



# ClinicalTrials.gov: Requirements and Implementation Strategies

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The *Food and Drug Administration Amendments Act of 2007 (FDAAA)* established a requirement for certain clinical trials to be registered at trial initiation and to report summary results after trial completion in the public registry and results database called [ClinicalTrials.gov](http://ClinicalTrials.gov).

This law is intended to facilitate enrollment in clinical trials, allow for tracking of the progress of such trials and address problems with the lack of timely dissemination of research findings. This article discusses key considerations, helpful hints and some lessons learned to help meet the requirements of *FDAAA* as well as the trial registration policy of the International Committee of Medical Journal Editors (ICMJE).

## Background and Requirements

ClinicalTrials.gov was launched in February 2000 by the National Library of Medicine (NLM), a component of the National Institutes of Health (NIH). Since its launch, the policies and laws related to registration of clinical trials have evolved, with *FDAAA* being the most comprehensive US law to date.<sup>1</sup>

*FDAAA* requires that a “responsible party” register and submit results for “applicable clinical trials” of drugs and devices. “Responsible party” and “applicable clinical trials” are defined in *FDAAA*, and further elaborated in NIH’s “Elaboration of Definitions of Responsible Party and Applicable Clinical Trial” document.<sup>2</sup>

Under *FDAAA*, the “responsible party” is responsible for submitting information for a clinical trial to the database. Briefly, the responsible party is defined as the sponsor or the principal investigator (if designated by the sponsor).

For trials conducted under an investigational new drug application (IND) or investigational device exemption (IDE), the IND or IDE holder is the sponsor. For trials not conducted under an IND or IDE, the sponsor is the “initiator” of the trial (e.g., NIH grantee

institution). Generally, applicable clinical trials include non-Phase 1/non-small feasibility, interventional studies of drugs, biological products or devices that have one or more sites in the US or are conducted under an IND or IDE. Specific criteria apply to applicable drug (including biologics) clinical trials and applicable device clinical trials.<sup>3</sup>

Under FDAAA, an applicable clinical trial must be registered in ClinicalTrials.gov via the Protocol Registration System (PRS) no later than 21 days after enrollment of the first participant.<sup>4</sup> Before participants are enrolled in applicable clinical trials, they must be notified through informed consent documents and processes that the clinical trial information will be available in ClinicalTrials.gov. This requirement was recently implemented when the US Food and Drug Administration (FDA) amended the informed consent regulations (21 CFR § 50.25(c)) and applies to applicable clinical trials initiated on or after 7 March 2012.<sup>5,6</sup>

After an applicable clinical trial is completed, the results must be submitted to ClinicalTrials.gov via the PRS no later than 12 months after reaching the “completion date” or within 30 days of approval, licensure or clearance of the drug or device. The FDAAA-defined completion date is described in ClinicalTrials.gov as the “primary completion date” and is the date that the final subject was examined or received an intervention for purposes of final collection of data for the primary outcome.

The results information to be submitted is summary-level data for each arm of the trial in a tabular format that includes the following modules: participant flow (number of participants starting and completing), baseline characteristics, outcome measures and statistical analyses, and adverse events.

In addition to the legal requirements of FDAAA, there are other policies of which sponsors and investigators should be aware regarding trial registration. Similar to FDAAA, ICMJE requires prospective registration in a public trials registry, such as ClinicalTrials.gov. However, the scope of the ICMJE policy is broader than FDAAA in terms of the types of studies that need to be registered because it requires registration of all clinical trials, defined as “any research project that prospectively assigns human subjects to intervention or concurrent comparison or control groups to study the cause-and-effect relationship between a medical intervention and a health outcome.”<sup>7</sup>

The ICMJE policy does not address the other elements that FDAAA mandates (i.e., summary results submission to ClinicalTrials.gov and a statement as part of the informed consent process). While the ICMJE requirement is not enforceable by law, overlooking the requirements set forth by ICMJE limits an investigator’s ability to publish in many journals.

Clinical research is conducted with the objective of contributing to generalizable medical knowledge, and scientific publications are the primary mechanism for sharing this knowledge. Thus, prior to initiating a trial, a sponsor or investigator will want to consider the requirements of both ICMJE and FDAAA.

