

SPECIAL REPORT

The Proposed Rule for U.S. Clinical Trial Registration and Results Submission

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Broad access to information about clinical trials and their findings is critical for advancing medicine, promoting public health, and fulfilling ethical obligations to human volunteers.¹ Traditional methods of information dissemination (e.g., presentations and publication) may nevertheless leave distortions and gaps in the knowledge base because the results of many trials are not published.²⁻⁴ Title VIII of the Food and Drug Administration (FDA) Amendments Act of 2007 (FDAAA)⁵ addressed some of these concerns by requiring the registration and submission of summary results information to ClinicalTrials.gov for certain clinical trials of drugs (including biologic products) and devices. The Department of Health and Human Services (HHS) recently published for public comment a proposed rule (or “Notice of Proposed Rulemaking [NPRM] for Clinical Trials Registration and Results Submission”)⁶ to clarify and expand (as permitted) the FDAAA requirements and ultimately facilitate compliance with the law. Separately, and in keeping with a long-standing principle that systematic dissemination of results is a critical step in realizing the value of the research investment,^{7,8} the National Institutes of Health (NIH) has issued a draft policy for public comment to promote registration and results submission to ClinicalTrials.gov.⁹ This policy is proposed to cover all NIH-funded clinical trials, regardless of study phase, type of intervention, or whether they are subject to the FDAAA requirements (Table 1).

In this article, we provide information about the FDAAA and NPRM to encourage the research community to submit comments on the proposed rule at www.regulations.gov/#!docketDetail;D=NIH-2011-0003. Comments submitted before February 19, 2015, will be considered in formulating the final rule.

BACKGROUND

Clinical trial registration, the systematic public disclosure of key descriptive information about a clinical trial at trial initiation, has long been recognized as an effective approach to help mitigate publication bias and other reporting biases.^{10,11} In 1997, U.S. law mandated the registration of trials of investigational new drugs for serious or life-threatening diseases,¹² resulting in the February 2000 implementation of ClinicalTrials.gov, a publicly accessible online database operated by the National Library of Medicine at the NIH.¹³ This law was followed by other international efforts, such as the policy of the International Committee of Medical Journal Editors (ICMJE),¹⁰ that helped increase trial registrations (Fig. 1). Although these advances made it much easier to know whether a trial existed, the availability of trial results has remained uneven.

OVERVIEW OF THE FDAAA

Title VIII of the FDAAA extended previous statutory requirements by broadening the scope of trials required to be registered at ClinicalTrials.gov to include controlled trials (other than phase 1 trials) of any FDA-regulated drug or biologic for any disease or condition and certain studies of FDA-regulated medical devices, excluding small feasibility studies but including FDA-required pediatric postmarket surveillance studies of a device. The “basic results” reporting provision of the FDAAA requires submission of summary findings for registered trials of FDA-approved, FDA-licensed, and FDA-cleared products in a tabular format for public posting at ClinicalTrials.gov (see text box). Information is to be submitted not later than 1 year after completion of data

Table 1. Comparison of Summary Requirements for the Proposed Rule, Draft NIH Policy, and ICMJE Policy.*

Requirement	FDAAA NPRM (Proposed Rule)	Draft NIH Policy	ICMJE Policy
Type of study†	Interventional studies considered “controlled”‡	Interventional studies considered “clinical trials”§	Any interventional study
Intervention type	Drugs, biologics, and devices	Any type of intervention, including surgical, behavioral, or other interventions	Any type of intervention, including surgical, behavioral, or other interventions
Trial phase	Any phase, except phase 1 drug trials and small feasibility trials of devices	Any phase	Any phase
Funding source	Any, whether private or public	NIH-funded, in whole or in part	Any, whether private or public
Scope of reporting	Registration and summary results	Registration and summary results	Registration only
Responsibility for ensuring reporting	Responsible party (sponsor or designated principal investigator)	NIH awardee	Author of manuscript
Enforcement mechanisms	Up to \$10,000 per day in civil monetary penalties; possible withholding of NIH and other federal grant funds	Possible suspension or termination of NIH funding; consideration of noncompliance in future funding decisions	Editor’s refusal to publish manuscript
Submission of comments	Open until February 19, 2015, at https://federalregister.gov/a/2014-26197	Open until February 19, 2015; e-mail comments to clinicaltrials.disseminationpolicy@mail.nih.gov	Not applicable; extant policy available at http://icmje.org/recommendations/browse/publishing-and-editorial-issues/clinical-trial-registration.html

* FDAAA denotes Food and Drug Administration Amendments Act, ICMJE International Committee of Medical Journal Editors, NIH National Institutes of Health, and NPRM Notice of Proposed Rulemaking.

