

NPRM at a Glance: Summary of Key Proposals

This Notice of Proposed Rulemaking (NPRM) describes proposed regulations for submitting clinical trial registration and summary results information to ClinicalTrials.gov, a publicly accessible database operated by the National Library of Medicine (NLM), part of the National Institutes of Health (NIH). The NPRM details proposed requirements for complying with the Food and Drug Administration Amendments Act of 2007 (FDAAA). It provided proposed interpretations of, and in some cases proposes modifications to, practices for registration and results submission used at ClinicalTrials.gov.

FDAAA and the NPRM aim to improve public access to information about specified clinical trials – information that is not necessarily available from other public sources. Neither FDAAA nor the proposed rule establish requirements for the design or conduct of clinical trials or for the data that must be collected during clinical trials. Rather, they specify how data that are collected and analyzed in accordance with a clinical trial protocol (study plan) must be submitted to ClinicalTrials.gov following the completion of a clinical trial. Key proposed provisions of the NPRM are summarized below. The complete NPRM is available in docket number NIH-2011-0003 at www.regulations.gov.

General scope

The proposed rule would apply, in general, to “responsible parties” for “applicable clinical trials.” A responsible party is the sponsor of the clinical trial or a designated principal investigator. It could be an organization (such as a drug or device manufacturer, a university or academic medical center, or a government research organization such as the NIH), or an individual who is the principal investigator for a clinical trial. The NPRM proposes an approach for determining who is the sponsor of a clinical trial and explains how a sponsor can designate a principal investigator as the responsible party (see proposed section 11.4(c)).

The proposed rule would apply not to all clinical trials, but primarily to those trials that meet the legal definition of an applicable clinical trial.¹ Applicable clinical trials include controlled, interventional studies of drugs, biological products, and devices that are regulated by the FDA, but exclude phase 1 studies of drugs and biological products and feasibility studies of devices. A pediatric postmarket surveillance of a device that is required by FDA also meets the definition of an applicable clinical trial. In general, clinical trials of products regulated by FDA will meet one or more of the following criteria: include one or more sites in the United States; study a drug, biologic, or device that is manufactured in the United States or its territories and is exported for use in a clinical trial outside the United States; or be conducted under an FDA investigational new drug application (IND) or investigational device exemption (IDE). The NPRM specifies an

¹ Some provisions also apply to certain other clinical trials for which information is voluntarily submitted, as described in proposed section 11.60)

approach for determining whether a particular clinical trial or study is an applicable clinical trial, using information that would be submitted at the time of registration. See proposed section 11.22(b).

Registration

The NPRM proposes that, in general, a responsible party must register an applicable clinical trial at ClinicalTrials.gov not later than 21 days after enrolling the first participant (see proposed section 11.24). Registration consists of submitting four categories of data elements that are specified in the NPRM: 1) descriptive information, 2) recruitment information, 3) location and contact information, and 4) administrative information. Most of the proposed data elements are taken directly from FDAAA, but the agency is proposing to exercise its authority to add certain data elements, including data elements that are necessary to implement other provisions of the law, provide more complete descriptions of the clinical trial and the intervention(s) studied, and indicate the status of human subjects protection review for the clinical trial. The complete list of proposed registration data elements is contained in proposed section 11.28 of the NPRM.

If a drug studied in an applicable clinical trial is available under expanded access, the proposed rule would require the responsible party to also submit a separate expanded access record (or link to an existing record) containing details about how to obtain access to the investigational drug.

Results Submission

The NPRM proposes to require a responsible party to submit summary results information to ClinicalTrials.gov for any applicable clinical trial that is required to be registered, regardless of whether the drugs, biological products, or devices under study have been approved, licensed, or cleared for marketing by the FDA (see proposed section 11.42). This proposal represents an expansion of the current statutory requirement, which requires the submission of summary results information only for applicable clinical trials of drugs, biological products, or devices that have been approved, licensed, or cleared by the FDA.

In general, results information is proposed to be submitted not later than 1 year after the completion date of the applicable clinical trial, where the completion date is defined as the date that the final subject was examined or received an intervention for purposes of data collection for the primary outcome measure. Results submission could be delayed for as long as 2 additional years if the responsible party submits a certification to ClinicalTrials.gov that either: 1) a drug, biological product, or device studied in the clinical trial is not yet approved, licensed, or cleared for marketing by the FDA *and* is still under development by the manufacturer; or 2) that the manufacturer is the sponsor of the clinical trial and has sought or will seek within 1 year approval, licensure, or clearance for a new use of a product studied in the trial. The proposed rule also permits responsible parties to request extensions to the results submission deadline for “good cause.” See proposed section 11.44

Consistent with current practice, the NPRM proposes that results information would consist of tables of data summarizing: 1) demographics and baseline characteristics of the enrolled participants, 2) primary and secondary outcomes, including results of any scientifically appropriate statistical tests, and 3) adverse events. Adverse event information would consist of one table that summarizes all serious adverse events experienced by participants enrolled in the clinical trial, by arm and organ system; and a second table that summarizes other adverse events that exceed a frequency of 5 percent in any arm of the clinical trial, regardless of whether the adverse events were anticipated or unanticipated. All results information would be aggregated, summary level data, not data for the individual subjects who participated in the clinical trial. Proposed section 11.48 provides a listing of all required results information.

The NPRM does not propose to require the responsible party to submit a written summary of the clinical trial and its results or to submit the full clinical trial protocol. It seeks public comment on the advantages and disadvantages of including technical and non-technical summaries in ClinicalTrials.gov and of requiring submission the full clinical trial protocol document or other information on the protocol that would assist in interpreting results information. It also seeks comment on additional information that could assist in understanding the available adverse event information.

Updates and Other Required Information

The NPRM proposes to require all submitted information to be updated at least once a year if there are changes. More rapid updating is proposed for several data elements to help ensure that users of ClinicalTrials.gov have access to accurate, up-to-date information about important aspects of a clinical trial (see proposed section 11.64). The proposed rule also requires timely corrections to any errors discovered by the responsible party or by NIH as it reviews submissions upon receipt (see proposed section 11.66).

Posting Submitted Information

The NPRM specifies that NIH will post results information not later than 30 days after it is submitted to ClinicalTrials.gov (see proposed section 11.52). For registration, the NPRM specifies that submitted information for applicable clinical trials of drugs and of devices that have been approved or cleared by the FDA will be posted not later than 30 days after submission. Consistent with FDAAA, NIH will not post registration information for applicable clinical trials of unapproved or uncleared devices (see proposed section 11.35). However, to enhance patient understanding of the results of these trials, NIH proposes to post certain descriptive information to be submitted with results information that is the same as a subset of information contained in the registration data elements (see proposed section 11.48(a)(6)).

Commenting on the proposed rule

The public may comment on any aspect of the proposed rule by submitting written comments to docket number NIH-2011-0003 at www.regulations.gov. Commenters are asked to indicate the specific section of the NPRM to which each comment refers. The agency will consider all comments in preparing the final rule.