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42 CFR Part 11
Clinical Trials Registration and Results Submission; Proposed Rule

DEPARTMENT OF HEALTH AND HUMAN SERVICES

42 CFR Part 11

[Docket Number NIH–2011–0003]

RIN 0925–AA52

Clinical Trials Registration and Results Submission

AGENCY: National Institutes of Health, Department of Health and Human Services.

ACTION: Notice of Proposed Rulemaking.

SUMMARY: This Notice of Proposed Rulemaking proposes requirements for submitting registration and summary results information, including adverse event information, for specified clinical trials of drugs (including biological products) and devices and for pediatric postmarket surveillances of a device to ClinicalTrials.gov, the clinical trial registry and results data bank operated by the National Library of Medicine (NLM). This proposed rule provides for the expanded registry and results data bank specified in Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) to enhance patient enrollment, provide a mechanism to track subsequent progress of clinical trials, provide more complete results information, and enhance patient access to and understanding of the results of clinical trials. The proposed requirements would apply to the responsible party (meaning the sponsor or designated principal investigator) for certain clinical trials of drugs (including biological products) and devices that are regulated by the Food and Drug Administration (FDA) and for pediatric postmarket surveillances of a device that are ordered by FDA.

DATES: Comments are due on or before February 19, 2015.

ADDRESSES: Individuals and organizations interested in submitting comments, identified by RIN 0925–AA52 and Docket Number NIH–2011–0003, may do so by any of the following methods:

- *Electronic Submissions:* Use Federal eRulemaking Portal: *http://www.regulations.gov.* Follow the instructions for submitting comments. To ensure timelier processing of comments, NIH is no longer accepting comments submitted directly to it by email. The NIH encourages you to continue to submit electronic comments by using the Federal eRulemaking Portal: *http://www.regulations.gov.*
- *Written Submissions:* You may submit written submissions by Fax at 301–402–0169, or by Mail/Hand Delivery/Courier (For paper, disk, or CD–ROM submissions) to: Jerry Moore, NIH Regulations Officer, Office of Management Assessment, 6011 Executive Boulevard, Suite 601, MSC 7669, Rockville, MD 20852–7669.

Instructions: We welcome comments from the public on all issues set forth in this proposed rule, and on specific issues identified in the document. All submissions received must include the agency name, the Docket No., and Regulatory Information Number (RIN) for this rulemaking. All comments received at *http://www.regulations.gov* may be posted without change, including any personal information provided. The *http://www.regulations.gov* Web site is an ''anonymous access'' system, which means NIH will not know your identity or contact information unless you provide it in the body of your comment.

You can assist us in considering your comment by referencing the number assigned to each key issue discussed in section III.C of this preamble or the number of the section of this proposed rule to which your comment relates.

For access to background documents or comments received, go to *http://www.regulations.gov* and insert the docket number found in the brackets in the heading of this document into the ''Search'' box and follow the prompts.

FOR FURTHER INFORMATION CONTACT: *Regulatory Process:* Jerry Moore, NIH Regulations Officer, Office of Management Assessment, telephone (301–496–4607) (not a toll-free number), Fax (301–402–0169), or by email at *jm40z@nih.gov*

Technical Information: Jerry Sheehan, Assistant Director for Policy Development, National Library of Medicine, National Institutes of Health, Department of Health and Human Services, telephone (301–496–6221) (not a toll-free number), Fax (301–402–2586), or by email at *sheehanjr@nlm.nih.gov.*

SUPPLEMENTARY INFORMATION:

Executive Summary

Purpose of This Regulatory Action

This proposed rule clarifies and expands requirements for the submission of clinical trial registration and results information to the ClinicalTrials.gov database, which is operated by the NLM. It implements the provisions of section 402(j) of the Public Health Service Act (PHS Act) (42 U.S.C. 282(j)), which were added by FDAAA to improve public access to information about certain clinical trials of FDA-regulated drugs, biological products, and devices and certain pediatric postmarket surveillances of a device. Under section 402(j) of the PHS Act, those responsible for specified clinical trials of FDA-regulated products have been required to submit registration information to ClinicalTrials.gov since December 26, 2007, summary results information for clinical trials of approved products since September 27, 2008, and adverse events information since September 27, 2009. Section 402(j) of the PHS Act requires the Secretary of Health and Human Services (HHS) to use rulemaking to expand the requirements for submission of summary results information, and authorizes the Secretary to use rulemaking to make other changes in the requirements for submission of registration and results information.

This proposed rule does not impose requirements on the design or conduct of clinical trials or on the data that must be collected during clinical trials. Instead it specifies how data that were collected and analyzed in accordance with a clinical trial's protocol are to be submitted to ClinicalTrials.gov. No patient-specific data are required to be submitted by this proposed rule or by the law this proposed rule is intended to implement.

Summary of the Major Provisions of the Regulatory Action

Applicable Clinical Trial

This proposed rule specifies which clinical trials of FDA-regulated drugs, biological products, and devices and which pediatric postmarket surveillances of a device, are applicable clinical trials for which information must be submitted to ClinicalTrials.gov. This proposal specifies an approach for determining whether a particular clinical trial or study is an applicable clinical trial, based on descriptive information that would be submitted at the time of registration.

Responsible Party

This proposed rule specifies that there must be one (and only one) responsible party for submitting information about an applicable clinical trial. The sponsor of an applicable clinical trial would be considered the responsible party, unless and until the sponsor designates a qualified principal investigator as the responsible party. This proposed rule specifies the approach for determining who would be considered the sponsor of an applicable clinical trial under various conditions, what qualifies a principal investigator to be designated a responsible party by a sponsor, and how responsibility reverts to the sponsor if a designated principal investigator is unable to fulfill the requirement to

submit information to ClinicalTrials.gov.

Registration

This proposed rule specifies requirements for registering applicable clinical trials at ClinicalTrials.gov. It would require that the responsible party register an applicable clinical trial not later than 21 days after enrolling the first participant, and it specifies the data elements of clinical trial information that must be submitted at the time of registration. The proposed data elements include the descriptive information, recruitment information, location and contact information, and administrative data elements listed in section 402(j) of the PHS Act, as well as additional data elements that are proposed under the Secretary's authority to modify the requirements for clinical trial information due at registration as long as such modifications improve, and do not reduce, the clinical trial information available to the public in ClinicalTrials.gov. We consider the proposed additional data elements necessary to enable the Agency to implement other statutory provisions, indicate the status of human subjects protection review of the trial, facilitate the public's ability to search and retrieve information from ClinicalTrials.gov, and help ensure that entries are unambiguous. Some of these additional data elements were included in ClinicalTrials.gov before FDAAA was enacted.

Expanded Access Information

Section 402(j) of the PHS Act requires the submission of information on how to obtain expanded access to investigational drugs used in applicable clinical trials, if the drugs are available through expanded access programs to patients who are not participating in relevant clinical trials. For an applicable clinical trial of a drug that is available under expanded access, this proposed rule would require the submission of a separate expanded access record containing details about how to obtain access to the investigational drug. If an expanded access record has already been submitted in conjunction with a different clinical trial of that same drug, the responsible party for the new clinical trial could link to the existing expanded access record rather than create a new one.

Results Submission

This proposed rule implements the statutory requirement for the submission of summary results information for applicable clinical trials of drugs, biological products, and devices that are approved, licensed, or cleared by FDA. It also proposes to extend the requirement for results submission to applicable clinical trials of drugs, biological products, and devices that are not approved, licensed, or cleared by FDA. This proposed rule would require the submission of tables of data summarizing demographics and baseline characteristics of the enrolled participants and primary and secondary outcomes, including results of any scientifically appropriate statistical tests.

In general, this proposed rule would require the submission of results not later than 1 year after the completion date of the clinical trial, which is defined as the date of final data collection for the primary outcome measure studied. Results submission could be delayed for up to 2 additional years with certification that either an unapproved, unlicensed, or uncleared product studied in the trial is still under development by the manufacturer or that approval will be sought for a new use of an approved, licensed, or cleared product that is being studied in the trial. This proposed rule also permits responsible parties to request extensions to the results submission deadlines for ''good cause''.

Adverse Events

This proposed rule would require the responsible party to submit information summarizing the number and frequency of adverse events experienced by participants enrolled in a clinical trial, by arm and organ system. It would require submission of two tables of information: one summarizing all serious adverse events; and another summarizing other adverse events that occurred with a frequency of 5 percent or more in any arm of the clinical trial, regardless of whether such adverse events were anticipated or unanticipated.

Updates and Other Required Information

This proposed rule would require that all submitted information must be updated at least annually if there are changes to report. More rapid updating would be required 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. This proposed rule also requires timely corrections to any errors discovered by the responsible party or the Agency during review of submissions.

Costs and Benefits

Based on our cost estimates, this regulatory action is not expected to have a significant impact on the economy. The costs consist primarily of the time needed to organize, format, and submit to ClinicalTrials.gov information that was prepared for or collected during the clinical trial (e.g., protocol information and clinical trial results). The benefits include greater public access to information about and evidence from applicable clinical trials (and other clinical trials) of FDA-regulated drugs, biological products, and devices, and greater clarity about what is required for those who are subject to the legal mandate to submit information to ClinicalTrials.gov.

Acronyms

AHRQ Agency for Healthcare Research and Quality
BLA Biologics License Application
CBER Center for Biologics Evaluation and Research, FDA
CDC Centers for Disease Control and Prevention
CDER Center for Drug Evaluation and Research, FDA
CDISC Clinical Data Interchange Standards Consortium
CDRH Center for Devices and Radiological Health, FDA
CFR Code of Federal Regulations
CONSORT Consolidated Standards of Reporting Trials
EMA European Medicines Agency
EU European Union
FAQ Frequently Asked Questions
FDA Food and Drug Administration
FDAAA Food and Drug Administration Amendments Act of 2007
FDAMA Food and Drug Administration Modernization Act of 1997
FD&C Act Federal Food, Drug, and Cosmetic Act
FOIA Freedom of Information Act
GCP Good Clinical Practices
HHS Department of Health and Human Services
ICH International Conference on Harmonisation of Technical Requirements of Pharmaceuticals for Human Use
ICMJE International Committee of Medical Journal Editors
ICTRP International Clinical Trials Registry Platform, WHO
IDE Investigational Device Exemption
IFPMA International Federation of Pharmaceutical Manufacturers and Associations
IND Investigational New Drug Application
IRB Institutional Review Board
IVD In Vitro Diagnostic
LPLV Last Patient Last Visit
MEDLINE® Medical Literature Analysis and Retrieval System Online
MedDRA Medical Dictionary for Regulatory Affairs
MeSH® Medical Subject Headings
MSSO Maintenance and Support Services Organization

NCT National Clinical Trial
NDA New Drug Application
NIH National Institutes of Health, HHS
NLM National Library of Medicine, NIH
NPRM Notice of Proposed Rulemaking
OHRP Office for Human Research Protections, HHS
OMB Office of Management and Budget
OTC Over-the-Counter
PDF Portable Document Format
PhRMA Pharmaceutical Research and Manufacturers of America
PHS Public Health Service
PI Principal Investigator
PRS Protocol Registration System
R&D Research and Development
RFA Request for Applications
RIA Regulatory Impact Analysis
RIN Regulatory Information Number
SAP Statistical Analysis Plan
SNOMED CT® Systematized Nomenclature of Medicine—Clinical Terms®
SPIRIT Standard Protocol Items for Randomized Trials
U.S.C. United States Code
WHO World Health Organization
XML Extensible Markup Language

Table of Contents

I. Overview of Statutory Provisions

This proposed rule would establish procedures and requirements for registering and submitting results information, including adverse event information, for certain clinical trials of drugs (including biological products) and devices and pediatric postmarket surveillances of a device necessary to implement section 402(j) of the PHS Act (42 U.S.C. 282(j)), as amended by Title VIII of FDAAA and including technical corrections made to FDAAA under Public Law 110–316 (referred to hereinafter as ''section 402(j) of the PHS Act'').

Title VIII of FDAAA, enacted on September 27, 2007, amends the PHS Act by directing the Secretary of HHS, acting through the Director of the National Institutes of Health (NIH or the Agency) to expand the existing clinical trial registry data bank known as ClinicalTrials.gov and to ensure that the data bank is publicly available through the Internet. Among other duties, NIH is directed to expand the data bank to include registration information for a broader set of clinical trials than were required to register under a previous law, the Food and Drug Administration Modernization Act of 1997 (FDAMA). Section 402(j) of the PHS Act specifies that identified entities or individuals, called responsible parties, are to submit registration information for certain applicable clinical trials of drugs (defined by section 402(j)(1)(A)(vii) of the PHS Act to include biological products) and devices, including any pediatric postmarket surveillance of a device required by FDA under section 522 of the FD&C Act. Section 402(j)(2)(A)(iii) of the PHS Act authorizes the Secretary of HHS to modify by regulation the data elements required for registration, provided that the Secretary provides a rationale for why such modification ''improves and does not reduce'' the information included in the data bank. The statute specifies certain deadlines by which registration information is to be submitted to the data bank.

Section 402(j)(3) of the PHS Act further directs the Agency to augment the registry data bank to include summary results information through a multistep process, as follows:

First, for those clinical trials that form the primary basis of an efficacy claim or are conducted after a product is approved, licensed, or cleared, the registry data bank is to be linked to selected existing results information available from the NIH and FDA (section 402(j)(3)(A) of the PHS Act). Such information includes citations to published journal articles focused on the results of applicable clinical trials, posted FDA summaries of FDA advisory committee meetings at which applicable clinical trials were considered, and posted FDA assessments of the results of any applicable drug clinical trials that were conducted under section 505A or 505B of the FD&C Act. Note that we use the term ''product'' hereinafter in this preamble to refer to either a drug (including a biological product), a device, or both, as each is defined in proposed § 11.10.

Second, for each applicable clinical trial subject to FDAAA, the responsible party must submit to the data bank results information required under section 402(j)(3)(C) of the PHS Act. Such information is to include tables of demographic and baseline characteristics of the ''patients who participated in the clinical trial'' (section 402(j)(3)(C)(i) of the PHS Act), i.e., the enrolled human subjects, and the primary and secondary outcome measures for each arm of the clinical trial, as well as a point of contact for scientific information about the clinical trial results and information on whether certain agreements exist between the sponsor and the principal investigator (PI) that limits the ability of the PI to discuss or publish the results of an applicable clinical trial after it is completed.

Third, section 402(j)(3)(D) of the PHS Act requires the Secretary to further expand the data bank by regulation ''to provide more complete results information and to enhance patient access to and understanding of the results of clinical trials.'' It requires consideration of specific issues in developing the regulations, in particular:

(1) Whether to require submission of results information for applicable clinical trials of products that are not approved, licensed, or cleared (whether approval, licensure, or clearance was sought) (See section 402(j)(3)(D)(ii)(II) of the PHS Act.); and if submission of clinical trial results information is required for such applicable clinical trials, the date by which that information is required to be submitted. (See section 402(j)(3)(D)(iv)(III) of the PHS Act.);

(2) Whether non-technical written summaries of the clinical trial and its results can be included in the data bank without being misleading or promotional. (See section 402(j)(3)(D)(iii)(I) of the PHS Act.);

(3) Whether technical written summaries of the clinical trial and its results can be included in the data bank without being misleading or promotional. (See section 402(j)(3)(D)(iii)(II) of the PHS Act.);

(4) Whether to require submission of the full clinical trial protocol or only such information on the protocol as may be necessary to help evaluate the results of the trial. (See section 402(j)(3)(D)(iii)(III) of the PHS Act.);

(5) Whether the 1-year period for submission of results information should be increased to a period not to exceed 18 months. (See section 402(j)(3)(D)(iv)(I) of the PHS Act.); and

(6) Whether requirements for results submission as proposed in this rule should apply to applicable clinical trials for which results information required under section 402(j)(3)(C) of the PHS Act is submitted before the effective date of the regulation imposing those requirements. (See section 402(j)(3)(D)(iv)(II) of the PHS Act.).

Section 402(j)(3)(D)(v) of the PHS Act further requires that the regulations shall establish:

(1) A standard format for the submission of clinical trial information. (See section 402(j)(3)(D)(v)(I) of the PHS Act.);

(2) Additional information on clinical trials and results written in nontechnical, understandable language for patients. (See section 402(j)(3)(D)(v)(II) of the PHS Act.);

(3) Procedures for quality control, with respect to completeness and content of clinical trial information, to help ensure that data elements are not false or misleading and are non-promotional. (See section 402(j)(3)(D)(v)(III) of the PHS Act.);

(4) Appropriate timing and requirements for updates of clinical trial information and whether and how such updates should be tracked. (See section 402(j)(3)(D)(v)(IV) of the PHS Act.);

(5) A statement to accompany the entry for an applicable clinical trial when primary and secondary outcome measures for such applicable clinical trial are submitted as a voluntary submissions after the date specified in section 402(j)(2)(C) of the PHS Act. (See section 402(j)(3)(D)(v)(V) of the PHS Act.); and

(6) Additions or modifications to the manner of reporting the data elements established under the results submission provisions of section 402(j)(3)(C) of the PHS Act. (See section 402(j)(3)(D)(v)(VI) of the PHS Act.).

Section 402(j)(3)(D)(vii) of the PHS Act requires the Secretary to convene a public meeting to solicit input from interested parties on those issues. The public meeting was convened on April 20, 2009, on the NIH campus. The public meeting attracted more than 200 registered participants and 60 written comments. All of the comments received prior to, during, and after the public meeting are available in the Clinical Trials Public Meeting Docket, ID: NIH–2009–0002, at Regulations.Gov: *http://www.regulations.gov/search/Regs/home.html#docketDetail?R=NIH-2009-0002.* We carefully reviewed the comments received in developing the proposed provisions that address the considerations enumerated in section 402(j)(3)(D) of the PHS Act. Many of the comments helped inform development of this proposed rule. For purposes of this rulemaking, we prepared a memorandum summarizing these comments and the issues commented upon [Ref. 1].

In addition, section 402(j)(3)(I)(i) of the PHS Act directs the Secretary to issue regulations to ''determine the best method for including in the registry and results data bank appropriate results information on serious adverse and frequent adverse events for applicable clinical trials (required to submit results under section 402(j)(3)(C) of the PHS Act) in a manner and form that is useful and not misleading to patients, physicians, and scientists.'' If regulations are not issued by September 27, 2009, then section 402(j)(3)(I)(ii) of the PHS Act specifies that the default provisions specified in section 402(j)(3)(I)(iii) of the PHS Act shall take effect, requiring the submission of certain information summarizing serious and frequent adverse events observed during an applicable clinical trial. Regulations were not issued by the deadline, so the default provisions required by sections 402(j)(3)(I)(ii) and (iii) of the PHS Act took effect on September 27, 2009. Section 402(j)(3)(I)(v) of the PHS Act indicates that adverse event information is ''deemed to be'' clinical trial information that is included in the data bank pursuant to the requirements for results submission under section 402(j)(3)(C) of the PHS Act.

