

ClinicalTrials.gov Webinar Series, March 2011

Key FDAAA Issues

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Hello. This presentation will cover key issues in the Food and Drug Administration Amendments Act, Section 801 related to trial registration and results reporting.

The Food and Drug Administration Amendments Act was passed on September 27, 2007. There was a cascading series of requirements that have taken place since that time as a consequence of this law. The registry was expanded and links were put in place to existing results as required by the law and this took place within 90 days of enactment of the law. The basic results database was developed and put into place within a year of enactment of the law. A public meeting was held and the adverse event module was put into place and became required 2 years after enactment of the law. And finally, expansion by rulemaking, which is currently ongoing as required by the law.

The FDAAA Section 801 includes a series of registration requirements.

First, it discusses which trials are covered by this provision. These are referred to as “applicable drug trials” and “applicable device trials.” The specific language in the law about the definition of these applicable trials can be found in the document referenced at the bottom of this slide and the NIH thinking about these legal requirements can be found there as well. These specific definitions will be further elaborated through rulemaking, which is currently ongoing. In general, however, it’s useful to think about these applicable trials as interventional studies that involve a drug, biologic, or device and this refers to drugs, biologics, and devices as defined through the FDA. The scope does not include phase 1 drug trials or small feasibility device trials. The scope involves trials [of drugs, biologics, and devices] that have U.S. FDA jurisdiction and these can be thought of as trials being conducted under an IND or IDE or having at least one site in the U.S. There are also other provisions as discussed in the documents already referenced. Finally, these provisions apply to trials that were ongoing as of the date listed here or were initiated after that date. Trials must be registered at trial initiation, but no later than 21 days after enrollment of the first participant.

The trial registration requirements must be fulfilled by an entity labeled the “responsible party” as defined in the law. The responsible party is defined as either the study sponsor or the principal investigator as designated by the study sponsor and I will elaborate in a few minutes. FDAAA elaborates which information must be provided about each trial, that it must be provided through the Web-based Protocol Registration System or the PRS for ClinicalTrials.gov, and the data can be entered through a Web-based system, either through an interactive mode or by uploading an XML file.

FDAAA also refers to requirements for basic results reporting. The scope of these requirements is similar to the scope of the registration requirements for trials with the caveat that results do not need to be reported for trials of unapproved drugs, biologics, or devices. However, once the drug, biologic, or device becomes approved – and this means approved for any indication by the FDA – the results would then have to be submitted. Summary results generally need to be reported within 12 months of the completion date as defined in FDAAA, which will be elaborated on in a few minutes. However, there can be a number reasons for delay in the submission of results as

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listed here— including the fact that the trial sponsor is seeking initial approval for a drug, device, or biologic that's being studied in the trial; the sponsor is seeking approval of a new use for the drug, biologic, or device that's being studied; or there's a provision for the NIH Director to grant an extension for good cause.

The law elaborates on which specific data elements or what information needs to be provided and it includes items as listed here: information about the flow of participants through the stages of the study; the baseline characteristics of the participants; the primary and secondary outcomes, including any scientifically appropriate tests of statistical significance; adverse event information; a point of contact for scientific information, and certain agreements, which are defined as restrictions on the principal investigators ability to discuss or publish results after the trial completion date.

FDAAA has specific enforcement provisions that are included, including notices of noncompliance that would be posted on the ClinicalTrials.gov record; civil monetary penalties of up to \$10,000 dollars per day; and the potential for withholding of NIH grant funds.

There are a few tricky things in determining if the trial is an applicable clinical trial. It's important to see the elaborations document that was referenced in an earlier slide and it will be important to stay tuned for the rulemaking process, which is ongoing at this time.

The one tricky thing is to determine if the study is an interventional study. One way to think about this is to think about whether or not the intervention is being given as part of the research protocol or given as part of routine medical care. If they're being given as part of the research protocol, that generally means it's an interventional study. Another way to phrase that is to ask whether or not the participants would have received the interventions in the same manner and intensity whether or not they were in the study. Another tricky thing is to determine whether or not the study includes a device. It's important to remember that the FDA regulates imaging [equipment] and other diagnostic tests, including in vitro diagnostics as devices. Therefore, for example, studies of imaging devices such as mammography or CT scans are generally device studies as defined through this law and would be, therefore, in scope for these provisions.

The definition of "responsible party" can also be tricky. As mentioned, it's either the sponsor of the trial as defined in the FDA regulations as listed here, or the principal investigator if the principal investigator is designated by the sponsor and meets certain criteria including the fact that the PI would have to be responsible for conducting the trial; would have to have access to and control over the data; has the rights to publish the results, and has the ability to meet all of the requirements of being the responsible party.

Our current thinking about the responsible party, which will be further elaborated through the rulemaking process is as follows: The first step is to determine the sponsor. The sponsor is either the IND or IDE holder if there is one; an NIH grantee if there is one; or, if neither of those two situations exist, the so-called initiator of the trial. In certain trials, it is theoretically possible to have more than one entity meet one of these definitions of sponsor, but it's important that only

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one be designated per trial and that the relevant people involved in the trial get together and determine who the sponsor is for that trial and indicate that in their ClinicalTrials.gov record. The sponsor may then designate the principal investigator if the conditions that were reviewed on the previous slide have been met. The responsible party has the legal responsibilities for implementing FDAAA, though, of course, others may help.

FDAAA also defines “completion date” in a way that is somewhat different than standard definitions such as “last patient, last visit.” The completion date is defined as the date that the final subject was examined or received an intervention for the purposes of final collection of data for the primary outcome. We sometimes refer to this in our documents as the “primary completion date,” to alert the viewer or the reader that this is a somewhat different definition of completion date than they’re used to.

Additional information about these FDAAA provisions or NIH current thinking about these provisions can be found at these sites.

Thank you.