† An investigational study is defined in the NPRM as “a clinical study or a clinical investigation [in which] participants are assigned prospectively to an intervention or interventions according to a protocol to evaluate the effect of the intervention(s) on biomedical or other health related outcomes.”

‡ These include all multigroup interventional studies but may exclude some single-group studies that do not involve a nonconcurrent control.

§ These include all interventional studies, except those that do not meet the revised NIH definition of “clinical trial” (<http://grants.nih.gov/grants/guide/notice-files/NOT-OD-15-015.html>).

collection for the primary outcome, but submissions can be delayed for up to 2 additional years for trials of FDA-approved products if the manufacturer certifies that FDA approval to market a new use of the studied product is or will be sought within 1 year. The FDAAA also establishes civil monetary penalties for noncompliance and directs federal agencies funding trials to verify that grantees are compliant before releasing remaining or allocating future grant funding. It is important to note that the ICMJE requires all trials, regardless of phase or intervention type, to be registered at the time of enrollment of the first patient.

The FDAAA has already had a considerable effect on trial registrations and results reporting (Fig. 2); we estimate that about half of the more than 15,000 posted results have not been published in a MEDLINE-indexed journal and are thus, practically speaking, available only from ClinicalTrials.gov.¹⁴ The ClinicalTrials.gov structured results approach consists of four modules in tabular format: the numbers and

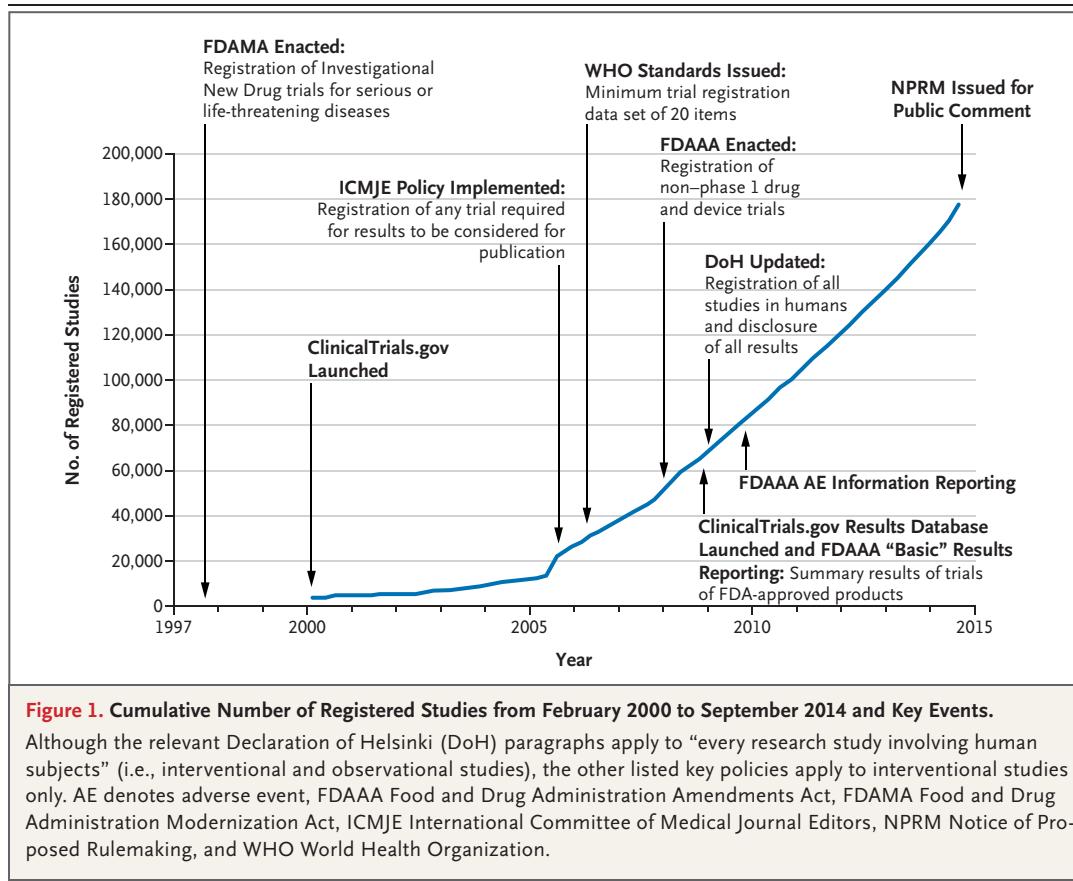
flow of participants in the trial, baseline demographic and clinical characteristics of the participants according to study group, primary and secondary outcomes, and adverse events. This results-reporting model was the basis for the new results database of the European Medicines Agency (EMA) and has also been proposed as an international standard in a recent World Health Organization statement.^{15,16}