Furthermore, section 402(j)(4)(A) of the PHS Act directs that the data bank accept ''voluntary submissions'' of complete registration or complete

results information for certain clinical trials for which such information would not otherwise required to be submitted, provided that the responsible party complies with requirements that could involve submission of information on additional clinical trials.

Section 801(c) of FDAAA requires the Secretary to issue guidance on how the requirements of section 402(j) of the PHS Act apply to a pediatric postmarket surveillance of a device, where that pediatric postmarket surveillance is not a clinical trial. This preamble and proposed rule address this topic and serve as the required guidance.

Section 402(j)(5) of the PHS Act specifies certain procedures and penalties related to non-compliance. Among other things, it directs NIH to post public notices of noncompliance in the data bank; requires report forms under certain HHS grants to include a certification that required registration and results submission under section 402(j) of the PHS Act are complete; prohibits HHS from funding responsible parties who do not fulfill their obligations under section 402(j) of the PHS Act; and grants FDA the authority to sanction responsible parties who fail to comply with section 402(j) of the PHS Act. Section 801(b) of FDAAA includes conforming amendments to the FD&C Act, which make failure to comply with specified requirements of section 402(j) of the PHS Act a prohibited act under the FD&C Act (See 21 U.S.C. 331(jj)(1)–(3).) Committing any such prohibited act could subject the violator to criminal and/or civil penalties, including civil money penalties.

Section 801(d) of FDAAA includes a preemption provision, which states that ''[u]pon the expansion of the registry and results data bank under section 402(j)(3)(D) of the Public Health Service Act, as added by this section, no State or political subdivision of a State may establish or continue in effect any requirement for the registration of clinical trials or for the inclusion of information relating to the results of clinical trials in a database.''

II. Background

There is ongoing public interest in the transparency of information concerning clinical trials. The collection and public availability of information about clinical trials and their results is seen by many as an important public health issue. Advocates have argued that a central resource of clinical trial information is a potentially valuable tool to track the existence and progress of clinical trials and communicate their results, both positive and negative, as well as to provide potential participants with broad access to information about clinical trials seeking participants.

A. Clinical Trials Registration Prior to Passage of FDAAA

Registration of a limited set of clinical trials has been required by U.S. law since the U.S. Congress mandated the establishment of a clinical trial registry in 1997. Section 113 of FDAMA amended the PHS Act to require HHS, acting through NIH and in coordination with FDA and the Centers for Disease Control and Prevention (CDC), to establish, maintain, and operate a data bank of information on clinical trials testing the effectiveness of drugs for serious or life-threatening diseases and conditions, whether federally or privately funded, that are conducted under an Investigational New Drug application (IND). The statute required the data bank to include a description of the purpose of each drug, participant eligibility criteria, the location of the clinical trial sites, and a point of contact for those seeking to enroll in the clinical trial. The FDAMA requirements, which were modified slightly in 2002 by the Best Pharmaceuticals for Children Act (Pub. L. 107–109, 115 STAT 1408, 1420–21), are currently codified at 42 U.S.C. 282(i).

NLM, a part of NIH, developed the registry, known as ClinicalTrials.gov, in response to this mandate and in support of NLM's statutory mission to improve access to information to facilitate biomedical research and the public health. (See 42 U.S.C. 286(a).) The registry became publicly available in February 2000. ClinicalTrials.gov is an Internet-based data bank that informs the public about the conditions and interventions being investigated in clinical trials, eligibility criteria, the location of trial sites, and contact information. It also provides links to additional public information about disorders and interventions relevant to the research described.

While FDAMA required the registration of only certain clinical trials conducted under an IND, ClinicalTrials.gov accepts submissions of information about a broader range of clinical studies, in keeping with the long-standing authorities and responsibilities of HHS, the NIH, and the NLM. The PHS Act expressly directs the Secretary of HHS to ''collect and make available through publications and other appropriate means, information as to, and the practical application of,'' research concerning the treatment ''of physical and mental diseases and impairments of man.'' (See 42 U.S.C. 241(a).) The NLM is expressly required to support ''the dissemination and exchange of scientific and other information important to the progress of medicine and to the public health'' (See 42 U.S.C. 286(a).) Consequently, since its creation, ClinicalTrials.gov has accepted registration information on different types of clinical trials, including trials of drugs for other than serious or life-threatening diseases or conditions, trials of medical devices, surgical procedures, and behavioral interventions, and has also accepted registration of information on other types of clinical studies, such as observational studies. Prior to passage of FDAAA, ClinicalTrials.gov contained information on more than 45,000 clinical studies.

The clinical trial data elements and descriptions used in ClinicalTrials.gov prior to FDAAA [Ref. 2] were developed following public notice and comment on two guidance documents: (1) A final guidance issued by FDA in 2002 describing the information to be submitted to the ClinicalTrials.gov registry pursuant to the registration requirement set forth in section 113 of FDAMA [Ref. 3] (See 67 FR 12022, Mar.18, 2002.); and (2) a draft guidance issued by FDA in January 2004 [Ref. 4] (See 69 FR 3923, Jan. 27, 2004.), proposing revisions to the final guidance issued in 2002 to include information on additional submissions required pursuant to the Best Pharmaceuticals for Children Act (Pub. L. 107–109, 115 STAT 1408, 1420–21). This draft guidance was not finalized.

Following establishment of ClinicalTrials.gov, the scientific community, general public, industry, and others engaged in high-profile, public discussions about the need for increased access to information about clinical trials [Ref. 5]. For example, studies revealed that selective publication of clinical trial results could give a misleading picture about serious adverse effects of widely marketed drugs and about increased risks of such effects in certain segments of the population [Ref. 6].

The scientific and lay communities called for a range of new measures to improve access to and transparency of information about clinical trials, including broader mandatory registration and results submission. Incomplete access to information about clinical trials was seen by some to adversely affect investigators, journal editors, research funders, clinicians and participants. Proponents of more comprehensive registration of clinical trials in a publicly available data bank came from many quarters [Ref. 7, 8, 9]. For example, in 2004, the International Committee of Medical Journal Editors

(ICMJE) adopted a comprehensive trial registration policy aimed at increasing public access to trial information and preventing the selective publication of certain results. The updated 2007 ICMJE policy requires, as a condition for publication, registration of ''any research study that prospectively assigns human participants or groups of humans to one or more health-related interventions to evaluate the effects on health outcomes'' prior to the enrollment of the first participant [Ref. 10]. Industry groups also adopted registration policies. For example, in 2005, the International Federation of Pharmaceutical Manufacturers and Associations (IFPMA) stated that ''all clinical trials [sponsored by member companies], other than exploratory trials, should be submitted for listing in a free, publicly accessible clinical trial registry within 21 days of the initiation of patient enrollment . . .''[Ref. 11]. In a follow-up statement, IFPMA allowed for the delayed release of information in any of five fields that ''may be regarded as sensitive for competitive reasons by the sponsor'' [Ref. 12]. Also in 2005, the World Health Organization (WHO) International Clinical Trial Registry Platform (ICTRP) Secretariat defined a 20-item minimum clinical trial registration dataset [Ref. 13]. The WHO minimum trial registration standard has been adopted broadly, including by the ICMJE, and does not allow withholding of the five fields considered ''sensitive'' by IFPMA. The European Union has passed legislation requiring the public disclosure of registration and results information for certain clinical trials of drugs that are conducted in European Union countries, including trials of drugs for pediatric indications. The European Medicines Agency (EMA) is engaged in a public consultation to develop detailed technical specifications for the information to be submitted [Ref. 14, 15].

Because ClinicalTrials.gov is compatible with and receptive to a variety of registration requirements, it may facilitate compliance with many laws and policies and attracts an extremely large and diverse group of data providers. Many trials are registered in ClinicalTrials.gov to satisfy the ICMJE policy, and the number of trials registered in ClinicalTrials.gov increased significantly after the announcement of the ICMJE policy [Ref. 16]. Clinical trial records in ClinicalTrials.gov account for more than 85 percent of trials in the registries searched by the WHO ICTRP Portal [Ref. 17]. We believe that the more comprehensive the data bank, the better suited it will be to serve public health goals, including those articulated in section 402(j) of the PHS Act. As a result, we continue to encourage sponsors and other entities associated with studies not subject to section 402(j) of the PHS Act to voluntarily register and submit the results of trials of all types of interventions and other types of clinical studies in ClinicalTrials.gov, bearing in mind that section 402(j)(4)(A) of PHS Act may apply to such submissions.

B. Implementation of Statutory Provisions Prior to Rulemaking

Due to the short statutory timelines for responsible parties to begin submitting registration and results information for applicable clinical trials under Title VIII of FDAAA, NIH proceeded to expand the ClinicalTrials.gov registry data bank immediately after enactment of FDAAA. The intent was to develop a data bank that would permit responsible parties to meet the statutory requirements to submit clinical trial information, even though regulations to clarify and expand those obligations had yet to be developed. In December 2007, NIH launched an expanded registry that could accommodate the submission of clinical trial registration information specified in section 402(j) of the PHS Act. It included all the registration data elements explicitly enumerated in section 402(j)(2)(A)(ii) of the PHS Act, as well as additional data elements that the Agency interpreted as necessary to meet other statutory requirements, maintain consistency with ClinicalTrials.gov data elements that were in place prior to FDAAA, and allow efficient operation of the data bank. Over time, the Agency posted information on the ClinicalTrials.gov Web site outlining its current thinking about the meaning of key terms defined in the statute, including ''applicable clinical trial'' and ''responsible party'' [Ref. 18].

In further expanding the data bank to accommodate the submission of results information specified in section 402(j)(3)(C) of the PHS Act, we commissioned a review of practices and standards used in existing results data banks [Ref. 19]; engaged in active dialogue with the clinical trial community, public and private sectors, including the patient community; and consulted with the NLM Board of Regents, which established a Working Group on Clinical Trials [Ref. 20] in late 2007 and held meetings open to the public in 2008 [Ref. 21] and 2009 [Ref. 22] that were announced in the **Federal Register** (73 FR 3473, Jan. 18, 2008; 74 FR 3627, Jan 21, 2009). We held discussions with other standards development bodies that are active in areas related to trial information, such as the Clinical Data Interchange Standards Consortium (CDISC) and Health Level Seven (HL7). We also reviewed and considered various approaches to preparing summary reports on the results of clinical trials, including the ICH–E3 Clinical Study Report format [Ref. 23], which is used to guide the submission of drug trial results to regulatory agencies in the U.S., Europe, and Japan, and the CONSORT statements [Ref. 24], which are used to guide the publication of trial results in the peer-reviewed literature. We found that the ICH–E3 format and CONSORT were designed to delineate the topics that should be included when preparing summary reports of trial results for their intended expert audiences (regulatory professionals and medical professionals, respectively). Both the ICH–E3 format and CONSORT recommend review and inclusion of information beyond that collected during an individual clinical trial. Neither addresses the communication of trial results to the general public, which is one of the intended audiences for data submitted to comply with section 402(j) of the PHS Act. We found no existing standards directly addressing the submission of summary results tables as required by Title VIII of FDAAA.

As a result of these consultations and the review of existing approaches to results reporting, we decided to develop a results data entry system that would enable responsible parties to submit information in a structured manner. Structured data entry is necessary to enable the clinical trials data bank to accommodate the full range of study design and data types common or emerging in the clinical trials community, while simultaneously ensuring that all required data elements are provided; optimize the presentation of submitted data, including adverse event information, for various types of users, including those with less experience in interpreting information about the relative risks and benefits associated with particular interventions; and allow for efficient search capabilities, including searching by the data fields specified by the statute. Structured data entry requires a responsible party to submit data in pre-specified fields. As a result, a data bank can be created to manage all of the information from different trials at the level of the individual fields. This approach contrasts with the collection of heterogeneous, free-text documents

(e.g., PDF documents). In the latter situation, NLM would be unable to make the displays consistent or create and populate a data bank that would support the search capabilities specified by section 402(j) of the PHS Act and needed to use the data bank. The development of a structured results data bank was consistent with the design of the existing ClinicalTrials.gov registry data bank, which launched more than seven years before the passage of FDAAA.

In the spring of 2008, we announced in the **Federal Register** the beginning of an iterative process to advance development of a data bank to support the submission of the results information specified by section 402(j)(3)(C) of the PHS Act (73 FR 29525, May 21, 2008). Any user with a ClinicalTrials.gov account (i.e., an account for submitting registration information via the ClinicalTrials.gov Protocol Registration System, or PRS) was subsequently able to enter real or test data into the test system and view the resulting clinical trial records. Mechanisms for data entry and display and descriptions of individual data items were refined in response to comments from users of the test system, leading to the launch of an operational results submission system in September 2008. Further improvements to the system were made based on the experience of responsible parties submitting comments and from the Agency in reviewing results information submitted under section 402(j)(3)(C) of the PHS Act.

The operational system for results information enables responsible parties to submit required information. Because section 402(j)(3)(C)(i) of the PHS Act calls for the information on demographic and baseline characteristics of the study sample to include information on ''the number of patients who dropped out of the clinical trial and the number of patients excluded from the analysis, if any,'' the operational system separates the collection of information about participant flow (i.e., the number of subjects who started the clinical trial, completed the clinical trial, and were excluded from the analysis or dropped out of the trial) from demographic and baseline data. Our review of a large number of clinical trials determined that the only demographic data consistently collected across all of these clinical trials were age and gender. The operational system therefore collects information about age and gender, facilitates submission of other commonly collected demographic data such as race or ethnicity, and allows definition and submission of other demographic data from the clinical trial. Responsible parties may define and submit information on baseline characteristics that are most relevant to the particular clinical trial.

The operational results submission system that became available in September 2008 also supported the voluntary submission of information about serious adverse events and other frequent adverse events. Responsible parties were able to voluntarily submit information on serious and other adverse events in a manner largely consistent with the statutory default provisions in section 402(j)(3)(I)(iii)(I) and (II) of the PHS Act. Prior to implementing the capability to submit adverse event information, we found through our consultations and discussions that, although regulatory requirements and standards exist for the reporting of adverse events experienced by participants during a clinical trial, there is no standard approach for summarizing adverse event data from an entire clinical trial for purposes of inclusion in a public data bank. We viewed the process of enabling voluntary submission of summary adverse event information in the initial results submission system, prior to the statutory default provisions taking effect, as a means of determining whether the statutory default provisions would represent a feasible and ''best method'' of including adverse event information, consistent with section 402(j)(3)(I)(i) of the PHS Act. To help the Agency determine whether the 5 percent threshold specified in section 402(j)(3)(I)(iii)(II) of the PHS Act was an appropriate cap for information about frequent adverse events, we permitted data submitters to submit summary data on non-serious adverse events using a threshold other than 5 percent . They could choose any higher or a lower threshold.

The Agency did not promulgate regulations implementing the best method for including adverse events within 18 months of the date of enactment of FDAAA due to the time needed to evaluate different strategies for submitting adverse event information. As a result, the statutory default provisions in section 402(j)(3)(I)(iii) of the PHS Act for submitting adverse events information were implemented in the data bank on September 27, 2009. Responsible parties submitting results information were required to submit ''a table of serious anticipated and unanticipated adverse events, grouped by organ system, with number and frequency of such event in each arm of the clinical trial'' and ''a table of anticipated and unanticipated adverse events that are not included in the [serious adverse event table] that exceed a frequency of 5 percent within any arm of the clinical trial, grouped by organ system, with number and frequency of such event in each arm of the clinical trial'' (See sections 402(j)(3)(I)(iii)(I) and (II) of the PHS Act.) While there is a requirement to submit non-serious adverse events with a frequency of 5 percent or more in any arm, responsible parties may submit data voluntarily on non-serious adverse events with a threshold of less than 5 percent. The system also accommodates the voluntary submission of information indicating the methodology used for assessing adverse events (systematic versus non-systematic) and the time period during which adverse event information was collected.

We and the community of responsible parties have gained considerable experience with results submission, including adverse event information, since September 27, 2008, when results submission was required by section 402(j)(3)(C) of the PHS Act for certain applicable clinical trials. As of April 24, 2013, summary results for about 8,700 clinical trials had been submitted by responsible parties, processed by the Agency and made publicly available in the data bank. Based on this experience, we have refined the design of the data entry system, developed instructional materials to assist responsible parties in preparing data for submission, and refined procedures for processing submitted information. Responsible parties have improved their procedures for collecting and preparing data for submission to the data bank. We have drawn upon this considerable experience and the lessons learned in formulating this proposed rule.

III. Overview of Proposed Rule

A. Structure of proposed rule

We propose to add a new Part 11 to Title 42 of the Code of Federal Regulations (CFR) to implement the statutory requirements set forth in section 402(j) of the PHS Act. This proposed rule is divided into four major subsections:

- Subpart A outlines the general provisions of this proposed rule. It specifies the purpose of the rulemaking, to whom this proposed rule applies, requirements for submission of truthful information, the form and manner of submitting information to the data bank at *ClinicalTrials.gov,* and definitions specific to this part.
- Subpart B specifies requirements for registering an applicable clinical

trial. It specifies who must register trials, which trials must be registered, when registration information must be submitted, where registration information must be submitted, what registration information must be submitted, and when submitted registration information will be posted.

- Subpart C specifies requirements for submission of results information, including adverse event information, for applicable clinical trials of drugs (including biological products) and devices that have been approved, licensed, or cleared by FDA and for applicable clinical trials of drugs (including biological products) and devices that have not been approved, licensed, or cleared by FDA. It specifies who must submit clinical trial results information; for which trials such information must be submitted; when such information is due, including provisions for delayed results submission and requesting extensions; where such information must be submitted; what clinical trial results information must be submitted; when such information will be posted; and the circumstances under which the NIH will grant a waiver of the results submission requirements.
- Subpart D specifies additional required submissions of information to the data bank, including the timing of updates and corrections to submitted information and mandatory submission of clinical trial information in the interest of public health for certain applicable clinical trials that otherwise would not be subject to the registration and results submission requirements of this part. It also specifies requirements affecting the voluntary submission of information about clinical trials for which the submission of registration and results information is not otherwise required under this part.