Early experience suggests organizations are not yet fully prepared to meet the requirements of FDAAA. A recent study in the *British Medical Journal (BMJ)* estimated that approximately 40% of industry-sponsored trials and 8% of other trials likely to be subject to FDAAA had results posted on ClinicalTrials.gov.<sup>8</sup> Although this study had limitations, such as not accounting for studies in which results had been submitted but not yet posted, it demonstrates the need for overall improvement in complying with FDAAA for trials sponsored both by industry and non-industry organizations.

## Helpful Hints

### **Develop Easy-to-use Tools**

An important factor to facilitate compliance for non-industry and industry organizations is creating standard processes that define requirements, roles and responsibilities. Notably, as part of FDA’s Compliance Program 7348.810 Bioresearch monitoring, FDA staff members conducting inspections are instructed to identify whether the sponsor has Standard Operating Procedures (SOPs) and to determine whether studies were registered on ClinicalTrials.gov.<sup>9</sup>

An essential tool is one that can help users identify applicable clinical trials based on the four main criteria stated in the law and further elaborated on by NIH. This tool may take the form of a checklist (**Table 1**) or flow diagram and should help a user make a preliminary judgment as to whether the trial should be registered.

**Table 1. Sample Checklist for Identifying Potential Applicable Clinical Trials Subject to FDAAA**

A study may be subject to the requirements of FDAAA*, if YES is answered to all 5 questions:		YES	NO
1.	Was the study either a. initiated after 27 September 2007? b. initiated on or before 27 September 2007, and ongoing as of 26 December 2007?		
2.	Is the study “interventional” (i.e., participants are assigned to interventions by protocol)?		
3.	Does the study evaluate a “drug,” “biological product” or “medical device” (whether or not approved for marketing in the United States)?		
4.	Is the study <b>other than</b> either a a. “Phase 1” drug or biological product trial (e.g., it is a Phase 2 study)? b. “small feasibility” device trial (e.g., it is a pivotal study)?		
5.	Does the study have at least one site located in the United States <b>or</b> is the study conducted under an IND or IDE?		

\* For a complete definition and description of “applicable clinical trial”, please see [http://prsinfo.clinicaltrials.gov/fdaaa.html.\(1,2\)](http://prsinfo.clinicaltrials.gov/fdaaa.html.(1,2))

Although there are still some areas of uncertainty in applying these criteria, these should not be viewed as barriers to helping protocol development teams assess whether their clinical trials would be subject to FDAAA requirements. Prospectively identifying trials likely to be applicable clinical trials will help answer questions downstream regarding whether the protocol will require registration, mandatory informed consent language and results submission. In addition, implementing automated or basic spreadsheet-based tracking of such trials will provide a useful tool for monitoring and ensuring that deadlines are met.

The FDAAA Issues component of the PRS Problems Report is intended to help organizations identify registered trials that may be subject to FDAAA and missing FDAAA-required registration data elements or posted results. The report is for informational purposes only and may unintentionally include or exclude trials that are not subject to FDAAA. The report is available in the PRS for organizations and individuals in real time and may be downloaded into a spreadsheet format for use outside the PRS.

### **FDAAA Does Not Equal ICMJE: How to Approach the Differences**

Identifying trials subject to FDAAA and ensuring they are registered in a timely manner does not ensure an organization or investigator will also be meeting the requirements of ICMJE. Although FDAAA and ICMJE policies are overlapping in scope, the ICMJE policy covers more kinds of trials and intervention types and requires earlier registration (**Table 2**).

Because registration is a condition of publication, the repercussions could surface when the study is submitted for publication and is rejected because the study was not registered at all or was not registered prior to enrollment of the first participant. To efficiently meet both ICMJE and FDAAA, an approach is to register all interventional studies prior to enrollment of the first participant and use FDAAA criteria to select which of those studies require inclusion of mandatory language in informed consent documents and results submission.