SELECTED KEY ISSUES

Although the NPRM contains detailed discussions of all proposed regulatory requirements, here we highlight key issues of particular interest to the research community and reference relevant sections of the NPRM where additional explanation can be found.

RESULTS OF TRIALS OF UNAPPROVED PRODUCTS

HHS proposes to require the submission of results for applicable clinical trials of unapproved products for several reasons, including to reduce



bias in publicly available information about investigational products stemming from selective disclosure of results, to assist those attempting to assess the benefits and harms of entire classes of drugs or devices, to avoid unnecessary duplication of trials of products shown to be unsafe or ineffective, and to inform the description of potential risks and benefits provided in consent forms for future studies (see Section III.C.5 of the NPRM). Here we note that the results of EMA-regulated clinical trials of drugs and biologic products are required to be posted publicly within 6 months to 1 year after trial completion regardless of their marketing-approval status.¹⁷ To mitigate concerns about the potential effects of disclosure on the competitive advantage of manufacturers, the proposal would permit a delay in the deadline for results submission of up to 2 years (a total of 3 years after trial completion) if the sponsor certifies that it intends to continue development of the studied product. The NPRM solicits public comment on this proposal.

PRIMARY AND SECONDARY OUTCOME MEASURES

The FDAAA requires that all prespecified primary and secondary outcome measures be described at registration and that outcome data be submitted as results, although the terms “primary,” “secondary,” and “outcome measures” are not defined. HHS proposes to define as “primary” the outcome measure that is specified in the power calculation in the protocol or that is considered the most important, although more than one may be appropriate under specific circumstances (e.g., “coprimary” outcome measures recommended by regulatory agencies¹⁸). The proposed definition of “secondary outcome measure” would include all prespecified outcome measures that are not designated as “primary” and for which a specific analysis plan exists, either in the protocol or the statistical analysis plan (see Section IV.A.5). Tertiary or exploratory measures may be submitted as “other prespecified outcome measures,” but they are not required.