Elements that are required to be considered in the rulemaking under section 402(j)(3)(D) of the PHS Act are addressed in the relevant subpart. For example, proposals related to results submission for applicable clinical trials of unapproved, unlicensed, or uncleared products are contained in subpart C (Results Submission), while those related to the updating of submitted clinical trial information are contained in subpart D (Additional submissions of clinical trial information).

B. General considerations in the rulemaking

As stated in section 402(j)(2)(A)(i) of the PHS Act, the data bank is intended ''to enhance patient enrollment and provide a mechanism to track subsequent progress of clinical trials.'' In addition to satisfying this obligation, we believe it is essential to continue to provide a comprehensive and robust data bank to encourage broad and widespread registration and submission of results of clinical trials and other types of clinical studies. Comprehensive registration and results submission for such studies is consistent with NLM's statutory obligations to disseminate information concerning research and to promote public health. It can provide information to potential research participants, reduce inadvertent and unnecessary duplication of clinical studies, help journal editors detect incomplete descriptions of the results of specific clinical trials, and allow analysis of the results of multiple clinical trials of the same or similar interventions, thus providing regulators, scientists, health professionals, and the public with more information regarding the potential benefits and harms of different interventions.

We also believe it is essential for the data bank to serve a wide variety of users. While the public is the ultimate beneficiary of the data bank and the information contained in it, the overall public benefit will derive from access to and use of the data by different constituencies within the general public. We believe that clinical researchers, systematic reviewers, experts in evidence-based medicine, regulators, drug and device manufacturers, human subjects protection review boards (including institutional review boards (IRBs)), healthcare providers, disease and patient advocacy groups, students and educators, and patients and their family members may be able to use the available information to learn more about FDA-regulated products, to increase the efficiency of drug and device development processes, and to improve the design and conduct of clinical research studies, among other uses.

Building a data bank that serves multiple users with varying degrees of expertise in analyzing and interpreting clinical trial data means that not all of the collected information will necessarily be easy for all users to interpret. Some members of the general public, for example, may have difficulty interpreting certain results information, including adverse event information, or putting it into context. To address such concerns, we currently provide and, consistent with sections 402(j)(3)(A)(ii)(I) and (II) of the PHS Act, intend to expand links to additional explanatory material, including general information about clinical trials; publicly available FDA, NIH, and systematic review information about the products being studied; NIH information about the conditions that are the focus of the clinical trial; peer-reviewed journal articles summarizing the results of clinical trials; and specified FDA information about the clinical trial. We intend to develop improved ways of displaying submitted clinical trial information and enabling users to search for it, as we continue to gain experience with the operational system and to consult with experts in risk communications and clinical trial research. We also expect to solicit public input on this topic using a variety of mechanisms.

It is important to note that this proposed rule does not impose any requirements for the design or implementation of a clinical trial or for the collection of information during a clinical trial. This proposed rule specifies requirements for submitting information that describes a clinical trial as it was designed, conducted, and analyzed. The proposed data submission requirements are intended to accommodate current and emerging practices in design and implementation of clinical trials. We expect that the information required to be submitted to ClinicalTrials.gov will have been developed and collected prior to the time it must be submitted to the data bank and for reasons distinct from compliance with section 402(j) of the PHS Act and this proposed rule. In general, required information would have been included in standard clinical trial documentation (e.g., the protocol), collected during the course of the clinical trial (e.g., the types of adverse events specified in the protocol), or produced by the analysis that was specified in the protocol (e.g., outcome measures and statistical tests).

C. Key issues considered in this proposed rule

In developing this proposed rule, we considered a number of issues associated with the implementation of the statutory requirements for registration under section 402(j)(2) of the PHS Act and results submission under section 402(j)(3)(C) of the PHS Act and with the expansion of the data bank via rulemaking, as specified in section 402(j)(3)(D) of the PHS Act. We discuss these issues in this section of the preamble and reflect their implementation in the specific proposals described in section IV. We welcome comments on the Agency's proposals for addressing each of these topics in this proposed rule and additional information that might inform their implementation.

1. Elaboration of statutory definitions

Section 402(j)(1)(A) of the PHS Act defines a number of terms that are essential to implementation of the statute and the development of this proposed rule. Among the most important are the terms applicable clinical trial and responsible party, which are key elements in defining the set of trials that are subject to the registration and results submission requirements of section 402(j) of the PHS Act and the individuals or entities that are responsible for submitting the required information, respectively.

(a) Applicable clinical trial. Section 402(j)(1)(A)(i) of the PHS Act defines the term applicable clinical trial as either an applicable device clinical trial or an applicable drug clinical trial, both of which are defined in section 402(j)(1)(A) of the PHS Act. Section 402(j)(1)(A)(ii) defines applicable device clinical trial as ''(I) a prospective clinical study of health outcomes comparing an intervention with a device subject to section 510(k), 515, or 520(m) of the [FD&C Act] against a control in human subjects (other than a small clinical trial to determine the feasibility of a device, or a clinical trial to test prototype devices where the primary outcome measure relates to feasibility and not to health outcomes); and (II) a pediatric postmarket surveillance as required under section 522 of the [FD&C Act].'' Section 402(j)(1)(A)(iii) defines an applicable drug clinical trial as a ''controlled clinical investigation, other than a phase I clinical investigation, of a drug subject to section 505 of the [FD&C Act] or to section 351 of [the PHS Act,]'' where ''clinical investigation'' has the meaning given in 21 CFR 312.3 or any successor regulation and phase I has the meaning given in 21 CFR 312.21 or any successor regulation.

This proposed rule, in § 11.10, adopts the statutory definitions of all three of these terms, replacing the phrase ''phase I'' in the definition of applicable drug clinical trial with the phrase ''phase 1'' to be consistent with the numbering scheme used in FDA regulations at 21 CFR 312.21. Because of the significance of these terms in determining which clinical trials are subject to the provisions of this proposed part, we include in section IV.A.5 of this preamble an extensive elaboration of their meanings, interpreting each component part of the definitions in a way that is consistent with existing use of the stated terms in relevant FDA regulations, which may differ from current usage in some segments of the clinical research community. We also propose in § 11.22(b) an approach for using a limited set of registration data elements to determine whether a particular study meets the definition of an applicable clinical trial. We believe there is significant advantage in having a simple mechanism for a responsible party to determine, based on a standard set of factors, whether a study meets the definition of an applicable clinical trial. Such a mechanism would reduce uncertainty among responsible parties about their data submission obligations under section 402(j) of the PHS Act and reduce their burden in making such a determination.

A key consideration in the elaborations and the mechanism for determining whether a study meets the definition of an applicable clinical trial is defining what it means for an applicable drug clinical trial to be ''controlled'' or for an applicable device clinical trial to compare an intervention against a control. We explain our interpretation of these phrases in the preamble, and we include in § 11.10 of this proposed rule a definition of the term ''control or controlled.'' Our proposed definition is consistent with the types of controls recognized by FDA in its regulations for clinical trials of drugs and devices (21 CFR 314.126(b)(2)(i)–(v) and 21 CFR 860.7(f)(1)(iv)(a)–(d)) in that it includes both concurrent controls, as would be used in trials with multiple arms, and non-concurrent controls, as may be used in single-arm trials that are expressly designed to compare the effect of an intervention to an historical control or to baseline data, e.g., with participants serving as controls. It is broader than the FDA definitions of ''adequate and well controlled'' in 21 CFR 314.126(b) and ''well controlled'' in 21 CFR 860.7(f) in that it does not imply a judgment about the adequacy or appropriateness of the control and the study design.

Based on this definition, we would consider any clinical trial with multiple concurrent arms to be controlled for purposes of determining whether it is an applicable clinical trial subject to this proposed Part. We would also consider some single-arm clinical trials to be controlled. Such trials include single-arm trials of FDA-regulated products that, as specified in their protocols, intend to evaluate an effect by comparing measures taken after an intervention to baseline measures taken from the participants prior to the intervention. Many of these studies have explicitly defined ''change from baseline'' measures identified in their protocols, i.e., they are designed to compare a measure taken after an intervention to the participant's state prior to the intervention. Other single-arm trials that we would consider controlled include, for example, studies with an identified measure of ''response rate'' or measures in which the state prior to or without the intervention can be assumed (e.g., studies in conditions that do not resolve without intervention, such as cancer).

We propose in § 11.28 that a responsible party who registers a single-arm trial indicate whether the trial protocol or statistical analysis plan specifies a control as defined in this part. While plans for analyzing collected data may change during the course of a study, we believe that the requirement that the control be specified in the protocol or statistical analysis plan will improve consistency in the interpretation of this requirement across trials. We considered requiring greater specification about the type of control, if any, used in the single-arm study, e.g., historical control (including subjects as their own control), but believe our proposed approach provides the information necessary for identifying applicable clinical trials while minimizing the burden on responsible parties. We propose in § 11.22(b) to use the information submitted by the responsible party to determine whether a trial meets the definition of an applicable clinical trial.

We invite comments on our proposed approach for identifying single-arm trials that would be considered controlled and on alternative ways to identify such trials. In particular, we invite comments on whether there are other specific, objective features of clinical trials that could serve as the basis for differentiating between single-arm studies that are and are not controlled. We also invite comments on and information about, the types of single-arm trials that meet the other criteria for an applicable clinical trial and do or do not meet our proposed definition of controlled.

(b) Responsible party. Section 402(j)(1)(A)(ix) defines the responsible party with respect to a clinical trial of a drug or device as: ''(I) the sponsor of the clinical trial (as defined in . . . 21 [CFR 50.3] . . . (or any successor regulation)); or (II) the principal investigator of such clinical trial if so designated by a sponsor, grantee, contractor, or awardee, so long as the principal investigator is responsible for conducting the trial, has access to and control over the data from the clinical trial, has the right to publish the results of the trial, and has the ability to meet all of the requirements . . . [of this part] for the submission of clinical trial information.'' We adopt this definition with minor, non-substantive

modifications in § 11.10 of this proposed rule.

Given the significance of the role that the responsible party plays in complying with section 402(j) of the PHS Act, we elaborate on the meaning and interpretation of this term in section IV.A.5 of this preamble. We have codified parts of the elaboration of the definition of responsible party in proposed § 11.4(c), which specifies procedures for determining the responsible party. We have also included a definition of the term sponsor in proposed § 11.10.

2. Modifications and Additions to the Elements of Clinical Trial Registration Information

The clinical trial registration information required by section 402(j)(2)(A)(ii) of the PHS Act includes 25 specific data elements grouped into 4 categories: Descriptive information, recruitment information, location and contact information, and administrative information. Additionally, section 402(j)(2)(A)(iii) of the PHS Act authorizes the Secretary, by regulation, to modify the statutory requirements for clinical trial registration information if a rationale is provided as to ''why such a modification improves and does not reduce'' such information. Proposed § 11.28 lists the clinical trial information that we propose to require at the time of registration. The definitions of specific data elements are provided in proposed § 11.10(b). For the most part, the proposed list of data items conforms to the list of items enumerated in section 402(j)(2)(A)(ii) of the PHS Act, restating, and, in many instances, clarifying the statutory data items. However, this proposed rule includes certain modifications and additions to the data items listed in 402(j)(2)(A)(ii) of the PHS Act that we conclude improve the clinical trial information available to the public and implement the requirements of the statute. We do not believe that any of the proposed modifications and additions reduces the clinical trial information available to the public. As further explained in section IV.B.4 of this preamble, a number of the proposed modifications and additions to clinical trial registration information listed in section 402(j)(2)(A)(ii) of the PHS Act are not new to some responsible parties and other users of the data bank who submitted information to ClinicalTrials.gov prior to FDAAA; many of the data elements are the same or similar to those collected in ClinicalTrials.gov prior to enactment of FDAAA.

Our proposed modifications and additions to clinical trial registration information take the following general forms.

(1) Structuring data entry for registration data elements to help the public use the data bank and compare entries, as required by section 402(j)(2)(B)(iv) of the PHS Act. We believe structured data entry for registration data elements helps satisfy the requirement at 402(j)(2)(B)(iv) to ''ensure that the registry data bank is easily used by the public, and that entries are easily compared,'' because it will enable users to search the data bank using the criteria listed in section 402(j)(2)(B)(i) of the PHS Act and will prompt responsible parties to submit complete and accurate information. We therefore propose to require responsible parties to enter defined components of certain data elements, such as study design, outcome measure, and IND or IDE number. For example, in § 11.10(b)(35), we propose to define the Food and Drug Administration IND or IDE number, a data element expressly required to be submitted at the time of registration by section 402(j)(2)(A)(ii)(IV)(cc) of the PHS Act (therein referred to as the ''IND/IDE protocol number'') to include the name of the FDA center that issued the IND or IDE (e.g., the Center for Drug Evaluation and Research (CDER), the Center for Biologics Evaluation and Research (CBER), or the Center for Devices and Radiological Health (CDRH)); the IND or IDE number; and any serial number that has been assigned by the sponsor to that filing. We believe these three components are necessary to provide complete information about IND/IDE number.

(2) Additions to allow effective implementation of, or compliance with, other provisions of section 402(j) of the PHS Act. For example, this proposed rule in § 11.28(a)(1)(xv) requires information about whether a product under study in a clinical trial is manufactured in the U.S. or one of its Territories because this information is necessary in some situations to determine whether or not a clinical trial meets the definition of an applicable clinical trial or would be considered a voluntary submission under section 402(j)(4)(A) of the PHS Act.

(3) Additions to improve the quality and consistency of information available in the data bank and enabling users to better search for, retrieve, and understand it. For example, in § 11.28(a)(1)(xi) of this proposed rule, we propose that responsible parties submit other current and former names for interventions studied in a clinical trial (if other such names exist) to help identify duplicative trial registrations and assist users in finding clinical trials for interventions that might be registered under different names (e.g., the name of the chemical compound, the brand name of an approved product, or an alias used during pre-marketing studies).

(4) Addition to indicate the ethical and scientific review status of the clinical trials listed in the data bank. We believe that it is essential that patients and practitioners searching ClinicalTrials.gov for information about clinical trials retrieve information on whether a clinical trial registered in ClinicalTrials.gov is undergoing or has undergone review procedures with respect to ethical and scientific considerations. A small number of applicable clinical trials may not be required by applicable law, regulation, and/or institutional policy to seek approval from a human subjects protection review board (e.g., if a waiver has been provided, the clinical trial is determined to be exempt in accord with applicable law and regulation, or the clinical trial is not subject to laws, regulations, or institutional policies that require review by a human subjects protection review board). In such cases, the proposed rule would require responsible parties to indicate that human subjects protection review board approval is not required by applicable law, regulation, or institutional policy. We recognize that provision of information on human subjects review status cannot guarantee the quality of a clinical trial or the safety of human subjects who are enrolled in it. Nevertheless, we believe that requiring responsible parties to indicate whether a clinical trial registered in ClinicalTrials.gov is undergoing or has undergone review by a human subjects protection review board may provide some measure of assurance in most situations.

We invite comments on our proposed modifications and additions to the data elements of clinical trial registration information, including the benefits and burdens associated with structuring certain registration data elements.

3. Posting of Registration Information for Applicable Device Clinical Trials

Section 402(j)(2)(D) of the PHS Act establishes the timelines for posting clinical trial registration information submitted by responsible parties in the data bank. For applicable drug clinical trials, section 402(j)(2)(D)(i) of the PHS Act requires NIH to post publicly clinical trial registration information not later than 30 days after it has been

submitted. For applicable device clinical trials of devices that previously have been approved or cleared by FDA, section 402(j)(2)(D)(ii)(II) of the PHS Act requires that clinical trial registration information be posted not later than 30 days after clinical trial results information is required to be posted by NIH. As discussed in detail in section IV.B.5(b) of this preamble, NIH has interpreted this provision as allowing NIH to post clinical trial registration information for applicable device clinical trials of these devices as soon as practicable. For applicable device clinical trials of devices that have not previously been approved or cleared, NIH intends that, consistent with section 402(j)(2)(D)(ii)(I) of the PHS Act, clinical trial registration information will be posted not earlier than the date on which FDA approves or clears the device and not later than 30 calendar days after the date of such approval or clearance.

While postponing the posting of clinical trial registration information for applicable device clinical trials for a device that previously has not been approved or cleared may protect the commercial interests of device manufacturers, there are a number of situations in which those who conduct such clinical trials may prefer to make such information publicly available in the data bank prior to the time frames allowed by section 402(j) of the PHS Act and this rulemaking. For example, based on experience to date, we believe that some sponsors and principal investigators prefer to make their registration information publicly available in the data bank because this would be an easy way to meet the ICMJE policy [Ref. 10], which requires public registration in a data bank prior to enrollment of the first patient as a precondition for consideration for publication. Others prefer to make registration information available to the public to assist with or expand upon efforts to recruit potential human subjects for a trial. In other cases, responsible parties might wish to make some of the registration information available to demonstrate to others (e.g., a funding organization or the sponsor) that a clinical trial has, in fact, been registered as required by section 402(j) of the PHS Act and this proposed regulation.

We considered, but do not propose, two potential mechanisms for addressing these situations: (1) Allowing a responsible party to give voluntarily the NIH permission to release clinical trial registration information for an applicable device clinical trial of a device that previously has not been approved or cleared for public posting in the data bank, and (2) allowing any individual or entity to whom the responsible party provides the NCT number for such a trial (i.e., the unique identifier that is assigned to a trial upon registration in the data bank) to access a very limited set of data sufficient to verify that the clinical trial of interest has been registered, but without revealing substantive information about the clinical trial, such as the focus of the clinical trial or the products involved. However, section 402(j)(2)(D)(ii) of the PHS Act provides that the ''Director of NIH shall ensure that clinical trial information for an applicable device clinical trial of an unapproved or uncleared device submitted in accordance with . . . [section 402(j)(2) of the PHS Act not be] posted publicly . . .'' before approval or clearance. Because neither of the mechanisms appears to be permissible under the statute, we have not proposed implementing either of these mechanisms in this rulemaking. We invite comments from the public on how, given the statutory language, the Agency may address the concerns of sponsors and responsible parties who wish to have clinical trial registration information for applicable device clinical trials of devices that previously have not been approved or cleared made publicly accessible in ClinicalTrials.gov when the responsible party so chooses.

