2. Reporting Requirements for Drug Trial Results under the FDA Amendments Act, Section 801.

Trial Completion Date	Approval Status 1 Yr after Trial Completion Date*	Results Reporting Required	Results Submission Date
Before Sept. 27, 2007†	Approved	No	None — results reporting not required
	Unapproved	No	None — results reporting not required
After Sept. 26, 2007‡	Approved	Yes	Within 1 yr of trial completion
	Unapproved	Yes, when approved	Within 30 days of approval for first indication

* “Approval” indicates that the drug has been approved for at least one indication 1 year after the trial completion date. According to the FDA Amendments Act, and “completion date” refers to “the date that the final subject was examined or received an intervention for the purposes of final collection of data for the primary outcome, whether the clinical trial concluded according to the prespecified protocol or was terminated.”

† Trials completed before September 27, 2007, are not required to report results.

‡ Exceptions may apply to some trials with completion dates between September 27, 2007, and December 25, 2007.

als of drugs that were approved before September 27, 2007, and that were no longer the subject of ongoing trials on or after September 27, 2007, do not need to be posted — and such drugs constitute the vast majority of the prescription drugs currently used by patients. Likewise, there is no requirement for posting the results of trials of drugs that were never approved.⁸ However, trials of previously approved drugs that have not been approved for a new indication will have to be posted, but not until 2 years after the completion date.

An earlier law enacted by the State of Maine⁹ that required reporting of results from trials initiated after October 15, 2002, for drugs marketed in that state will be preempted once Section 801 is fully implemented. However, for the time that the Maine law remains in effect, public dissemination of results for some of the trials that are not covered under the FDA Amendments Act will be required by the State of Maine. The state recently issued guidelines for drug manufacturers reminding them of the need to comply with state law (the guidelines are available at www.maine.gov/dhhs/boh/documents/CT_reportingupdate9-08.pdf).

CLINICAL TRIALS RESULTS DATABASES

ClinicalTrials.gov, the largest single registry of clinical trials, had more than 67,000 registered trials as of January 31, 2009. It contains trials representing a broad range of intervention types (e.g., drug, device, surgical intervention, and procedural intervention) from 157 countries. Under the terms of the FDA Amendments Act, ClinicalTrials.gov will substantially improve access to both registration and summary results information for new and ongoing trials of drugs and devices.

True public access to results depends on the existence of reports that are available to the public and on the convenience and accuracy with which the database can locate those reports. Right now there are three sources of results that meet these criteria: PubMed and other bibliographic databases (e.g., EMBASE) that provide indexes of publications, FDA analyses and documents that can be accessed through the FDA Web site (e.g., Drugs@FDA) and ClinicalTrials.gov, and existing industry results databases, which have limited search capabilities (e.g., GlaxoSmithKline Clinical Study Register [<http://ctr.gsk.co.uk/welcome.asp>] and the site sponsored by the Pharmaceutical Research and Manufacturers of America [PhRMA] [www.ClinicalStudyResults.org]).

The database of results from trials listed at ClinicalTrials.gov, searchable with the customized ClinicalTrials.gov search engine,¹⁰ will add another source of information about trial results. Ultimately, access to trial results is still insufficient if it is not possible to determine whether and how many sets of trial results may be missing. Unfortunately, none of these sources of results (i.e., publications, FDA reviews, industry-sponsored databases, or ClinicalTrials.gov entries) will necessarily contain a complete set of all clinical trial results for a given drug or device, either individually or among them.

THE NEED FOR ADDITIONAL LEGISLATION

Although incorporation of the NLM initiatives in the ClinicalTrials.gov database will be a great step forward, it is worth noting that the taxpayer already contributes to the maintenance of a treasure trove of clinical trial data at the FDA to

which the public has very limited access. The FDA reviews and analyzes all trial results submitted in support of an application for approval to market drugs, biologics, or devices. According to the law, the FDA must treat much of the data on clinical trials it receives from sponsors, and its own analyses of these data, as “confidential commercial information” and is prevented from publicly disclosing this information. Therefore, any drug trial information released to the public by the FDA is often heavily redacted to prevent illegal disclosures.¹¹ Such redacted disclosure often occurs only in response to one or multiple requests made under the Freedom of Information Act, and even then the disclosure is often made only after a prolonged delay. Section 916 of the FDA Amendments Act institutionalizes this limitation by mandating that the FDA publish on its Web site key information related to an approval of an application (the action package) for a drug that contains a previously approved active ingredient only after it has received three requests under the Freedom of Information Act.