For each reported outcome measure, HHS

Ten Common Misconceptions about the FDAAA.	
1.	<p>Myth: Only investigational new drug (IND) and investigational device exemption (IDE) trials are subject to the registration and results-reporting provisions of the Food and Drug Administration (FDA) Amendments Act of 2007 (FDAAA).</p> <p>Fact: All applicable clinical trials of FDA-regulated drugs, biologic products, and medical devices initiated after September 27, 2007, or initiated on or before that date and that were still ongoing as of December 26, 2007, are required to be registered under the FDAAA. These include trials that are exempt from IND requirements or that have abbreviated IDE requirements, such as comparative effectiveness studies of two different approved products.</p>
2.	<p>Myth: The FDAAA does not apply to trials of medical procedures, radiologic devices, dietary supplements, imaging technologies, or in vitro diagnostics.</p> <p>Fact: The FDAAA covers studies of FDA-regulated drugs, biologics, and devices. Dietary supplements may be regulated as drugs, depending on their specific use in the trial. Many trials of procedures examine FDA-regulated devices. Many diagnostic products, including imaging, radiologic, and in vitro diagnostics, are regulated as medical devices by the FDA. The draft National Institutes of Health (NIH) policy and the International Committee of Medical Journal Editors (ICMJE) policy regarding registration apply to any study of an intervention to influence a biomedical or health-related outcome.</p>
3.	<p>Myth: The FDAAA applies to industry-sponsored studies only.</p> <p>Fact: The FDAAA applies to applicable clinical trials that meet the reporting requirements, regardless of funding source.</p>
4.	<p>Myth: Clinical trials with no external sources of funding (“unfunded” studies) and “pilot studies” are not subject to the FDAAA.</p> <p>Fact: The FDAAA applies to all applicable clinical trials that meet the registration and results-reporting requirements, regardless of funding source. The law excludes drug studies that are considered “phase 1” trials, as defined in FDA regulations, and small feasibility studies of devices. Any “pilot study” that otherwise meets the definition of an applicable clinical trial may be subject to the FDAAA. The draft NIH policy and ICMJE policy require registration of all trials regardless of phase.</p>
5.	<p>Myth: The FDAAA requires the submission of data at the level of individual participants.</p> <p>Fact: The FDAAA covers the reporting of summary (or aggregate) results data only.</p>
6.	<p>Myth: The FDAAA dictates what information must be collected in an applicable clinical trial and how the study must be designed.</p> <p>Fact: The FDAAA specifies how and when descriptive information about a clinical trial and the results data collected and analyzed according to a study protocol must be submitted to ClinicalTrials.gov. It does not establish requirements for the design or conduct of clinical trials or what data must be collected.</p>
7.	<p>Myth: The FDAAA requires the real-time reporting of adverse events during the conduct of the trial.</p> <p>Fact: The FDAAA requires the submission of information that summarizes the anticipated and unanticipated adverse events that were collected during a trial. This information is required to be submitted to ClinicalTrials.gov only after trial completion.</p>
8.	<p>Myth: Trials conducted in locations entirely outside the United States are not covered by the FDAAA.</p> <p>Fact: Even if a trial is conducted entirely outside the United States, it may be an applicable clinical trial subject to the FDAAA if the trial is conducted under IND or IDE regulatory requirements or if the studied drug, biologic, or device was manufactured in the United States and exported for use in the trial. The draft NIH policy and ICMJE policy require that trials be registered regardless of the locus of their performance.</p>
9.	<p>Myth: Single-group trials are never subject to the FDAAA.</p> <p>Fact: Single-group trials that involve nonconcurrent controls (e.g., historical controls or change from baseline) but otherwise meet the definition of an applicable clinical trial are subject to the FDAAA.</p>
10.	<p>Myth: The FDAAA applies only to trials of FDA-regulated drugs, biologics, and devices that are being studied to treat diseases and medical conditions (i.e., therapeutic products).</p> <p>Fact: The FDAAA is not limited by the intended purpose of a studied intervention. Prevention, diagnostic, screening, and other trials that meet the mandatory reporting provisions must be registered, and if the intervention under study is approved, licensed, or cleared by the FDA, the results must be submitted to ClinicalTrials.gov. The requirements of the draft NIH policy and ICMJE policy apply regardless of FDA jurisdiction.</p>