4. Application of Rule to a Pediatric Postmarket Surveillance of a Device That Is Not a Clinical Trial

In section 801(c), FDAAA requires the Secretary of HHS to issue guidance on how section 402(j) of the PHS Act applies to a pediatric postmarket surveillance of a device that is not a clinical trial. Section 402(j)(1)(A)(ii)(II) of the PHS Act defines the term applicable device clinical trial to include ''a pediatric postmarket surveillance as required under section 522 of the [FD&C] Act.'' This proposed rule in § 11.10 defines ''pediatric postmarket surveillance of a device'' as ''the active, systematic, scientifically valid collection, analysis, and interpretation of data or other information conducted under section 522 of the [FD&C] Act about a marketed device that is expected to have significant use in patients who are 21 years or younger at the time of diagnosis or treatment. A pediatric postmarket surveillance of a device may be, but is not always, a clinical trial.''

FDA may order a pediatric postmarket surveillance of a device under section 522 of the FD&C Act for any class II or class III device, as defined by 21 U.S.C. 360c(a) and 21 CFR 860.3, meeting any of the following criteria: Its failure would be reasonably likely to have serious adverse health consequences; it is expected to have significant use in pediatric populations; it is intended to be implanted in the body for more than 1 year; or it is intended to be a life-sustaining or life-supporting device outside a device user facility. (See 21 U.S.C. 360l(a).) Pediatric postmarket surveillances under section 522 of the FD&C Act can take various forms, including a detailed review of the complaint history and the scientific literature, non-clinical testing, observational studies, and controlled clinical trials [Ref. 25].

Because section 402(j)(1)(A)(ii)(II) of the PHS Act defines the term ''applicable device clinical trial'' to include pediatric postmarket surveillances of a device, such surveillances must be registered, and clinical trial results information must be submitted for them. Our proposed approach for applying the registration requirements to a pediatric postmarket surveillance of a device that is not a clinical trial is described in proposed § 11.28(b). Our proposed approach for applying the results submission requirements to a pediatric postmarket surveillance of a device that is not a clinical trial is described in proposed § 11.48(b). A pediatric postmarket surveillance of a device that is a clinical trial would be subject to the general requirements of this proposed rule, including the clinical trial registration and results submission requirements in proposed §§ 11.28(a) and 11.48(a), respectively. Further elaboration of these proposals is contained in section IV.B of this preamble.

5. Submission of Results Information for Applicable Clinical Trials of Unapproved, Unlicensed, or Uncleared Products

(a) General requirements and rationale. Section 402(j)(3)(D)(ii)(I) of the PHS Act requires the submission of results information for: (1) Each applicable drug clinical trial for a drug that is approved under section 505 of the FD&C Act or licensed under section 351 of the PHS Act; and (2) each applicable device clinical trial for a device that is cleared under section 510(k) of the FD&C Act or approved under section 515 or 520(m) of the FD&C Act. By contrast, section 402(j)(3)(D)(ii)(II) of the PHS Act requires that the Secretary establish, through regulation, whether or not results information must be submitted for applicable clinical trials of unapproved, unlicensed, or uncleared

products, whether or not approval, licensure, or clearance was sought. If the Secretary requires, by regulation, the submission of results information for unapproved, unlicensed, or uncleared products, then section 402(j)(3)(D)(iv)(III) of the PHS Act authorizes the Secretary to determine, by regulation, ''the date by which such clinical trial information shall be required to be submitted,'' taking into account (a) the process under section 402(j)(3)(E)(iii) of the PHS Act for ''delayed submission of results with certification'' when approval, licensure, or clearance is sought; and (b) whether there should be a delay of submission when approval, licensure, or clearance will not be sought.

Pursuant to our authority under section 402(j)(3)(D)(ii)(II) of the PHS Act, we have decided to propose that results information be submitted for applicable clinical trials of drugs and devices that are not approved, licensed, or cleared by FDA, regardless of whether approval, licensure, or clearance is sought. In addition, pursuant to our authority under section 402(j)(3)(D)(iv)(III) of the PHS Act, we propose deadlines for submitting this results information that, as required by statute, take into account both the certification process under section 402(j)(3)(E)(iii) of the PHS Act for delayed submission of results when approval, licensure, or clearance is sought and whether there should be delayed submission of results when approval, licensure, or clearance will not be sought. As discussed in section III.D of this preamble, these proposals would apply to applicable clinical trials of unapproved, unlicensed, or uncleared products that reach their completion dates on or after the effective date of this rule, as well as certain applicable clinical trials of unapproved, unlicensed, or uncleared products that reach their completion dates prior to the effective date of the rule.

We believe our proposal to require results submission for applicable clinical trials of unapproved, unlicensed, or uncleared products is in furtherance of the express statutory purpose of the expanded data bank, which states that the Secretary shall expand the registry and results data bank ''[t]o provide more complete results information and to enhance patient access to and understanding of the results of clinical trials.'' (See section 402(j)(3)(D)(i) of the PHS Act.) In developing our proposal, we considered a number of factors, many of which were raised at the Public Meeting [Ref. 1], notably the potential public health benefits of timely disclosure of results information for clinical trials of drugs that are not approved, biological products that are not licensed, and devices that are not approved or cleared; the potential effects of disclosure on the competitive advantage of drug and device manufacturers, including incentives to invest in the development of new products intended to improve public health; and other results submission requirements and policies (e.g., those of the EMA). Other considerations include the relative burden on the responsible party of submitting results for clinical trials of unapproved drugs, unlicensed biological products, and unapproved or uncleared devices, the date by which results must be submitted, and practical issues of implementation and compliance.

The Agency finds compelling the arguments in support of a requirement to submit the results of applicable clinical trials of unapproved, unlicensed, or uncleared products. The availability of such information in ClinicalTrials.gov could have several potential public health benefits. Systematic disclosure of results of applicable clinical trials of unapproved, unlicensed, or uncleared products would mitigate the bias in information available to the public about studied medical products that stems from selective disclosure of clinical trial results [Ref. 26]. Currently, sponsors, researchers, and product manufacturers often voluntarily and selectively release to the public partial information about the results of specific studies, including those of unapproved, unlicensed, or uncleared products, via scientific publications and abstracts, press releases, and other announcements. Requiring the submission of results of applicable clinical trials of unapproved, unlicensed, or uncleared products in a systematic and standardized format would provide a more current and complete picture of results of clinical trials of FDA-regulated products, therefore reducing a potential source of bias.

The public availability of results information about trials of unapproved, unlicensed, and uncleared drugs (including biological products) and devices would also help protect the safety of participants who volunteer to be in clinical trials by reducing the likelihood that people will unknowingly design, approve, or participate in clinical trials that are unnecessary (e.g., because similar clinical trials have already been conducted but not published), or that are potentially harmful (e.g., because similar interventions have been shown to be harmful or ineffective in previous, unpublished clinical trials). It would also help potential human subjects make more informed decisions about participating in a clinical trial by providing them and their care providers with information about the results of a broader set of clinical trials of various interventions that have been studied for a disease or condition of interest. Investigators and human subjects protection review boards that already have access to unpublished information from the sponsor of a clinical trial or the manufacturer of a drug or device would have access via ClinicalTrials.gov to information about other clinical trials of similar unapproved, uncleared, or unlicensed products that might help them in designing or considering the potential risks and benefits of participation in a clinical trial.

In addition, submission of results of clinical trials of unapproved, unlicensed, or uncleared products would broaden the evidence base for systematic reviewers and others involved in assessing the benefits and harms of classes of drugs and devices. Many clinical trials compare unapproved, unlicensed, or uncleared drugs and/or devices with approved, licensed, or cleared drugs and/or devices, and the submission of results of such clinical trials could increase access to additional information about the marketed products for their approved, licensed, or cleared uses. In addition, many unapproved, unlicensed, or uncleared products are similar to products that are approved, licensed, or cleared and in the marketplace. This is particularly true of the unapproved, unlicensed, or uncleared versions of products that are studied in clinical trials that contribute to the evidence base for subsequent approval, licensure, or clearance of a different version of the product. Preliminary or alternative versions of a drug, for example, may differ from the approved or licensed version in dose, form, or inactive ingredients, even if they contain the same active ingredient(s). Results of clinical trials of unapproved products could therefore enhance the knowledge base for understanding classes of products.

There is also a compelling ethical rationale for making available to the public the results from clinical trials that involve human subjects, regardless of the approval status of the product. Part of the agreement made with human subjects who agree to participate in clinical trials is that knowledge that is obtained in the clinical trial will be available for use in advancing biomedical science [Ref. 27].

Submission and subsequent posting of the results of applicable clinical trials of unapproved drugs, unlicensed biological products, and unapproved or uncleared devices to ClinicalTrials.gov that reach their completion dates on or after the effective date of a final rule would help to achieve that goal, especially for clinical trials for which results are never published in the scientific literature.

We also are aware of ongoing regulatory efforts by the EMA to make results of clinical trials of drugs conducted within the EU available in a publicly accessible data bank, regardless of the approval status of the drug [Ref. 28, 29, 30]. Already, all clinical trials of drugs performed within the EU are registered in EMA's EudraCT database, with information on phase 2, 3, and 4 clinical trials and all pediatric clinical trials made public through the EU Clinical Trials Register (*https://www.clinicaltrialsregister.eu/*). In June 2010, EMA issued for public comment the draft implementing technical guidance on the EudraCT results data bank. The technical guidance specifies summary results information that would be submitted to the data bank for public posting. The specified summary results information differs from the detailed information that would be submitted to EMA as part of a Marketing Authorization Application. As noted in that document, EMA has worked with ClinicalTrials.gov staff to harmonize common data elements used by the two results data banks, which we view as a way of simplifying the process of submitting results to EudraCT and ClinicalTrials.gov, for those trial that are required to submit results to both data banks. Many clinical trials that would be subject to EMA regulations requiring the disclosure of clinical trial results would likely be applicable clinical trials subject to section 402(j) of the PHS Act. We believe that if clinical trial results information is available via another publicly accessible data bank (such as EudraCT), a number of the concerns that have been expressed about disclosure in ClinicalTrials.gov would no longer be applicable. The use of common data elements would promote harmonization of results information in EudraCT and ClinicalTrials.gov and simplify data submission for clinical trials that would be summarized in both databases.

We recognize that the posting of results information about clinical trials of unapproved, unlicensed, and uncleared products presents special challenges. Such information would be accessible to care providers and their patients and would describe uses of products that are not approved, cleared, or licensed. Even for approved, cleared, or licensed uses the posted result information would contain information that is not included in approved labeling and that requires further interpretation for understanding potential risks and benefits. We believe that the results information from any individual clinical trial should be considered not on its own, but in the context of the broader set of information available about the product and alternative products. In keeping with current practice, we intend to establish links from clinical trial records in ClinicalTrials.gov additional sources of information, including but not limited to the FDA and NIH information specified in section 402(j)(3)(A)(ii) of the PHS Act (we would indicate that the links were added by the NIH and not by the responsible party). As discussed further in section III.C.11, we would also provide information to assist users in better understanding and interpreting the information available in ClinicalTrials.gov, including materials that describe the general purpose and content of the data bank, the limitations of the data presented, and cautions that the information should be used in conjunction with advice from healthcare professionals.

We believe that all of these benefits can be best achieved by requiring the submission of results information for all applicable clinical trials involving unapproved, unlicensed, or uncleared products, regardless of whether FDA approval, licensure, or clearance is sought. Limiting results submission to those applicable clinical trials of unapproved, unlicensed, or uncleared products for which product development has been abandoned by industry would minimize industry concerns about disclosing potentially valuable information to competitors, but would do little to address concerns about bias in the disclosure of information. Considerable information of potential scientific, clinical, and public significance would still be hidden from public view and would continue to be unavailable for consideration by human subjects protection review boards in assessing proposed clinical trials, by individuals considering participation in them, or by other researchers who are planning similar clinical trials or clinical trials of similar products. Even if investigators and human subjects protection review boards have access to information from a clinical trial sponsor, they will not have access to the full range of unpublished results of other clinical trials that might be relevant to a clinical trial under consideration. We believe that concerns about commercial competitiveness resulting from disclosure of results information from clinical trials of products that are not approved, licensed, or cleared by the FDA can be mitigated by delaying the results submission deadline for applicable clinical trials of products that are still under development, as described later in this section. Indeed, disclosure of results information for clinical trials of products that are still under development could improve the efficiency of research and development (R&D) investments by reducing the likelihood that private companies, universities, and the U.S. Government will waste resources repeating studies of interventions that have already been conducted. In addition, limiting disclosure to applicable clinical trials of products for which product development has been abandoned would be difficult to administer because only the sponsor and/or manufacturer are in a position to determine that product development has been abandoned for all potential uses. Moreover, as noted by some industry commenters, product development is often suspended for periods of time before being resumed when company priorities change or a developmental product is transferred to another company. Information about unapproved products still in product development pipelines might therefore remain undisclosed for long periods of time, depriving the public of the benefits that could result from disclosure even in situations where non-disclosure might provide little commercial advantage.

We therefore propose, as authorized by section 402(j)(3)(D)(ii)(II) of the PHS Act and as specified in proposed § 11.42(a), to require submission of clinical trial results information for applicable clinical trials that reach their completion dates on or after the effective date of the rule and that involve a drug, biological product, or device that is not approved, licensed, or cleared for any indication, regardless of whether the sponsor seeks approval, licensure, or clearance. We believe that requiring this information to be submitted is consistent with the statute's stated purpose in expanding the registry and results data bank ''[t]o provide more complete results information and to enhance patient access to and understanding of the results of clinical trials.'' (See section 402(j)(3)(D)(i) of the PHS Act).

In considering the deadlines for submitting results information for applicable clinical trials of unapproved,

unlicensed, or uncleared products, as required by section 402(j)(3)(D)(iv)(III) of the PHS Act, the Agency recognized a need to balance several considerations namely: Commercial interests in protecting information about products under development, public health benefits of timely access to results information, the burden associated with submission of results information, and administrative burden. We also considered the statutory requirements of section 402(j)(3)(D)(iv)(III) of the PHS Act to take into account: (1) the certification process for delayed submission of results under section 402(j)(3)(E)(iii) of the PHS Act ''when approval, licensure, or clearance is sought'' for a product studied in an applicable clinical trial; and (2) ''whether there should be a delay of submission when approval, licensure or clearance will not be sought.''

As further described below, we propose to require results submission for applicable clinical trials involving unapproved, unlicensed, or uncleared products not later than 1 year after the completion date of the clinical trial, unless the responsible party submits a certification under section 402(j)(3)(E)(iii) of the PHS Act prior to that deadline indicating that initial approval, licensure, or clearance is being sought or may at a future date be sought.

Delayed submission of results of applicable clinical trials involving products that are unapproved, unlicensed, or uncleared would be permitted only if the responsible party certifies under section 402(j)(3)(E)(iv) of the PHS Act that the sponsor or manufacturer intends to continue with product development, meaning that it is either seeking, or may at a future date seek, initial approval, licensure, or clearance of the product under study in an applicable clinical trial. For applicable clinical trials of unapproved, unlicensed, or uncleared products, results submission may be delayed only if section 402(j)(3)(E)(iv) of the PHS Act applies. In determining whether section 402(j)(3)(E)(iv) of the PHS Act applies to a particular applicable clinical trial, we took into consideration the fact that section 402(j)(3)(D)(iv)(III)(aa) of the PHS Act indicates that the certification process under section 402(j)(3)(E)(iii) of the PHS Act applies ''when approval, licensure, or clearance *is sought*'' (emphasis added), whereas section 402(j)(3)(D)(iv)(III)(bb) of the PHS Act states that the Secretary shall determine, by regulation, ''whether there should be a delay of submission when approval, licensure, or clearance *will not be sought*'' (emphasis added). We consider these two provisions together to mean that delayed submission of results with certification is allowable if initial approval, licensure, or clearance is sought, meaning that the sponsor or manufacturer intends to continue with product development and thus either is seeking, or may at a future date seek, approval, licensure, or clearance. This proposed rule does not include a provision extending delayed submission when approval, licensure, or clearance will not be sought.

Delayed submission of results would not be available to a responsible party who either meets the criteria in section 402(j)(3)(E)(iv) of the PHS Act to certify but does not submit a certification prior to the deadline under the process set forth in section 402(j)(3)(E)(iii) of the PHS Act, or who does not meet the statutory criteria to submit a certification. In such instances, we propose that results be due not later than 1 year after the completion date, unless an extension for good cause is requested and granted under section 402(j)(3)(E)(vi) of the PHS Act. This deadline is consistent with the time frame in section 402(j)(3)(E)(i) of the PHS Act for submitting results information. Specifically with regard to applicable clinical trials of drugs (including, biological products) or devices for which approval, licensure, or clearance will not be sought, we interpret the phrase ''will not be sought'' to mean that the sponsor or manufacturer has no intention of developing a marketable product or otherwise has abandoned product development. For these trials, the Agency believes that the public benefits of disclosure of results information outweigh any private, commercial interests. We recognize that, in many cases, whether initial approval, licensure, or clearance is, or may at a future date be, sought is information that will be known only to the sponsor or manufacturer of the drug, biological product, or device and may not even be known to them at the time a clinical trial is completed, especially for an earlier stage trial, such as a phase 2 applicable drug clinical trial. Instead, the sponsor or manufacturer may know only that it intends to continue with product development, such as through the conduct of a subsequent clinical trial. Accordingly, the Agency needs a way to verify that the sponsor or manufacturer is seeking, or may at a future date seek, initial approval, licensure, or clearance. Therefore, as a condition of delaying results submission for unapproved, unlicensed, or uncleared products, we propose in § 11.44(c), to require the responsible party to certify that the sponsor or manufacturer intends to continue with product development and either is seeking, or may at a future date seek, approval, licensure, or clearance. See section 402(j)(3)(E)(iv) of the PHS Act. If the responsible party elects to submit a certification for delayed submission, it is the responsible party's obligation to verify that the particular applicable clinical trial meets the proposed § 11.44(c) criteria, as explained in this preamble. We recommend that if the sponsor has designated the PI as the responsible party under the process described under proposed § 11.4(c), the sponsor should be prepared to communicate with the responsible party to help ensure the accuracy of any certification that is made.

If after submission of a certification that section 402(j)(3)(E)(iv) of the PHS Act applies to a specific applicable clinical trial, the drug, biological product, or device studied in the applicable clinical trial becomes approved, licensed, or cleared for the indication studied in the applicable clinical trial, results information would be due 30 calendar days after approval, licensure, or clearance. If, after submission of a certification that section 402(j)(3)(E)(iv) applies to the applicable clinical trial, initial approval is no longer being sought (i.e., product development is abandoned), we likewise do not believe that continued delays in results submission are warranted, and we recommend that the responsible party should submit results information as soon as practicable.