Although FDA reviews of many approved products are posted online, the FDA Web site does not contain all data for all trials — or even most of the data for most of the trials — of approved products. In addition, because the law places limitations on the data the FDA is allowed to release, some of the review documents released are so heavily redacted that their content is largely incomprehensible. Even Section 916, which requires the posting of FDA reviews of trial results for approved drugs, does “not authorize the disclosure of any trade secret, confidential commercial or financial information.” Thus, mandatory disclosures under the FDA Amendments Act will still be heavily redacted because of current legislative restrictions.

The public health would be well served if the FDA were to post all reviews for all products after their approval.^{12,13} The FDA has committed to posting, in a timely manner, reviews of trials submitted with new drug applications for drugs approved since 1998, but it has rejected recommendations from the Institute of Medicine that it post all reviews for supplemental new drug applications (e.g., applications for use of approved products for a new indication), stating that doing so would be overly burdensome.¹³ Since the requirements under the FDA Amendments Act are

not retroactive, the FDA may continue to refrain from posting older trials that contain data relevant to drugs on the market before September 27, 2007, which represent the vast majority of drugs currently used by patients and are therefore of great interest to patients and their physicians.

As mentioned, the FDA must currently consider data or analyses for certain trials to be confidential commercial information, including those concerning products under development, products that have been abandoned and for which approval is no longer being pursued, and products already on the market for which approval for a new indication is being sought. The balance of public interest in terms of protecting commercial interests during product development, avoiding unnecessary human experimentation, and informing current patients and potential research subjects about risks and benefits varies among these three groups. However, it is clear that research participants and patients have an interest in dissemination of these data to facilitate the ethical development and use of safe and effective drugs.

For example, there were apparently several suicides among participants who received the marketed selective serotonin-reuptake inhibitor duloxetine as part of a study of urinary incontinence.¹⁴ Despite the fact that the drug was already on the market for another indication (and that concerns had been raised about the risk of suicidality), the FDA review of these data was not made publicly available (nor were the data themselves) because the data were part of an application for a new indication that was never approved. The argument that such data are “confidential commercial information” and must be withheld so that potential competitors do not benefit runs counter to the principles of ethical human research, which require that risks to human volunteers be minimized and that human participation in research leads to generalizable knowledge. Knowledge cannot be generalized if the FDA is forced by legislation to withhold it from the public.

Although some protection of commercial interests is undoubtedly necessary to ensure ongoing drug development, the withholding of critical information about the safety or efficacy of marketed drugs from the public is unacceptable both ethically and scientifically. I believe that relevant FDA data on clinical trials and the agency’s analyses of all these data should be made publicly

Table 3. Proposed Legislative Changes to Section 801 of the FDA Amendments Act.*

Drug or Product Status	Current Posting Requirement	Proposed Change	Proposed Action to Enact Change	Comment
Trial completed before Sept. 27, 2007	No	All available clinical trial data to be posted	Legislation to remove confidentiality of results in FDA database; enactment would require additional funding	Avoids need for sponsor to post data on drugs that may now be generic
Trial completed after Sept. 26, 2007	Yes, after approval	Legislation to remove confidentiality of FDA database on all results for a new indication after approval	Enactment would require additional funding	Retains confidentiality for new (not approved) indications being investigated until there have been 2 yr of inactivity
Not approved before Sept. 27, 2007, or never approved	No	All available clinical trial data to be posted after 2 yr of inactivity	Legislation to remove confidentiality of results in FDA database after 2 yr of inactivity; enactment would require additional funding	Frees sponsor from requirement to release data
Abandoned by sponsor for particular indication	No	All available clinical trial data to be posted after 2 yr of inactivity	Posting by sponsor in ClinicalTrials.gov and legislation to remove confidentiality of results in FDA database after 2 yr of inactivity; enactment would require additional funding	Trial results not to be posted until there have been 2 yr of inactivity
In phase 1 trial	No	All safety data to be posted within 1 yr of trial completion	Legislation to remove confidentiality of results concerning safety in FDA database; enactment would require additional funding	Data not related to safety remain confidential until there have been 2 yr of inactivity
Safety data on approved drugs being studied for new (not yet approved) indication	No	All safety data to be posted within 1 yr of trial completion	Legislation to remove confidentiality of results concerning safety in FDA database; enactment would require additional funding	Data not related to safety remain confidential until there have been 2 yr of inactivity
Under development (not yet approved)	No	None	Not applicable	Data are confidential