Registration of a study in ClinicalTrials.gov that is not an applicable clinical trial (e.g., Phase 1 trial) does not obligate the responsible party to submit results for that trial to the database. In addition, if results are submitted to ClinicalTrials.gov, the ICMJE will not consider this to be “prior publication” of the research results.<sup>10</sup>

### **Identify People With the Right Skills**

Equally important as creating tools to define the requirements is identifying the responsible party and assigning the appropriate personnel to assist with registering the trial and submitting results. The submission of the summary protocol and results information can

**Table 2. Summary of FDAAA and ICMJE Registration and Results Requirements**

	FDAAA	ICMJE
<b>Registration</b> <b>Scope</b>	<ul style="list-style-type: none"> <li>applicable clinical trials (Table 1)</li> </ul>	<ul style="list-style-type: none"> <li>interventional studies (any intervention type, phase, or geographic location)</li> </ul>
<b>Registration</b> <b>Timing</b>	<ul style="list-style-type: none"> <li>not later than 21 days after enrollment of the first participant</li> </ul>	<ul style="list-style-type: none"> <li>prior to enrollment of the first participant</li> </ul>
<b>Results</b> <b>Scope</b>	<ul style="list-style-type: none"> <li>same as registration, but limited to studies of FDA-approved drugs, biologics or devices</li> </ul>	<ul style="list-style-type: none"> <li>not applicable</li> </ul>
<b>Results</b> <b>Timing</b>	<ul style="list-style-type: none"> <li>not later than one year after the “primary completion date” (final data collection for the primary outcome measure)</li> </ul>	<ul style="list-style-type: none"> <li>not applicable</li> </ul>
<b>Informed Consent</b> <b>Language</b>	<ul style="list-style-type: none"> <li>required for new “applicable clinical trials” as of 7 March 2012.</li> </ul>	<ul style="list-style-type: none"> <li>not applicable</li> </ul>

be considered a part of the scientific process associated with a trial and is more than just an administrative task.

Submitting registration information to the PRS is relatively straightforward since there is typically not much interpretation required if the protocol is complete. The results section, while straightforward when it comes to entering appropriately compiled data, is more complex and is conceptually comparable to preparing the foundation for a scientific publication describing study results.<sup>11</sup>

Someone who was actively involved in the study and is familiar with the subtleties of the study design and analysis, such as early closure of the study and its potential impact on study outcomes, is best suited to prepare the data in the results section. This person should also understand the manner in which adverse event information was collected and have the ability to map it into the appropriate data fields in ClinicalTrials.gov.

These steps may be straightforward for a simple two-arm randomized, controlled study, but additional thought will need to be given to optimizing data presentation with complicated multi-step study designs or studies with distinct cohorts. Lessons learned have shown basic results entries have fewer errors and quality review comments from ClinicalTrials.gov when the appropriate person (e.g., study statistician, principal investigator) is tasked to prepare results information. Also, it is important to keep in mind that no matter who is involved with the submission process, the responsible party is ultimately liable for the data submitted.

### **Additional FDA Requirements Under FDAAA**

FDAAA required FDA to amend certain informed consent regulations to include information about ClinicalTrials.gov. The specific statement for informed consent documents should only be used for clinical trials subject to FDAAA and not for other types of studies not subject to the law. FDA published a guidance with additional information regarding this final rule in February 2012.<sup>12</sup>

FDA also requires sponsors of an IND or IDE to submit a signed Form 3674 when filing certain investigational and/or marketing and postmarketing applications/submissions.<sup>13</sup> Box 9 of the form contains the certification statement where the organization indicates whether the application/submission includes registered applicable clinical trials and whether they are in compliance with FDAAA.

### **What's Left Unanswered?**

The Department of Health and Human Services will issue regulations further clarifying which trials are required to be registered and have results submitted, the specific format and content of the information to be submitted, as well as the associated deadlines



for these activities. The public will have the opportunity to comment when a Notice of Proposed Rulemaking (NPRM) is published in the *Federal Register*. It is important to note, however, that in the absence of regulations, the law is still in effect and organizations should not wait until the proposed and final rules are issued to begin their ClinicalTrials.gov programs.

## Conclusions

As noted earlier, organizations seem to have been slow to implement processes to comply with FDAAA. Whatever the reasons may be, there are manageable and straightforward steps to take to increase compliance.

The focus can begin with the criteria to identify an applicable clinical trial and follow-up with the subsequent requirements throughout the study lifecycle. Once this is understood, standard processes can be developed. With some innovation and creativity, forms can be generated to capture this information, as can automated notifications to help track deadlines.

Equally important is ensuring that dedicated or specialized individuals are engaged in the process to eliminate registration and results errors. As the rulemaking process advances, it will be easier to adapt existing processes to address any new information.

ClinicalTrials.gov is a valuable public resource, and its utility will be fully realized if all organizations implement processes to ensure their trials are posted in accordance with FDAAA and ICMJE.

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