Furthermore, we do not believe that a delay in submitting results for applicable clinical trials of unapproved, unlicensed, or uncleared products should be indefinite, enduring until a responsible party proactively asserts that product development has been abandoned or until the product is approved, licensed, or cleared. We therefore propose to limit the allowable delay period for results submission for applicable clinical trials of unapproved, unlicensed, or uncleared products to 2 years after the submission of a certification for delayed results submission. The certification would have to be submitted prior to the date on which results information would otherwise be due (e.g., 12 months after the completion date), and we would permit only one certification to be submitted for each clinical trial. Product development can extend over long periods of time and may even be suspended or remain inactive for significant periods of time, whether due to limited financing, changes in

corporate policy, revised strategic plans, or other reasons. While sponsors or manufacturers may find commercial advantage in protecting clinical trial results during this extended period, those advantages must be weighed against the disadvantages of denying access to results information to the research community, healthcare providers, and the public for an extended period.

The proposed 2-year time limitation reflects a balance between the need to protect competitive advantage and the desire for public access to clinical trial results. Within this time frame, a sponsor or manufacturer would often make a decision about whether to initiate another clinical trial or submit a marketing application or premarket notification to the FDA. A subsequent pre-market clinical trial of a drug would likely be an applicable clinical trial that would be registered at ClinicalTrials.gov, making public information about the sponsor's intention to pursue product development. The total delay in disclosure of results of up to 3 years after the completion date would provide sponsors with significant lead time in product development over potential competitors.

(b) Additional results information for applicable clinical trials of unapproved or uncleared devices. Once clinical trial results information is submitted, section 402(j)(3)(G) of the PHS Act requires public posting of that information no later than 30 days after the date of submission (See proposed § 11.52, which implements this statutory requirement). Thus, clinical trial results information for applicable clinical trials of both approved, licensed, and cleared, products and unapproved, unlicensed, and uncleared products will be publicly posted no later than 30 calendar days after submission. Section 402(j)(2)(D)(ii)(I) of the PHS Act requires the clinical trial information submitted upon registration of applicable device clinical trials of devices that have not previously been approved or cleared not be posted earlier than the date on which FDA approves or clears the device studied in the applicable clinical trial. (See section III.C.3. of this preamble.) Therefore the proposed timelines for submitting and publicly posting clinical trial results information in §§ 11.44 and 11.52 may result in the public availability of clinical trial results information for applicable device clinical trials for unapproved or uncleared devices before the information submitted during registration is posted for these same trials.

We believe that posting clinical trial results information without the corresponding public availability of certain descriptive information that is the same type of information that is included as part of registration would fail to provide the necessary context for understanding clinical trial results information and would significantly limit access to and understanding of posted results data. This is why journal articles and other reports of the results of clinical trials routinely include information about the disease or condition and interventions under study, the inclusion and exclusion criteria for participants, the location(s) of the trial, etc. Without such information, results data about patient demographics, outcomes, and adverse events would be uninterpretable and inaccessible. For example, patients and other users typically access clinical trial results by searching for (and retrieving) clinical trials with specific characteristics, e.g., that involve a particular intervention or type of intervention, study a particular disease or condition, recruit certain types of subjects, take place during a particular time period, are conducted in a specific location or particular facility, are sponsored by a particular organization, or match a title or identification number they have found in other public sources. This type of information is not included as part of clinical trial results information under proposed § 11.48(a) but is the same type of descriptive information submitted upon registration, e.g., Brief Title, Intervention Name, Study Start Date, Completion Date.

Similarly, to enhance their understanding of the clinical trial results, researchers, healthcare providers, patients and other users of ClinicalTrials.gov need information about the purpose of the study, its design, the intervention(s) studied, the types of subjects eligible to participate, the duration of the study, and the outcome measures. They need to know whether the clinical trial is completed, if data are still being collected for other outcome measures, or if the clinical trial was terminated prematurely. They need to understand whether information has been submitted for all anticipated outcome measures and corresponds to the outcome measures that the clinical trial was designed to achieve (or did the outcome measures change during the course of the study). They also need information to assist them in comparing results with the results of other clinical trials and with other publicly available information about a clinical trial of interest and other trials. They also need to know whether the clinical trial was reviewed for human subjects protection and who had authority over the conduct of the trial. In addition, they need to know who submitted the information and when it was last verified (i.e., to indicate whether it might be out of date). Such information is not readily available from submitted results information, but is the same type of descriptive information provided during registration, e.g., Primary Purpose, Study Design, Primary Outcome Measure(s), Secondary Outcome Measure(s), Eligibility Criteria, Overall Recruitment Status, Oversight Authorities, Human Subjects Protection Review Board Status, Responsible Party, by Official Title, and Record Verification Date (See proposed § 11.28(a).

Section 402(j)(3)(D)(i) of the PHS Act states that the purpose of granting the Secretary rulemaking authority to expand the results information in the data bank is ''[t]o provide more complete results information and to enhance patient access to and understanding of the results of clinical trials.'' We believe it would be extremely challenging for the public to understand clinical trial results information without having access to certain descriptive information that is the same type of information submitted during trial registration. Thus, to ''enhance patient access to and understanding of the results,'' it is necessary for patients to have access to this descriptive information when clinical trial results information is posted, not only for applicable drug clinical trials of both approved and unapproved drugs (See section 402(j)(2)(D)(i) and section IV.B.5 of this preamble), but also for applicable device clinical trials of both approved or cleared devices and unapproved or uncleared devices.

Section 402(j)(3)(D)(ii)(II) of the PHS Act grants the Secretary discretion in what can be required through rulemaking to be submitted as part of clinical trial results information for applicable device clinical trials of devices that have not been approved or cleared. Specifically, it allows the Secretary to require the submission of results information that is ''described in clause (iii).'' Clause (iii), or section 402(j)(3)(D)(iii) of the PHS Act, states that the regulations ''shall require, in addition to the elements described in [section 402(j)(3)(C)]. . .[s]uch other categories as the Secretary determines appropriate'' (section 402(j)(3)(D)(iii)(IV) of the PHS Act). Thus, for applicable device clinical trials of unapproved or

uncleared devices, the Secretary can require, through rulemaking, submission of not only those results that are required under section 402(j)(3)(C) of the PHS Act, but ''such other categories'' of information as the Secretary determines appropriate.

To ''enhance patient access to and understanding of the results of the clinical trials'' as required by section 402(j)(3)(D)(i) of the PHS Act, we interpret ''such other categories'' of results information for applicable device clinical trials of unapproved or uncleared devices to include, among other things, certain descriptive information that is the same type of information that was required to be submitted under section 402(j)(2)(A)(ii) of the PHS Act. Accordingly, we propose under § 11.48(a)(6) to require responsible parties to submit this descriptive information as part of clinical trial results information for applicable device clinical trials of unapproved or uncleared devices. Because this descriptive information would be defined as part of clinical trial results information, it would be posted no later than 30 calendar days after it has been submitted, pursuant to section 402(j)(3)(G) of the PHS Act. See proposed § 11.48(a)(6) and section IV.C.4(g) of this preamble for a list of proposed required data elements.

Requiring responsible parties for applicable device clinical trials of unapproved or uncleared devices to resubmit information they would have submitted previously to the data bank under proposed § 11.28(a), in order to comply with proposed § 11.48(a)(6), would be inefficient and impose an unnecessary burden on responsible parties. It would also introduce the possibility that information provided at the time of results submission would be inconsistent with the information provided at the time of registration and require the Agency to perform a second quality review of information submitted at registration. To promote efficiency and lessen the burden on responsible parties, we propose to require these responsible parties to fulfill the proposed requirement under § 11.48(a)(6) by affirming in the data bank when submitting clinical trial results information that they are submitting information that is already contained in the databank as part of their submission of clinical trial results information and that such information has been updated as specified in § 11.64(c) and is to be included as clinical trial results information. Once this affirmation is made, the information listed in proposed § 11.48(a)(6) that had been previously submitted to the data bank, would automatically populate the results information data fields and be posted when results information is posted. This proposal would help us ensure that the clinical trial results information necessary ''to enhance patient access to and understanding of the results of clinical trials,'' consistent with section 402(j)(3)(D)(i) of the PHS Act is available to the public.

6. Submission of Non-Technical and Technical Summaries of Trial Results

Section 402(j)(3)(D)(iii)(I) of the PHS Act specifies that the regulations shall require ''[a] summary of the clinical trial and its results that is written in non-technical, understandable language for patients, if the Secretary determines that such types of summary can be included without being misleading or promotional.'' Section 402(j)(3)(D)(iii)(II) of the PHS Act specifies that the regulations shall require ''a summary of the clinical trial and its results that is technical in nature, if the Secretary determines that such types of summary can be included without being misleading or promotional.

We interpret the provisions in sections 402(j)(3)(D)(iii)(I) and (II) of the PHS Act to mean that the proposed regulations are to require the submission of non-technical and technical narrative summaries if such summaries can be produced in such a way that they will not be misleading or promotional to potential users of the data bank. We believe it is necessary to demonstrate that narrative summaries of applicable clinical trials can be consistently produced in a way that will not be misleading or promotional.

If non-technical or technical narrative summaries can be consistently produced without being misleading or promotional, patients, members of the general public, clinicians and researchers might benefit from brief, well-written, accurate, and objective summaries of the results of individual clinical trials. Such summaries might assist the public, clinicians, and researchers in understanding salient information about the characteristics of the participants in a specific applicable clinical trial and the benefits and harms experienced by those participants in that clinical trial. In fact, some users of ClinicalTrials.gov might find narrative summaries easier to understand than the summary results tables. Although summarized evidence from multiple clinical trials and observational studies, when available, would provide a more complete overall picture of a clinical trial's results, summaries of individual trials that are accurate and objective could also be useful, particularly for clinical trials that present the first evidence of benefits and harms for specific products or population groups, based on the experience of participants in that clinical trial.

Another consideration is the optimum format for narrative, non-technical summaries. For example, two existing widely-endorsed and used formats intended for reporting results of individual clinical trials for technical or expert audiences are the CONsolidated Standards for Reporting Trials (CONSORT) Statement [Ref. 31], a checklist of best practices for producing journal articles that report the results of clinical trials of any type of intervention; and the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) topic E3—Structure and Content of Clinical Study Reports (ICH E3) [Ref. 23], a required format for summarizing results of individual clinical trials of drugs in submissions to FDA and to agencies that regulate the use of drugs in other countries. Both of these formats require narratives and data tables, including information that is already submitted to ClinicalTrials.gov to meet the registration and results submission requirements under section 402(j) of the PHS Act.

The CONSORT Statement specifically addresses various ways in which reports of clinical trial results can be misleading and how to avoid these pitfalls, generally by providing additional types of information, such as limitations in trial design, participant populations, etc. The CONSORT Statement strongly recommends ''that at a minimum, authors should discuss the results of their trial in the context of existing evidence. This discussion should be as systematic as possible and not limited to studies that support the results of the current trial. Ideally, we recommend a systematic review and an indication of the potential limitation of the discussion if this cannot be completed'' [Ref. 31]. The ICH E3 format does not specifically address the potential for misleading narratives, but it does emphasize the need to address many specific topics whose omission might lead to a misleading summary, e.g., appropriateness of measurements, statistical analysis plans, determination of sample size, protocol deviations. The ICH E3 guidance document also addresses the importance of context by stating that ''Clinical relevance and importance of the results should be also discussed in light of other existing data'' [Ref. 23].

Another question to be addressed is whether a single, brief summary of an individual clinical trial can provide sufficient background or context to avoid being potentially misleading to a clinician or patient interested in the clinical significance of the results. Individual trials can contain a large number of primary and secondary outcome measures (more than 120 in some submissions to ClinicalTrials.gov), which would make it extremely difficult to prepare succinct summaries without presenting selective information about the outcome measures or adverse events, a process that can introduce bias into the summary. On the other hand, all of the data required in results reporting would be available alongside the technical and non-technical summaries, providing all data on outcome measures. In addition, we rely on publication of clinical trials results through scientific journals so scientists are accustomed to analyzing and reporting often complex data from their clinical trials. ClinicalTrials.gov links to publications where available to provide the user with additional information.

In addition to reviewing the relevant literature, we consulted with the FDA Risk Communication Advisory Committee (meeting summary available at: *http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/RiskCommunicationAdvisoryCommittee/ucm116558.htm*) and considered public comments from the public meeting held in April 2009 [Ref. 1]. We agree with those who commented that further research on this complex issue is warranted. Accordingly, NIH plans to undertake an evaluation to assess the value to the public of such summaries and whether they can be provided in a manner that is objective and not misleading. We are therefore deferring the decision about whether or not to require the submission of narrative summaries. We invite further public comment on methods that we might employ to help answer this question so that we can explore this issue more thoroughly before making a final determination.

Consistent with section 402(j)(3)(A)(ii)(II), NIH will continue to provide links, where possible, from individual clinical trials listed in ClinicalTrials.gov to related peer-reviewed literature and other authoritative information related to the intervention(s) studied or the disease or condition addressed. To avoid potential confusion, such links are indicated to have been added by the Agency and not by the responsible party.

7. Submission of the Full Protocol

Section 402(j)(3)(D)(iii)(III) of the PHS Act provides that the regulations shall require submission of ''[t]he full protocol or such information on the protocol for the trial as may be necessary to help to evaluate the results of the trial.'' This requirement could be satisfied in any of several ways: (1) Requiring submission of additional structured data elements derived from, or describing, the protocol; (2) requiring submission of portions of the final protocol or other narrative information about the conduct of the study that is associated with the protocol (e.g., a statistical analysis plan, if not part of the protocol); or (3) requiring submission of the full protocol at the time of results submission, meaning the final version of the protocol, including all protocol amendments, in a format such as PDF.

Evaluating the results of a clinical trial involves the careful study and appraisal of the clinical trial methodology, so that results can be interpreted and their significance assessed. It can require detailed information about the conduct of a clinical trial, including the methods of participant selection, randomization, and assignment to arms; methods of collecting baseline and clinical trial data; specific information about the interventions used in the clinical trial (e.g., other elements of care that were provided in addition to the specified interventions studied in the clinical trial); and assessment of adverse events. It can also require information on the statistical techniques used to analyze collected results information.

We received comments on submission of protocols at the public meeting in April 2009 [Ref. 1]. At that time, commenters did not know what other registration and results information would be proposed in this NPRM for submission to ClinicalTrials.gov and could not take those requirements into account in their comments. Most comments addressed the question of whether or not to require submission of the full protocol and did not consider other approaches to meeting the statutory requirement in section 402(j)(3)(D)(iii)(III) of the PHS Act. Given the proposals for submission of additional registration and results information detailed in section IV of this preamble, we are not proposing to require submission of the full protocol or other ''information on the protocol.''

We invite public comment on whether the registration and results information that is proposed for submission in this NPRM is sufficient to meet the statutory requirement in section 402(j)(3)(D)(iii)(III) of the PHS Act to provide ''information on the protocol'' as may be necessary to help evaluate the results of the clinical trial or whether submission of additional information, including submission of the full protocol, should be required. Comments should address the relative benefits and burdens of preparing and submitting any additional information and should indicate how such information will help evaluate the results of the clinical trial. We will consider such input in formulating the final rule.

8. Increasing the Time Period for Submitting Results Information

Section 402(j)(3)(D)(iv)(I) of the PHS Act requires that the Secretary determine, by regulation, whether the deadline for submission of clinical trial results information of 1 year after the completion date of the applicable clinical trial—the deadline established in section 402(j)(3)(E)(i) of the PHS Act, which does not apply when a certification for delay is submitted or a request for extension is granted—should be increased from 1 year to a period not to exceed 18 months. The public comments on this matter helped inform our view [Ref. 1]. We believe there is value in making results information for primary outcome measures available within 1 year of the completion date. We therefore have decided not to propose lengthening the deadline for submitting results information, but to propose specific mechanisms for accommodating extended data collection for secondary outcomes to avoiding the premature unblinding of trials.

Proposed § 11.44(a)(1) provides that clinical trial results must be submitted no later than 1 year after the completion date of the clinical trial, unless a certification for delay is submitted or a request for extension is granted. In accordance with the statutory definition in section 402(j)(1)(A)(v) of the PHS Act, the term ''[c]ompletion date'' is defined in proposed § 11.10—for a clinical trial—to mean ''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 pre-specified protocol or was terminated. In the case of clinical trials with more than one primary outcome measure with different completion dates, this term refers to the date upon which data collection is completed for all of the primary outcomes.''

We interpret the phrase ''primary outcome'' to be synonymous with the phrase ''primary outcome measure.'' In the event that clinical trial results data for all pre-specified secondary outcome measures have not been collected by the completion date, proposed § 11.44(a)(2) provides a process for submitting ''partial results'' to the data bank. In particular, the responsible party will remain responsible for submitting results information for each remaining secondary outcome measure until the responsible party has submitted results data, including associated adverse event data, for all pre-specified outcome measures. Such results information must be submitted no later than 1 year after the date on which the final subject was examined or received an intervention for purposes of final data collection for the secondary outcome measure at issue. In cases where results submission under our proposed schedule would necessitate unblinding a trial, and doing so would affect a pre-specified secondary outcome measure, responsible parties should submit a request for an extension of the deadline for good cause, which must contain the elements outlined in proposed § 11.44(e). As discussed in greater detail in section IV.C.3(d) of this preamble, we believe that the need to preserve the scientific integrity of an applicable clinical trial for which data collection is ongoing would, in general, constitute good cause for an extension.

Based on our experience with approximately 1,200 data providers who have submitted results data to ClinicalTrials.gov, 1 year after the completion date of a clinical trial appears to be a reasonable amount of time for electronic data submission. We are aware of other results submission requirements (e.g., in Germany and the European Union) that define completion date as last patient, last visit (LPLV), instead of the final data collection for primary outcome as defined in section 402(j)(1)(A)(v) of the PHS Act. The European Union proposal would require results to be submitted within 6 months of the LPLV date of completion [Ref. 28].

To inform our proposal, we reviewed in the summer of 2009 a set of 230 randomly selected clinical trials registered in ClinicalTrials.gov. We found that about 80 percent of the clinical trials listed a single time frame for all pre-specified primary and secondary outcome measures. In other words, completion date as defined in section 402(j)(1)(A)(v) of the PHS Act and LPLV are identical for most of the clinical trials.