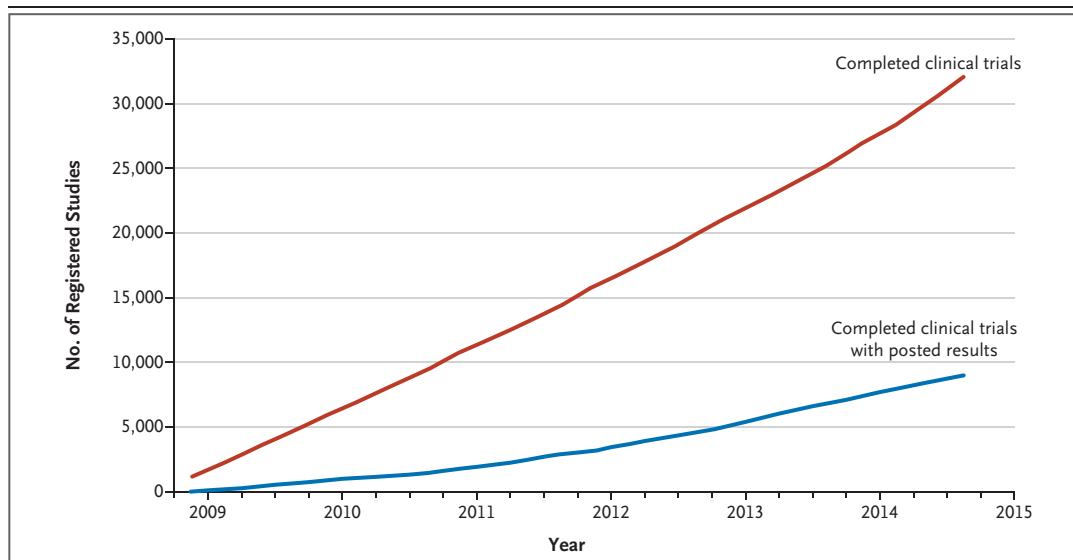


Figure 2. Cumulative Number of Registered Clinical Trials with at Least One U.S. Site from October 2008 to September 2014.

Completed clinical trials are shown according to completion date, and completed clinical trials with posted results are shown according to the results-submission date. The data reflect records posted on ClinicalTrials.gov as of November 26, 2014. The Study Completion Date data element was used when the Primary Completion Date data element was not listed.

also proposes to require at registration a description of the specific measurement (e.g., blood pressure), specific metric (e.g., mean change from baseline), and time frame (e.g., at 3 months) (see Section IV.B.4.[1]). We have previously described the fact that some entries (e.g., “efficacy”) are too vague to serve the intended purpose.¹⁴ More precise entries are needed to help readers understand what was measured and to assess any changes made to an outcome measure. This proposal is consistent with current recommended practice at ClinicalTrials.gov and the World Health Organization international registration standard.¹⁹ The NPRM solicits public comments on these proposed requirements.

INFORMATION ON ADVERSE EVENTS

Since September 2009, all results submissions to ClinicalTrials.gov must include two tables of information about collected anticipated and unanticipated adverse events: all serious adverse events according to study group and all other adverse events that exceed a frequency of 5% within any study group. The NPRM proposes minor modifications to this approach. In addition,

the proposed rule invites comments on the benefit and burden of requiring the submission of several other types of information related to adverse events (see Section III.C.15). One type of information is the time frame during which adverse-event data were collected; this information (currently optional) could assist in comparing the relative frequency of adverse events across trials. A second type is the approach used to collect adverse-event data, whether systematic (e.g., each participant is asked about a specific symptom) or nonsystematic; this information (currently optional) could assist in interpreting differences in adverse-event rates across trials.

A third type of information is an all-cause mortality table, consistent with reporting guidelines,^{20,21} that lists all participant deaths from any cause; this information would make it possible to determine the total number of deaths during a trial per study group. Currently, deaths may be reported in different modules or not reported at all (e.g., as a reason for noncompletion in participant flow or as an adverse event, such as myocardial infarction, without specification that a participant died).

A fourth type of information is whether ad-

verse events are considered by the sponsor or investigators to be caused by the studied intervention. Although this information is required by some regulators for real-time reporting of adverse events during a study (to determine whether study-design or consent changes are necessary),²² there is a lack of consensus about the value of these subjective judgments for summary reporting after trial completion, when adverse-event rates across study groups are available for empirical analysis.²³

CONCLUSIONS

The FDAAA expanded the types and increased the quality of public reporting about clinical trials. It changed the status quo in which sponsors and investigators decided whether, when, and how to report trial results and helps ensure that researchers make relevant data available to inform current practice and future research. The expansion of ClinicalTrials.gov after the enactment of the FDAAA has already engendered substantial benefits by providing more information to potential research participants, reducing inadvertent and unnecessary duplication of clinical studies, helping journal editors detect incomplete descriptions of the results of specific clinical trials, and allowing analyses of the results of multiple trials of the same or similar interventions.

In the recently issued NPRM, HHS proposes additional specificity to the FDAAA provisions and proposes further enhancements authorized by the law. The 90-day comment period offers the public an opportunity to provide feedback on ways to improve the proposals specified in the NPRM as part of the rule-making process and the draft NIH policy. We encourage the clinical research community and all interested parties to contribute to this process by submitting substantive comments to the docket at the website listed above. Additional explanatory material and guides to the NPRM can also be found in the docket.^{24,25}

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