* Inactivity is defined as the occurrence of one of the following: the FDA reaches a negative decision on a new drug application (NDA) and no additional studies have been submitted to the FDA for 2 years; the sponsor withdraws the NDA and no additional studies have been submitted to the FDA for 2 years; or no additional studies have been submitted to the FDA for 2 years.

available for all approved drugs and for drugs and indications no longer being actively pursued (Table 3).

Under the FDA Amendments Act, the secretary of health and human services is specifically directed to consider, during the 3-year rule-making process, whether or not to extend the results-reporting requirements to unapproved products. It seems reasonable to propose that reporting should be extended to include drug trials to which the following circumstances apply: 2 years have elapsed since the FDA reached a “negative” decision on the new drug applications, or 2 years have elapsed since a company withdrew a new drug application, or a fixed period of time (e.g., 2 years) has elapsed after the last data were received by the FDA, without any additional studies submitted to the FDA, implying that clinical development has for practical purposes stopped. In addition, consideration should be given to the posting of phase 1 results (currently excluded under the FDA Amendments Act) after 2 years of inactivity as defined above. Safety data should be posted without a 2-year delay to rapidly inform institutional review boards and others reviewing similar drugs or devices.

Two years of inactivity would seem to be an adequate period for protection of legitimate concerns about maintaining confidentiality during drug development while also releasing information in a reasonably timely fashion to protect the public. However, safety data concerning patients should not be subject to such delays to protect commercial advantage. Posting of trial results would honor the pact between research participants and society that expects that data gathered through their participation in a trial will be made available in a timely manner to help future patients. Also relevant is knowledge of adverse outcomes associated with products similar to those currently on the market, even if the marketed product is for a different indication.

Many of the changes proposed to supplement Section 801 of the FDA Amendments Act (summarized in Table 3) can be accomplished relatively easily by enacting legislation to open up the FDA’s database on clinical trials to the public — which has paid for the FDA’s analysis. However, imposing a requirement on companies to post the results of clinical trials for drugs approved before September 2007 — especially results that might be decades old and not readily available — would

be an unreasonable burden, however desirable the outcome. In addition, after patent protection expires and generic drugs enter the market, the company that developed the original drug may no longer market the drug. Access to old clinical trial data may also be problematic if substantial time has elapsed since completion of the trials and drug approval. In these and all other cases, removing the legislative provisions that define even ancient clinical trial data held by the FDA as “confidential commercial information” would allow the agency to post the data in its hands without imposing unreasonable retrospective demands on the companies concerned. Of course, to post such data, the FDA and the NLM will require additional funds from Congress (Table 3).

CONCLUSIONS

Ethical clinical research should contribute to generalizable knowledge and improve human health. The dedication of patients who take the risks to participate in clinical research is dishonored when their data remain secret. Section 801 of the FDA Amendments Act will greatly expand the type and amount of information available on clinical trials. The use of these data and the enhanced public access to the FDA’s database on clinical trials proposed in this article will greatly improve the ability of investigators and others to assess the full set of results for a given intervention, whether FDA-approved or not, eventually leading to more accurate systematic reviews, better clinical decision making, improved patient care, and improved research efficiency and safety.

Dr. Wood reports serving on the National Library of Medicine Board of Regents Working Group on Clinical Trials, on the scientific advisory board of Sapphire Therapeutics, and on the board of directors of Oxigene and holding stock in Symphony Capital. No other potential conflict of interest relevant to this article was reported.

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