We recognize that many factors, such as rate of participant enrollment, may contribute to when final data are collected for the primary outcome measure. Thus, we propose that the responsible party: (1) As specified in § 11.10(b)(17) provide a reasonable estimate of the completion date upon registering the clinical trial (the Agency interprets ''estimated completion date'' as used in section 402(j)(3)(E)(i)(I) of the PHS Act to be synonymous with ''expected completion date'' as used in section 402(j)(2)(A)(ii)(I)(jj) of the PHS Act); and (2) update the information to indicate the actual completion date in accordance with the time frame established in § 11.64(b)(1)(viii). We note, if the estimated completion date of a clinical trial changes before or during the clinical trial, the responsible party would be required to update estimated completion date information consistent with § 11.64.

Updating the estimated completion date promptly to reflect the actual completion date is important because, as proposed, responsible parties would need to submit clinical trial results information not later than 1 year after the actual completion date (unless they submit a certification for delayed results submission or a request for a good-cause extension is granted). Hence, as described in proposed § 11.64, we propose to require that responsible parties update the completion date in ClinicalTrials.gov not later than 30 calendar days after a change. As with other data elements at ClinicalTrials.gov, all changes to posted information are tracked publicly at the ClinicalTrials.gov archive.

9. Retroactive Submission of Additional Results Information

Section 402(j)(3)(D)(iv)(II) of the PHS Act provides that the Secretary shall, by regulation, determine ''whether the clinical trial information described in [section 402(j)(3)(D)(iii) of the PHS Act] should be required to be submitted for an applicable clinical trial for which the clinical trial information described in [section 402(j)(3)(C) of the PHS Act] is submitted to the registry and results data bank before the effective date of the regulations.'' The clinical trial information described in section 402(j)(3)(D)(iii) of the PHS Act refers to: (1) technical and non-technical narrative summaries of the clinical trial, (2) the protocol or other information on the protocol to help evaluate the results of the trial, and (3) other categories of information as determined to be appropriate by the Secretary.

As explained in sections III.C.6 and III.C.7 of this preamble, we do not propose in this rule a requirement for the submission of technical or nontechnical narrative summaries or for the submission of the full protocol (although we invite public comment on both topics). We propose to require submission of ''other categories of information'' in two situations: When a responsible party submits results for applicable clinical trial of a device that has not been cleared or approved (see section IV.C.4.f of this preamble); and when a responsible party submits results information voluntarily under section 402(j)(4)(A) of the PHS Act. Neither of these situations would apply to clinical trials for which results information is submitted prior to the effective date of the rule because responsible parties would not be required prior to the effective date of the rule to submit results of applicable clinical trials of devices that are not approved or cleared; nor would they be subject to the voluntary submissions provisions in section 402(j)(4)(A) of the PHS Act. Therefore, we do not propose to require the submission of clinical trial information described in section 402(j)(3)(D)(iii) of the PHS Act for an applicable clinical trial for which the clinical trial results information is submitted to ClinicalTrials.gov before the effective date of the regulations. As described in section III.D of this preamble on Effective Date, we do, however, propose to require the responsible party for an applicable clinical trial that reaches its completion date prior to the effective date of the final rule to submit all of the results information specified in proposed § 11.48 if the responsible party has not submitted results information prior to the effective date of the rule. Requiring the submission of this information would improve the uniformity and consistency of information available in the data bank for applicable clinical trials.

10. Standard Data Formats

Section 402(j)(3)(D)(v)(I) of the PHS Act provides that regulations regarding the submission of expanded results information shall also establish ''a standard format for the submission of clinical trial information under [section 402(j)(3)(D)(v)(I) of the PHS Act] to the registry and results data bank.'' Proposed § 11.48 of this proposed rule implements standard data formats for results information, including adverse event information, taking into consideration comments made at the public meeting [Ref. 1].

As discussed in sections II.B and III.C.12 of this preamble, NLM is adopting a tabular, structured data entry

system to promote objective reporting, optimize data display, permit effective searching of ClinicalTrials.gov, and facilitate cross-trial comparisons. To the extent possible, our proposal for submitting adverse event information is consistent with ICH–E3 formats (see *http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM073113.pdf*) and Body Organ System Class for grouping adverse events by organ system, as required by the statutory default provisions in section 402(j)(3)(I)(iii) of the PHS Act. We have developed a mechanism for uploading results data in an automated electronic fashion using eXtensible Markup Language (XML) files. We do not believe that uploads of data tables in other formats will allow for the comparability and consistency desired across trials and do not include such a mechanism in our proposal.

11. Additional Information to Improve Patient Understanding of Submitted Information

Section 402(j)(3)(D)(v)(II) of the PHS Act requires that the regulations establish ''additional information on clinical trials and results that is written in nontechnical, understandable language for patients[.]'' We interpret this provision to mean, in part, that the regulations must specify additional expanded results information that responsible parties would be required to submit to ClinicalTrials.gov to assist patients in understanding and interpreting other submitted clinical trial information.

As discussed elsewhere in this preamble (see sections III.C.2 and III.C.15) and in several sections of this proposed rule, we propose additional data elements or types of information that responsible parties must submit to enhance the interpretability of submitted information related to registration and results, including adverse events. In developing the proposed regulation, we took into account numerous suggestions that were made at the public meeting about resources that could be included in the data bank to assist patients in understanding and interpreting information in the data bank [Ref. 1].

Although section 402(j)(3)(D)(v)(II) of the PHS Act does not require the Agency to develop and provide additional information in ClinicalTrials.gov to assist users in better understanding and interpreting the submitted clinical trial information, we have paid careful attention to comments about how the ClinicalTrials.gov Web site might be improved. ClinicalTrials.gov already contains site-level resources to assist patients and other users in obtaining and understanding information on clinical trials in the data bank, e.g., FAQs on understanding clinical trials, a glossary of clinical trial terms, and an introduction that describes the general purpose and content of the data bank and cautions that the information should be used in conjunction with advice from healthcare professionals. In addition, each clinical trial record contains links to definitions that explain to the public standard terms such as ''condition'' and ''intervention;'' and, where it exists, to information at select consumer health Web sites that is relevant to the clinical trial. Such information includes: resources related to the conditions being studied, from MedlinePlus (*http://www.nlm.nih.gov/medlineplus/*) and the Genetics Home Reference (*http://ghr.nlm.nih.gov/*); resources related to the intervention(s) being investigated, from the NLM Drug Information Portal (*http://druginfo.nlm.nih.gov/*) and FDA's Web site (*www.fda.gov*); and publications related to the clinical trial, including freely available abstracts if available, from PubMed (*http://www.ncbi.nlm.nih.gov/pubmed/*). As noted in section III.C.6 of this preamble, we intend to add links from clinical trial records to other sources of related, authoritative health information (e.g., information from government sources and/or peer reviewed publications). Such information will be labeled as being added by NLM.

12. Quality Control Procedures

Section 402(j)(3)(D)(v)(III) of the PHS Act provides that the regulations shall also establish procedures for quality control ''with respect to completeness and content of clinical trial information,'' including using representative samples, in order ''to help ensure that data elements are not false or misleading and are non-promotional[.]'' In developing such procedures, the Agency is to consider the experience gained through the pilot quality control project, described in section 402(j)(5)(C)(i) of the PHS Act. The pilot quality control project is ''to determine the optimal method of verification to help ensure that the clinical trial information submitted under . . . [section 402(j)(3)(C) of the PHS Act] is non-promotional and is not false or misleading in any particular . . .'' (See section 402(j)(5)(C)(i) of the PHS Act). Comments submitted to the docket and discussed at the public meeting also have been considered in developing the quality control procedures [Ref. 1].

We note that Section 801(d)(2) of FDAAA includes a Rule of Construction, which states that the ''submission of clinical trial information, *if submitted in compliance* with [section 402(j) of the PHS Act], that relates to the use of a drug or device not included in the official labeling of the approved drug or device shall not be construed by the Secretary of Health and Human Services or in any administrative or judicial proceeding, as evidence of a new intended use of the drug or device that is different from the intended use of the drug or device set forth in the official labeling of the drug or device.'' Public Law 110–85, section 801(d)(2) (emphasis added). Section 801(d)(2) further states that the availability of clinical trial information through the data bank, if submitted in compliance with such subsection, shall not be considered as labeling, adulteration, or misbranding of the drug or device under the FD&C Act.

Consistent with many of the comments we received, we have designed the ClinicalTrials.gov results submission system to encourage objective reporting. As discussed in section III.C.10 of this preamble, the tabular, structured data entry system developed for ClinicalTrials.gov promotes objective reporting, optimizes the data display and permits effective searching of the data bank. In addition, as discussed in section III.C.6 of this preamble we have not included a proposed requirement to submit non-technical and technical narrative summaries of the results of a clinical trial. We intend to study this issue further and are inviting additional public comment on it. At present, procedures for quality control relate to the review of structured data that would be required to be submitted to ClinicalTrials.gov under this proposed rule.

(a) Pilot Quality Control Project. As a preliminary step toward satisfying the required pilot quality control project under section 402(j)(5)(C)(i) of the PHS Act, we conducted a quality control study that consisted of two parts as follows: (1) review of the results of more than 4,500 clinical trials submitted under section 402(j)(3)(C) of the PHS Act after September 27, 2008; and (2) an initial validation study of the ClinicalTrials.gov results data bank, conducted under contract by researchers at the Oregon Health Science University [Ref. 32].

The first part of the quality control study led to the development of detailed quality review criteria [Ref. 33, 34].

Since the launch of the ClinicalTrials.gov results data bank, each submission of results information has been reviewed for apparent validity, meaningful entries, logical and internal consistency, and formatting. We have tried to ensure that submitted results information is objective and contains no comments about conclusions, clinical implications, or comparisons with other studies or other data. Table 1 lists common types of errors, deficiencies and inconsistencies with specific examples that were seen during this time period. Data submitters were notified of errors, deficiencies and/or inconsistencies found during this first part of the quality control study and asked to revise their submissions. During this period, clinical trial results information was not posted in ClinicalTrials.gov until the errors, deficiencies and/or inconsistencies identified by the quality review had been addressed by responsible parties. In some cases, corrected information was not provided until more than 30 days had passed from the initial submission.

To assist responsible parties in avoiding such errors, deficiencies and inconsistencies, we developed and continue to refine documentation explaining how to meet the quality review criteria; identified and compiled lists of frequent errors, deficiencies and inconsistencies in submitted results information; and provided system support to help responsible parties minimize such errors, deficiencies and inconsistencies. We also have provided intensive user support for responsible parties who are new to the online results submission process, whether through data entry using Web-based forms or automated uploading of data files. We have developed and posted draft educational materials, such as tips on improving results submissions and ways to avoid common errors, deficiencies and inconsistencies observed in submissions to date. All such documents are available at *http://prsinfo.clinicaltrials.gov/fdaaa.html.* We will continue to provide support to responsible parties and, based on these interactions, develop new or updated materials in order to facilitate and streamline preparation of results data for submission to ClinicalTrials.gov and to help ensure that the submissions meet the quality review criteria.

TABLE 1—SOME COMMON TYPES OF ERRORS, DEFICIENCIES AND INCONSISTENCIES IDENTIFIED IN RESULTS SUBMISSIONS

Data quality category	Description	Example	Explanation
Lack of apparent validity	Data not plausible based on information provided.	Outcome measure indicating a mean value of 263 hours per day of sleep.	Measure of mean hours per day can only have values in the range of 0–24. Value of ''263'' is not valid.
Incomplete Information	Information insufficient to convey intended meaning.	Outcome measure description states ''clinical evaluation of adverse events, laboratory parameters and imaging''; data reported as 100 and 96 participants, in each arm.	Data are uninformative. Unclear to what counts of 100 and 96 participants refer. Outcome measure description not sufficiently descriptive to understand specific outcome.
Incomplete information	Information insufficient to convey intended meaning.	Outcome measure assessed on a scale, which is not explained; data reported as mean values of 3.2 and 4.1 in the two arms.	Data are uninformative without an explanation of what the scale is assessing and the range and direction of scores (e.g., whether 3.2 is better or worse than 4.1 on a 5-point scale).
Internal inconsistency	Data not consistent with descriptive information.	Outcome measure title is ''time to disease progression;'' data reported as 42 & 21 participants, in each arm.	A time-to-event measure requires a unit of time such as days or months.
Internal inconsistency	Data in one section are not consistent with data in another section.	Baseline characteristics & participant flow entered as 2-armed study with a total of 400 participants; outcomes entered for 3 arms with 600 participants.	If there is a third group, then Baseline Characteristics and Participant Flow modules must reflect this or group descriptions in Outcomes should explain their origin.

These efforts have produced significant improvements in the quality of initial submissions of results information to ClinicalTrials.gov. Whereas in 2008 only 5 percent of submissions met the quality review criteria when first submitted, by 2012 approximately 36 percent of initial submissions met the quality review criteria. Improvements in the percentage of initial results submission that meet our quality review criteria may be a consequence of three factors: (1) greater familiarity among responsible parties and sponsors with the system and the associated rules, (2) better resource materials from ClinicalTrials.gov, and (3) growing awareness that the task of entering results requires involvement of personnel with a full understanding of the trial design and results. The number of responsible parties submitting data has increased each quarter.

The second part of the quality control study compared the consistency of posted results information for phase 3 or 4 clinical trials of drugs that were completed prior to January 1, 2009 and had submitted results by November 17, 2010 with results information published in peer reviewed journals and documents made publicly available on the FDA Web site, such as medical reviews. A publication was identified for only 32 percent of the 342 trials that were sampled, and in 82 percent of the publication-trial pairs at least one discrepancy was found between the data submitted to ClinicalTrials.gov and the data contained in the peer-reviewed journal article. Discrepancies occurred in almost all fields analyzed, including number of arms, primary and secondary outcome measures (the name of the measure as well as the actual data), total enrollment, and number of serious adverse events. In cases where the publication addresses a subset of the data in the trial, the apparent discrepancies could be correct reflections of the clinical trial results for the population covered [Ref.38].

The study results demonstrate that comparisons with publications cannot be used in real time to validate results submissions to ClinicalTrials.gov. For the great majority of clinical trials, no publications are available for comparison at the time results are submitted to the data bank. In addition, for clinical trials of products that have not been approved, licensed, or cleared, or for which a new indication is being

studied but has not yet been approved, licensed, or cleared, information about the clinical trial ordinarily is not available on FDA's Web site at the time results are submitted to ClinicalTrials.gov. Thus, we do not believe that comparisons with publications or FDA documents would provide a feasible or effective method of routinely screening submitted clinical trial records with results to help ensure that the clinical trial information is non-promotional and not false or misleading in any particular.

As required by section 402(j)(5)(C)(i), we plan to continue conducting the pilot quality control project in coordination with the Commissioner of Food and Drugs until the effective date of this regulation to determine the optimal method of verification to help ensure that the clinical trial information submitted under section 402(j)(3)(C) of the PHS Act is non-promotional and is not false or misleading in any particular. In addition, we will continue to use comparisons with random samples of publications or public FDA documents to identify problems and improve our procedures. In addition, if we become aware of a publication or FDA document that appears to contain information that is inconsistent with a submitted clinical trial record, we will consult with FDA on the appropriate next steps.

(b) Proposed Quality Control Procedures. Based on the public comments we received, experience with the preliminary steps of the pilot quality control project, and consistent with current practice, we intend to continue a form of quality control at the time of clinical trial registration or submission of clinical trial results information that is similar to the procedures we have been using for the past several years. The quality control process will not affect the statutory deadlines for submitting or publicly posting submitted clinical trial information.

Our quality control process cannot determine the veracity of the data submitted, and all entries in ClinicalTrials.gov will carry a disclaimer to that effect. Our quality control process is intended to help ensure that clinical trial information posted on ClinicalTrials.gov has face validity and is free from obvious errors. The identification of two or more data elements within a clinical trial record that are internally inconsistent is an effective method of identifying errors since, by logic, both pieces of data cannot be correct. By providing responsible parties with information as to which elements of submitted clinical trial information do not meet specified quality review criteria, we can better facilitate access by the public to information that is not obviously incomplete, incorrect, or inconsistent.

Overall, our proposed quality control process for submission of clinical trial registration information or clinical trials results information will consist of two sequential components as follows: (1) an automated system-based check, followed by (2) a detailed, manual review. In the first component, the ClinicalTrials.gov system would alert responsible parties to machine-detectable errors in the data entered (e.g., certain types of missing information that is required, certain types of impossible values, certain types of internally inconsistent data). The number of automated checks the system performs has increased over time as we have gained experience with the types of errors that occur and devised additional automated rules for detection. We will continue to refine the automated checks in order to assist submitters in detecting and minimizing errors, deficiencies, and inconsistencies in the information they are submitting.

Once clinical trial information has passed the automated checks and been submitted, we would begin the second component of quality control: the detailed, manual review. We would review all data submissions that pass the automated system checks in order to identify, based on detailed quality review criteria, additional apparent errors, deficiencies, or inconsistencies that are not detected by the automated checks. If problems are identified in the detailed, manual review, we would send an electronic notification to the responsible party, indicating that the submission contains apparent errors, deficiencies and/or inconsistencies listing the errors, deficiencies and/or inconsistencies found, and requesting correction. Consistent with the proposal in § 11.66 regarding correction of clinical trial information, responsible parties would be required to correct the errors, deficiencies and/or inconsistencies not later than 15 calendar days after being informed of them by the Agency or otherwise becoming aware of them (e.g., if they discover the errors, inconsistencies, and/or deficiencies themselves), whichever is later. (See the discussion of the corrections provision in section IV.D.4 of this preamble).

We expect to complete the quality control process and to receive submissions of corrected clinical trial information prior to the deadlines for posting such information publicly, as established by sections 402(j)(2)(D) and 402(j)(2)(G) of the PHS Act. We recognize that in some situations, the quality review process may not be completed prior to the statutory posting deadlines, and we will have to post submitted information that has not been corrected. Clinical trial information posted without having completed the quality control review and any necessary correction by the responsible party will include a statement indicating that it has not completed the quality control process. Users searching ClinicalTrials.gov will be able to elect to include or exclude clinical trial registrations or clinical trial results information that have not yet completed the quality control process proposed in this NPRM. When revised information correcting the noted errors has been submitted and the revised information has passed the quality control process, the statement that the clinical trial record has not completed the quality control process would be removed from the posted record. However, the information that was initially posted prior to completion of the quality control review would appear in the archived history for that clinical trial entry, and the archived version would indicate that it had been posted with a notice. The electronic notification sent to the responsible party would inform responsible parties of these facts.

We believe additional precautions must be taken with clinical trial registration information that has not completed quality review. Clinical trial registration information may be used by patients and healthcare providers who are considering enrollment in a clinical trial. Although we will post information submitted when clinical trials are registered consistent with the time frames in section 402(j)(2)(D) of the PHS Act and with the statement described above, we will not assign an NCT number until information submitted has completed our quality control process. Thus, if the quality control process and any necessary data correction by the responsible party have not been completed within calendar 30 days after an applicable drug clinical trial has been registered, the information submitted will be posted without an NCT number. This approach is consistent with the practice that has been in effect since ClinicalTrials.gov was launched in 2000. This approach would ensure that the existence of an NCT number for a specific clinical trial remains an indicator both that a publicly posted clinical trial has been registered and that the registration of the clinical trial has gone through the proposed two-stage quality control process. Use of NCT numbers is

required in certain submissions to FDA and in reports to NIH and other HHS agencies from relevant grantees and contractors as evidence that clinical trials have been publicly registered, as required by section 402(j) of the PHS Act, and by other stakeholders, including journal editors, as evidence of public disclosure of certain protocol information. In our experience in operating the registry component of ClinicalTrials.gov, we have found that clinical trial registration information can be reviewed quickly and that responsible parties can submit corrected information in a matter of days.

Other elements of quality control are described in proposed § 11.66 and section IV.D.4 of this preamble. We recognize that clinical trial data elements that are submitted as free-text could be phrased in a manner that might be considered promotional or misleading. We solicit comment on ways in which the descriptions of the data elements in the proposed codified could be improved to help ensure that submitted clinical trial information is not promotional or misleading. We also seek comment on standards we could use for determining when clinical trial information should be considered to be promotional. Finally, we solicit comment regarding how the pilot quality control project may help ensure that the clinical trial information submitted under paragraph (j)(3)(C) is non-promotional and not false or misleading under paragraph (j)(5)(D).

We note that compliance with our quality control process, including the requirements set forth in § 11.66, does not necessarily constitute a legal defense to enforcement pursuant to section 301(jj) of the FD&C Act (21 U.S.C. 331) and 303(f) of the FD&C Act (21 U.S.C. 333(f)).

13. Updating Submitted Clinical Trial Information

Section 402(j)(3)(D)(v)(IV) of the PHS Act provides that the regulations shall also establish ''the appropriate timing and requirements for updates of clinical trial information, and whether and, if so, how such updates should be tracked.'' Section 402(j)(4)(C) of the PHS Act, separately requires responsible parties to submit updates of clinical trial registration information to ClinicalTrials.gov not less than once every 12 months (except for certain specified data elements for which more rapid updates are required), and the Director to post such updates publicly in the data bank. With regard to the requirement in section 402(j)(3)(D)(v)(IV) of the PHS Act to establish, by regulation, ''the appropriate timing and requirements for updates of clinical trial information . . .,'' we interpret the term ''clinical trial information'' to mean both information submitted when a clinical trial is registered and clinical trial results information, consistent with the definition of ''clinical trial information'' in section 402(j)(1)(A)(iv) of the PHS Act. In addition, our proposed requirements for updates apply to adverse event information because adverse event information is deemed to be clinical trial results information under section 402(j)(3)(I)(v) of the PHS Act. Our proposals take into consideration comments made at the public meeting [Ref. 1].

Proposed § 11.64(a)(1) provides that, in general, updates of clinical trial information must be provided every 12 months, unless there are no changes during the previous 12 months. Proposed § 11.64(a)(2) specifies that a responsible party must submit updates until the final clinical trial results information has been submitted for all primary and secondary outcome measures and all adverse events collected in accordance with the protocol. After all such results information has been submitted, a responsible party's obligation to update the record would end unless and until the responsible party becomes aware of errors in the submitted clinical trial information. In that case, the responsible party would need to submit corrected information as specified in proposed § 11.66.

Proposed § 11.64(b) identifies several data elements that must be updated not later than 30 days after a change occurs (e.g., Overall Recruitment Status and Availability of Expanded Access), requires updates to U.S. FDA Approval, Licensure, or Clearance Status not later than 15 calendar days after the change occurred, and specifies that if a protocol is amended in such a manner that changes are communicated to participants in the clinical trial, updates to relevant clinical trial information must be submitted no later than 30 calendar days after the protocol amendment is approved by the human subjects protection review board. A responsible party would also be required to update the Record Verification Date any time the responsible party reviews the complete clinical trial record for accuracy, even if no other updates are submitted at that time. The above exceptions to the 12-month period for updates are considered important for patients using the data bank to search for clinical trials for which they might qualify and for the Agency in administering other provisions of section 402(j) of the PHS Act. In addition, proposed § 11.64(c) would require a responsible party to update, as necessary, any previously submitted clinical trial information at the time results information is submitted to ClinicalTrials.gov (the responsible party would then be required to update the Record Verification Date data element). Doing so will improve the accuracy of information that is used by ClinicalTrials.gov to automatically prepopulate some elements of results information. Further discussion of these update requirements appears in the description of proposed § 11.64 in section IV of this preamble.

As set forth in proposed § 11.64(d)(2), all prior clinical trial information, including past updates of posted submissions, are tracked in the ClinicalTrials.gov archive, in which the full history of changes to clinical trial information for any clinical trial is accessible to the public. Note that, as discussed in section III.C.13 of this preamble, the time frames for updating registration and results information do not apply to corrections of errors, corrections of falsified data, and other corrections of clinical trial information, which should be made in accordance with the time frames proposed in § 11.66. (See section 402(j)(5)(D)(i) of the PHS Act.)

14. Statement To Accompany Certain Trials and Other Issues Related to Voluntary Submissions

Section 402(j)(3)(D)(v)(V) of the PHS Act provides that the regulations shall also establish ''a statement to accompany the entry for an applicable clinical trial when the primary and secondary outcome measures for such clinical trial are submitted under paragraph (4)(A) [voluntary submissions] after the date specified for the submission of such information in paragraph (2)(C)[.]'' Some applicable clinical trials are not subject to mandatory registration or submission of results information because they were not initiated after, or ongoing as of, the dates established in section 402(j)(2)(C) of the PHS Act (i.e., 90 days after the date of enactment of FDAAA). They would be considered ''submitted under paragraph (4)(A)'' if the responsible party submits the information voluntarily to ClinicalTrials.gov or if the responsible party is required to submit the information under section 402(j)(4)(A) of the PHS Act because the applicable clinical trial is included in a marketing application or premarket notification submitted to FDA. Submitted information might consist of

registration information and/or results information. We interpret section 402(j)(3)(D)(v)(V) of the PHS Act to require a statement to be posted with the clinical trial registration and/or the results information for such applicable clinical trials because primary and secondary outcome measures are required at the time of both registration and submission of results information. See 402(j)(2)(A)(ii)(ll) and (3)(C)(ii) of the PHS Act.

We note that for applicable clinical trials subject to section 402(j)(4)(A) of the PHS Act, it would be permissible for information about the primary and secondary outcome measures to be submitted after the deadline established for clinical trial registration under section 402(j)(2)(C) of the PHS Act. We interpret section 402(j)(3)(D)(v)(V) of the PHS Act to require a statement that clarifies that the submission was not subject to the deadlines imposed by section 402(j) of the PHS Act for clinical trial registration and submission of results information. Such a statement would be valuable in demonstrating to users of ClinicalTrials.gov that the submitted information is not out-of-compliance with the statutory deadlines for submitting information about the primary and secondary outcomes. Some commenters recommended specific language for the statement to accompany these voluntary submissions (Ref. 1).

We propose in § 11.60(b) that the following statement accompany each applicable clinical trial for which clinical trial information is submitted voluntarily to ClinicalTrials.gov under section 402(j)(4)(A) of the PHS Act or proposed § 11.60(a): ''Clinical trial information for this applicable clinical trial was submitted under section 402(j)(4)(A) of the Public Health Service Act and 42 CFR 11.60 and is not subject to the deadlines established by sections 402(j)(2) and (3) of the Public Health Service Act or 42 CFR 11.24 and 11.44.'' Proposed § 11.60 provides that a responsible party may voluntarily submit complete clinical trial information for trials of FDA-regulated drugs or devices that are not applicable clinical trials, such as phase 1 trials, but only if certain conditions are met. If a responsible party registers or submits clinical trial results information voluntarily for such a clinical trial, section 402(j)(4)(A) of the PHS Act requires that such information be complete, and that clinical trial information be submitted with respect to certain ''triggered'' applicable clinical trials. These requirements are discussed further in section IV.D.1 of this preamble.

15. Adverse Event Information

Section 402(j)(3)(I)(i) of the PHS Act requires the Secretary, by regulation, to ''determine the best method for including in the registry and results data bank appropriate results information on serious adverse and frequent adverse events for applicable clinical trials . . . in a manner and form that is useful and not misleading to patients, physicians, and scientists.'' Such regulations are to be issued not later than 18 months after the date of enactment of FDAAA (i.e., by March 27, 2009). Section 402(j)(3)(I)(ii) of the PHS Act specifies that if such regulations are not issued by the date that is 24 months after the date of the enactment of FDAAA (i.e., by September 27, 2009), a set of default provisions in sections 402(j)(3)(I)(iii)(I) and (II) of the PHS Act (referred to hereinafter as ''the statutory default provisions'') take effect. The statutory default provisions require submission of two tables of information, as follows: (1) ''A table of anticipated and unanticipated serious adverse events grouped by organ system, with number and frequency of such event in each arm of the clinical trial'' (section 402(j)(3)(I)(iii)(I) of the PHS Act), referred to hereinafter as the ''serious adverse events table''; and (2) ''A table of anticipated and unanticipated adverse events that are not included in the [serious adverse events] table . . . that exceed a frequency of 5 percent within any arm of the clinical trial, grouped by organ system, with number and frequency of such event in each arm of the clinical trial'' (section 402(j)(3)(I)(iii)(II) of the PHS Act). In this proposed rule and in ClinicalTrials.gov, we refer to adverse events that do not fit the definition of a serious adverse event as ''other adverse events,'' and we refer to the adverse event table in (2) as the ''other adverse events table.''

The statutory default provisions set forth in sections 402(j)(3)(I)(iii)(I) and (II) of the PHS Act became mandatory as of September 27, 2009. For a year prior to this date, responsible parties were able to submit adverse event data voluntarily and adjust the threshold for other adverse events to the level of their choice. Such an approach allowed us to test whether frequency thresholds other than 5 percent were better suited to the submission of information about other adverse events and might constitute the ''best method'' for submitting information about other adverse events. Responsible parties were also able to submit comments on the way ClinicalTrials.gov collected adverse event information so that we could improve the design and implementation of the system. [*See:* Docket NIH–2009–0002]

Our proposal for submitting adverse event information in § 11.48(a)(4) is based on the statutory default provisions in sections 402(j)(3)(I)(iii)(I) and (II) of the PHS Act, with some modifications. We believe that the Secretary has authority to modify the statutory default provisions by regulation under section 402(j)(3)(D)(v)(VI) of the PHS Act, which specifies that the regulations shall establish ''additions or modifications to the manner of reporting of the data elements established under [section 402(j)(3)(C) of the PHS Act].'' Section 402(j)(3)(I)(v) of the PHS Act deems adverse event information to be ''clinical trial information included in [the] data bank pursuant to . . . [section 402(j)(3)(C) of the PHS Act],'' and we believe that this clinical trial information is coextensive with the ''data elements established under . . . [section 402(j)(3)(C) of the PHS Act][,]'' referred to in section 402(j)(3)(D)(v)(VI) of the PHS Act. Therefore, we conclude that the Secretary has authority, under section 402(j)(3)(D)(v)(VI) of the PHS Act, to modify the statutory default provisions for submission of adverse event information via regulation, provided that such modifications represent ''additions or modifications to the manner of reporting [adverse event information] . . .''

We propose to maintain the requirement under the statutory default provisions in sections 402(j)(3)(I)(iii)(I) and (II) of the PHS Act to submit two tables of information summarizing anticipated and unanticipated adverse events that were collected in accordance with the protocol, i.e., one table for all serious adverse events and one table for other adverse events that exceed a frequency of 5 percent within any arm of the trial. We would continue to allow the submission of other adverse events with a frequency of less than 5 percent on a voluntary basis, as many data submitters have continued to do. Consistent with the statutory default provisions, our proposal would require submission of information on all such adverse events, not only those that are unanticipated or considered attributable to interventions studied in the clinical trial, to the extent that the collection of these data was specified in the protocol for the trial. By including information on adverse events, regardless of whether or not they were considered anticipated or attributed to the intervention(s) studied in the clinical trial, ClinicalTrials.gov would provide an

objective summary of the adverse events that were collected during the trial.

We do not intend for our proposal to cause an investigator to collect adverse event information of a type or in a way that is not specified in the protocol. For clinical trials for which the protocol specifies collection of only a limited set of adverse events (e.g. unanticipated adverse reactions), we would require the responsible party to submit to ClinicalTrials.gov a summary of the information that was collected during the clinical trial about serious adverse events and other adverse events that exceed a frequency of 5 percent within any arm of the trial. In addition, as specified in proposed § 11.48(a)(4)(ii)(H), we would require the responsible party to describe how the types of adverse events collected in the clinical trial differ from the types of adverse events and serious adverse events defined in proposed § 11.10. We believe this proposal would provide responsible parties with a convenient means of submitting required adverse event information without causing them to collect and submit information that is not specified in the protocol. It would also permit users of ClinicalTrials.gov to understand how submitted adverse event information differs in scope and kind from the adverse event information defined in this part.

Implementing the statutory default provisions for adverse event information entails an interpretation of the requirement to submit information describing the ''number and frequency'' of adverse events. Sections 402(j)(3)(I)(iii)(II) and (III) of the PHS Act do not specify whether the number and frequency of adverse events refer to the number of participants who experience an adverse event and the frequency relative to the number of participants assessed for that adverse event (i.e., the number of participants who were ''at risk'' for experiencing that adverse event) or to the absolute number of adverse events or occurrences, independent of the number of participants involved. When an adverse event occurs only once in a participant, the two methods of summarizing adverse event data are equivalent (i.e., the number of participants experiencing an adverse event is equal to the number of events that occurred). However, when an adverse event occurs multiple times in a single participant, information about the number of adverse events without information about the number of affected participants could be confusing. For example, if the submitted information indicates that 20 headaches occurred in an arm with 100 participants, it would be unclear how many participants experienced headaches: the number could range from as many as 20 participants with one headache each to as few as one participant with 20 headaches.

We interpret the statutory default provisions to require submission of information about the number of participants who experienced an adverse ''event'' and the total number of participants at risk for the adverse event. This interpretation is consistent with existing conventions for summarizing adverse event information (e.g., CONSORT Statement on Harms) and supports the important objective of summary results submission, which is to allow users to compare the number of participants who may have benefited from a particular intervention with the number who experienced adverse events during a trial. Consistent with requirements in effect at ClinicalTrials.gov since September 2009, we propose that responsible parties submit both the number of participants who experienced an adverse event and the total number of participants at risk for the adverse event. ClinicalTrials.gov provides features to simplify submission of the number at risk (e.g., when the number at risk is the same for all adverse events submitted) and would use this information in combination with the number of participants affected to compute the frequency automatically.

We also believe there is value in making information available about the number of adverse events. Since September 2009, responsible parties have had the option of voluntarily submitting the total number of occurrences of each adverse event in addition to the number of participants affected. Many responsible parties have submitted this information voluntarily; nearly half of the results submitted in 2012 for clinical trials that appear to meet the definition of applicable clinical trials included the total number of occurrences for adverse events. We will continue to provide a mechanism for responsible parties to voluntarily provide event level information for adverse events.

We considered, but do not propose, requirements for responsible parties to provide the total number of occurrences of each serious adverse event and the number of such occurrences considered, as of a specific date, to be attributable to the intervention(s) under study. Participants in many clinical trials have serious conditions that cause adverse events; they are also subject to the accidents and other unpredictable health events that affect the general population. During the course of a clinical trial, participants may die or suffer other serious adverse events due to causes that are unrelated to the interventions they are receiving as part of the clinical trial. Evaluating whether a specific adverse event is likely to have been caused by an intervention studied in the clinical trial can be valuable while the clinical trial is ongoing and data are still being collected because it can lead to modifications in the clinical trial to better protect the human subjects. The value of attribution at the level of an individual adverse event is less certain after a clinical trial has completed and all clinical trial data have been collected. The determination of attribution is, by its nature, subjective, influenced by various biases, and can change over time within a given clinical trial. The ''gold standard'' for assessing possible causal relationships between an adverse event (or a series of adverse events) and an intervention after completion of a clinical trial is an empirical comparison of the adverse events that occurred in different arms of the clinical trial. Because adverse event information would be submitted to ClinicalTrials.gov after completion of a clinical trial (as long as three years after the completion date if the responsible party submits a certification for delayed results submission), we do not propose a requirement for including attribution information. We invite public comment on any aspect of this issue, as well as information about current practices for attribution of serious adverse events that might help us to refine proposed requirements for submission of adverse event information.

To further assist users in understanding and interpreting submitted adverse event information, we propose to require the submission of additional information, based on our experience in operating ClinicalTrials.gov to-date. Some of this information is already collected on a voluntary basis in ClinicalTrials.gov, and some has been required since September 2009, but one data element is new.

We propose to continue to require responsible parties to submit information about adverse events by organ class for each arm and for each table (serious adverse events and other adverse events), as required by the statutory default provisions in section 402(j)(3)(I)(iii)(I) and (II) of the PHS Act. We propose to require responsible parties to use the organ system classes specified in the Medical Dictionary for Regulatory Affairs (MedDRA) (*http://www.meddramsso.com/*) to classify the specific adverse event terms (e.g., nausea) by organ system. Our

experience with voluntary and mandatory adverse events submission since September 2008 indicates that responsible parties are able to use these classes effectively and that a single set of organ system classes provides a consistent way to display information about adverse events between tables for a trial and across trials.

We also propose to require responsible parties to submit the total number of participants affected by an adverse event at the organ system level. This information would be required for each arm of the clinical trial and for each adverse event table (serious adverse events and other adverse events). Section 402(j)(3)(I)(iii) of the PHS Act requires the listing of adverse events by organ system. We believe that one purpose of this provision is to enable comparisons across arms even when there are variations in the level of specificity or granularity of the data submitted. Unless the total number of participants with adverse events is provided at the level of the organ system, the serious adverse event and other adverse event tables will not be able to support such comparisons. For example, if one trial lists 5 participants with ''rash'' under the ''Skin and subcutaneous tissue disorders'' organ system category and another lists 2 participants for each of three specific types of rashes under the same category, it is not possible to know which trial had more participants with adverse events affecting the skin, because certain participants in the second trial could have suffered more than one type of rash. Thus, in order to obtain an important benefit of listing adverse events by organ system, we believe that it is necessary to require responsible parties to submit the total number of participants affected by any adverse event within each organ system for which adverse event data were collected. For organ systems that do not have a submitted adverse event, ClinicalTrials.gov will automatically assume that the total number of participants affected by that organ system is 0 (zero) for serious adverse events, and less than the 5 percent threshold for other adverse events, which will reduce the burden of this proposed requirement.

We also propose to continue to require responsible parties to submit information about the total number of participants affected by any adverse event for each arm in each table. As described earlier in this section, it is our view that this information permits better interpretation of the adverse event data by clearly presenting how many participants were affected by any adverse event in a given arm of the clinical trial.

We also considered, but do not propose to require submission of several other types of information describing the collection of adverse events in a clinical trial. Responsible parties are currently able to submit some of this information voluntarily. We invite public comment on the potential benefit and burden of requiring that the following types of information be submitted to ClinicalTrials.gov. We will consider comments in preparing the final rule.

Time frame: Time frame information would specify when during the clinical trial adverse event information was collected. Information on different types of adverse events may be collected during different time frames in a clinical trial. Some adverse events are recorded only during specific portions of the trial, while others may be recorded throughout the duration of the trial [Ref. 35, 36, 37]. Time frame information could assist users of ClinicalTrials.gov in interpreting correctly and comparing the relative occurrence of adverse events across different clinical trials. Submission of this information is currently optional. Responsible parties provided time frame information with more than half of the results information submitted in 2012 for probable applicable clinical trials.

Collection approach: Collection approach information would indicate the type of approach taken to collect adverse event information, either ''systematic assessment'' or ''non-systematic assessment.'' Systematic assessment involves use of a specific method of ascertaining the presence of an adverse event, e.g., the use of checklists, questionnaires, or specific laboratory tests at regular intervals. Non-systematic assessment relies on spontaneous reporting of adverse events, such as unprompted self-reporting by participants. The approach used to assess adverse events affects comparability of information across clinical trials. For example, clinical trials using non-systematic assessment typically will record fewer adverse events than those using systematic assessment [Ref. 37]. Therefore, knowledge of the type of approach used to identify adverse events may help users of ClinicalTrials.gov to interpret differences in the rates of adverse events in different clinical trials. Submission of assessment type information currently is optional in ClinicalTrials.gov. Responsible parties who choose to submit this information select from the set of descriptors available in ClinicalTrials.gov (either ''systematic assessment'' or ''non-systematic assessment''). To simplify data entry, responsible parties are able to indicate the assessment type for the adverse event table as a whole or by each adverse event in the table. Of results for probable applicable clinical trials submitted in 2012, 76 percent included information about the approach to collecting some adverse events.

All-cause mortality information: An all-cause mortality table would consolidate information about all participant deaths from any cause following assignment to an arm, by arm, for the clinical trial. Although information related to deaths may be part of other clinical trial results information, the total number of deaths that occurred during the clinical trial might not be readily apparent (e.g., submitted adverse event information might indicate a number of subjects who experienced a myocardial infarction, but would not necessarily indicate how many of the subjects died from the event). Submission of all-cause mortality information would be consistent with some clinical trial reporting guidelines [Ref. 23, 38], but it might need to be accompanied by additional explanatory information that would assist users in interpreting it correctly, e.g., to indicate that deaths may not have been associated with the interventions studied in the clinical trial.

Standard vocabulary for adverse event terms. We also considered, but do not propose to require that adverse event terms be submitted according to a standard vocabulary. Although use of a single vocabulary might improve the comparability of adverse event data across trials represented in ClinicalTrials.gov, we do not believe it is reasonable to require responsible parties to submit adverse event data using a specific vocabulary. There is no agreed-upon standard adverse event vocabulary that is used in collecting and categorizing adverse event data for the full range of clinical trials. ClinicalTrials.gov currently allows responsible parties to indicate voluntarily any standardized vocabulary they have used when collecting adverse event data. Examination of the data voluntarily provided to date confirms that various versions of MedDRA are widely used by the pharmaceutical industry as the source of adverse event terms, but not by other entities (e.g., device manufacturers, non-industry organizations) that sponsor and conduct clinical trials. Other organizations use a variety of vocabularies, including SNOMED CT, which is an HHS-required standard for certification of electronic

health record products, or use no standard vocabulary at all. A requirement to submit adverse event data using a particular vocabulary would add significantly to the data submission burden for any responsible party who had used a different (or no) standard terminology in collecting adverse event data. In addition, requiring data collected under one terminology to be converted to a different terminology for submission to the data bank would carry unacceptable risks of data loss or misrepresentation. Such conversion is also a potentially much more difficult and time-consuming task than assigning high-level organ system classes to individual adverse event terms. As an alternative, we considered proposing that a single standard vocabulary be used to submit adverse event data for all clinical trials that are initiated after some date in the future (e.g., 2017). We rejected this approach because we do not think there is sufficient consensus on a standard vocabulary that is suitable for the full range of applicable clinical trials, and because ideally, data submission standards should follow data collection standards.

We understand that adverse event data from individual clinical trials are inherently difficult to interpret or to compare with similar data from other trials of the same intervention. Many factors may contribute to differences in the adverse events data collected in different trials, including differences in patient populations, differences in the methods or duration of adverse events collection, or in the types of adverse events collected. In addition, adverse event information available in ClinicalTrials.gov for a clinical trial most likely will differ from the adverse event data included in published reports or FDA documents discussing the same clinical trial, which may contain information on only a subset of adverse events for specific trials or provide aggregated information from multiple clinical trials. To avoid confusion with adverse event information available from sources other than ClinicalTrials.gov and to assist ClinicalTrials.gov users with varying degrees of expertise in clinical trial design and data analysis in understanding the adverse event data contained in the data bank, we will include a prominent notice and explanation in ClinicalTrials.gov describing the types of adverse events that are listed in clinical trial records and how they might differ between clinical trials and from information available in other sources. In addition, we will consider steps such as (1) linking to and offering on the ClinicalTrials.gov site other resource materials describing issues that need to be considered when interpreting adverse event information (e.g., issues of attribution, participants at risk); (2) creating a default public display that highlights certain data (e.g., all serious adverse events and other adverse events with frequencies above a certain threshold, such as 20 percent); and (3) providing mechanisms to allow the user to customize the display (e.g., by adjusting the frequency threshold).

We invite comments on all aspects of our proposed requirements for submission of adverse events information for clinical trials, including: (1) The benefit and burden of the proposed modifications to the statutory default provisions, including the number of participants affected by adverse events at the organ system level for both serious adverse events and other adverse events; (2) the potential benefit and burden of the additional information considered but not included in the proposal, such as the number of occurrences of each serious adverse event (in addition to the number of participants affected by a serious adverse event), the number of occurrences of each serious adverse event considered causally related to the intervention(s) studied, the time frame for collecting adverse events, the collection approach (systematic vs. non-systematic), and all-cause mortality information; (3) ways to reduce the data submission burden without reducing the value of the data submitted; and (4) approaches to increasing standardization in the vocabularies used in submitting adverse event information. We also invite and encourage the submission of any other information on current practices for collection, attribution, and summarization of adverse event data that might help us to refine the proposed requirements for submission of summary adverse event information.

16. Privacy Considerations

We believe that, in general, the information submitted to ClinicalTrials.gov for the vast majority of applicable clinical trials subject to this proposed rule would pose no privacy concerns. Registration and results information submitted to ClinicalTrials.gov pursuant to this proposed rule would consist of summary level data only and would not contain personally identifiable information. It would consist of the same type of information that would be expected to be included in a journal article or other routine form of public scientific communication. In addition, participants would be aware that summary data would be posted at ClinicalTrials.gov. FDA regulations require that informed consent forms for applicable clinical trials of drugs and devices include a specific statement to inform potential participants that certain information about the clinical trial will be submitted to ClinicalTrials.gov, where it will be publicly posted [see 21 CFR § 50.25(c)].

We also believe that in most cases it would not be possible to re-identify individuals who participated in a clinical trial based on the data submitted to ClinicalTrials.gov. For clinical trials of common diseases, or that recruit large numbers of participants, and/or recruit participants from multiple locations, the summary information submitted to ClinicalTrials.gov would be unlikely to contain characteristics that would enable re-identification of study participants. Even the information submitted for small trials with limited numbers of sites and few study participants would, in general, provide no clear basis for re-identification.

The risk of re-identification could be greater in particular types of clinical trials, such as small clinical trials that study treatments for rare diseases and have few recruitment sites or that recruit subjects from only small, well-defined populations. For some such clinical trials, we believe that a responsible party could submit required results information in a way that minimizes opportunities for re-identification. For example, if a trial of a rare disease recruits a participant of 90 years or more, the responsible party could consider submitting demographic information by grouping subjects into broader age categories or providing the mean age of all subjects in each arm of the trial, rather than breaking out the data for that one subject.

In those situations in which a responsible party believes results information could not be submitted in a way that is consistent with this proposed rule without risk of re-identification, the responsible party could alternatively request a waiver of results submission requirements, as permitted by section 402(j)(3)(H) of the PHS Act and proposed in § 11.54 of this rule. We believe such situations would be rare and such a waiver request would need to be evaluated on a case-by-case basis.

We invite public comment on other situations that might raise privacy concerns and on other approaches that we could propose to address them in a

way that is consistent with the requirements of section 402(j) of the PHS Act.

D. Effective Date/Compliance Date

1. Effective Date

We propose that the effective date of these regulations be established as 45 days after the date on which the final rule is published in the **Federal Register**. As of the effective date, the ClinicalTrials.gov system would be modified to be consistent with the final rule. As such, a responsible party that submits information into the data bank on or after the effective date must do so consistent with the final rule.

2. Compliance Date

We propose that the compliance date for these regulations be established as 90 days after the effective date of the rule. We interpret this to mean that a responsible party would have until the compliance date of the rule to come into compliance with the requirements of this proposed Part. Accordingly, by the compliance date of the rule: (a) Responsible parties for all applicable clinical trials initiated on or after, or ongoing as of, the effective date would have to comply with the clinical trial registration information requirements of proposed subpart B; (b) responsible parties for all applicable clinical trials required to submit clinical trial results information by a date that is on or after the effective date of the rule (including such trials whose completion dates were prior to the effective date of the rule, but for which results are due on or after the effective date of the rule under section 402(j)(3)(E) of the PHS Act) would have to comply with the clinical trial results information requirements of proposed subpart C; (c) responsible parties that make voluntary submissions of clinical trial information on or after the effective date of the rule would have to comply with proposed § 11.60 and any other applicable provisions of the final rule; and (d) responsible parties that submit clinical trial information to ClinicalTrials.gov, for both applicable clinical trials and clinical trials voluntarily submitted to the data bank under proposed § 11.60, on or after the effective date of the rule, would be required to update such clinical trial information in accordance with the requirements of proposed § 11.64(c).

Consistent with the foregoing, in instances in which submission of clinical trial registration or results information ordinarily would have been due between the effective date and the compliance date of the rule, the responsible party would have until the compliance date to submit the required clinical trial information. For example, if under this proposed part, clinical trial results information were due for an applicable clinical trial on a date that is 30 days after the effective date of the rule, the responsible party for that applicable clinical trial would have until the compliance date to submit such information. That said, because we propose to modify ClinicalTrials.gov consistent with the final rule as of the effective date of the rule, responsible parties seeking to come into compliance with the final rule after the effective date but prior to the compliance date would be able to do so.

We recognize that there will be situations in which the determination of one submission deadline will be conditioned upon an earlier submission deadline. In such situations, the Agency would consider the deadline pursuant to section 402(j) of the PHS Act and the final rule, notwithstanding the compliance date, as the applicable date for purposes of determining a subsequent deadline. For example, responsible parties that submit a certification to delay results submission under section 402(j)(3)(E)(v) of the PHS Act or proposed § 11.44(b)(1) must subsequently submit clinical trial results information no later than two years after the date of the certification. (See section 402(j)(3)(E)(v)(III) of the PHS Act and proposed § 11.44(b)(2).) If the deadline for the certification to delay results submission falls between the effective date and compliance date of the rule, then the responsible party would have until the compliance date to submit the certification. However, the subsequent deadline—i.e., the date by which clinical trial results information is due—would remain 2 years after the certification would have been due absent the compliance date.

We believe that the proposed 90-day delay between the effective date and the compliance date of the final rule would provide ample time for responsible parties of applicable clinical trials to come into compliance with the final rule. This proposed 90-day delay is the same number of days provided after the date of enactment of section 402(j) of the PHS Act for ongoing applicable clinical trials to submit registration information.

3. Registration Information

Clinical trial registration information submitted on or after the effective date of the rule would need to comply with the clinical trial registration information requirements of proposed subpart B. Furthermore, if an applicable clinical trial is ongoing as of the effective date of the rule and clinical trial registration information for that trial had been submitted prior to the effective date of the rule, the responsible party would need to submit any revised or additional registration information necessary to comply with proposed § 11.28 by the compliance date. This would help ensure that complete clinical trial registration information, as defined in this proposed rule, is available to the public for all ongoing applicable clinical trials subject to this proposed part. This also would ensure that certain information that was not previously required in order to register a clinical trial with ClinicalTrials.gov, but which is essential to the implementation of the proposed regulation, will be included in the data bank for all applicable clinical trials ongoing as of the effective date of the rule.

By contrast, if an applicable clinical trial reached its completion date prior to the effective date of the rule, and thus would not be ongoing as of the effective date of the rule, the responsible party would not be required to submit the additional registration information that would be required by proposed § 11.28. The responsible party would nevertheless be expected to have provided, at minimum, registration information containing all of the data elements specified in section 402(j)(2)(A)(ii) of the PHS Act, as they were available in ClinicalTrials.gov at the time of registration, namely, Brief Title, Brief Summary, Primary Purpose, Study Design, Study Phase (for an applicable drug clinical trial), Study Type, Primary Disease or Condition or Focus of the Study, Intervention Name, Intervention Type, Study Start Date, Completion Date (listed in ClinicalTrials.gov as ''Study Completion Date''), Target Number of Subjects (listed in ClinicalTrials.gov as ''Enrollment''), Primary and Secondary Outcome Measures, Eligibility Criteria, Gender, Age Limits, Whether the Trial Accepts Healthy Volunteers (listed in ClinicalTrials.gov as ''Accepts Healthy Volunteers?''), Overall Recruitment Status, Individual Site Status, Availability of Expanded Access (for an applicable drug clinical trial) (listed in ClinicalTrials.gov as ''expanded access record''), Name of the Sponsor, Responsible Party by Official Title (listed in ClinicalTrials.gov as ''Responsible Party Information''), Facility Name and Facility Contact Information (either facility-specific or central contact information), Unique Protocol Identification Number, Secondary ID, IND/IDE number (listed in ClinicalTrials.gov as ''IND/IDE Protocol''), and Record Verification

Date. We also would expect the responsible party to have updated these data elements as necessary, consistent with the section 402(j)(4)(C) of the PHS Act. For example, for each of the applicable clinical trials in this category, we would expect that the Completion Date data element would have been updated not later than 30 calendar days after the completion date of the clinical trial to reflect the ''actual'' completion date of the clinical trial. See section 402(j)(4)(C)(i)(IV) of the PHS Act.

We recognize that the data elements listed in the previous paragraph do not provide sufficient information for the responsible party to demonstrate (or for the Agency to determine) in all cases whether a clinical trial that was registered in ClinicalTrials.gov prior to the effective date of the rule meets the definition of an applicable clinical trial and thus whether results information was required to be submitted. The need to determine whether a clinical trial is an applicable clinical trial, in all cases, is one of the reasons we have proposed in § 11.28 to require the submission of several additional data elements as part of clinical trial registration information, e.g., Single Arm Controlled as part of Study Design (for single-armed studies); Product Manufactured in U.S.?; and U.S. FDA Approval, Clearance, or Licensure Status. Responsible parties may voluntarily submit such additional data elements for clinical trials that were registered and reached their completion dates before the effective date of this rule. Submission of this information will enable the clinical trial record to indicate whether or not the clinical trial is an applicable clinical trial subject to section 402(j) of the PHS Act.

4. Results Information

We interpret the approval status of a product studied in an applicable clinical trial (i.e., either ''unapproved, unlicensed, or uncleared'' or ''approved, licensed, or cleared'') to be the approval status of the product on any given date. For example, if a drug being studied in an applicable clinical trial was unapproved as of the completion date, at that time, the applicable clinical trial would be of an unapproved product. However, if and when the study drug receives FDA approval (for any indication), the applicable clinical trial would be of an approved product as of the date of FDA approval.

(a) Applicable clinical trials that reach their completion dates on or after the effective date of the rule. Responsible parties would be required to submit clinical trial results information specified in proposed subpart C for all applicable clinical trials that are required to be registered in ClinicalTrials.gov under section 402(j) of the PHS Act or this proposed rule that reach their completion dates on or after the effective date of the rule. This requirement would apply to applicable clinical trials of unapproved, unlicensed, or uncleared products as well as approved, licensed, or cleared products.

(b) Applicable clinical trials that reach their completion dates prior to the effective date of the rule—approved, licensed, or cleared products. In general, the responsible party for an applicable clinical trial of an approved, licensed, or cleared product that reaches its completion date prior to the effective date of the rule would not be required to submit the additional clinical trial results information required under proposed § 11.48 if the responsible party has already submitted the clinical trial results information required under section 402(j)(3)(C) of the PHS Act. This reflects the Agency's decision, as further described in section III.C.9 of this preamble, not to exercise its authority under section 402(j)(3)(D)(iv)(II) of the PHS Act to require ''the clinical trial information described in [section 402(j)(3)(D)(iii) of the PHS Act] . . . to be submitted for an applicable clinical trial for which the clinical trial information described in [section 402(j)(3)(C) of the PHS Act] is submitted to the registry and results data bank before the effective date of the regulations.'' We interpret the phrase ''is submitted'' to mean ''is required to be submitted,'' in order to make clear that this provision would also apply to those responsible parties who were required to submit results under section 402(j)(3)(C) of the PHS Act, but failed to do so.

There are three scenarios in which we propose to require the responsible party for an applicable clinical trial of an approved, licensed, or cleared product that reaches its completion date prior to the effective date of the rule to submit the additional clinical trial results information under proposed § 11.48:

First, in certain cases, an applicable clinical trial may reach its completion date prior to the effective date of the rule, but the clinical trial results information is neither due nor submitted until after the effective date of the rule. For example, under section 402(j)(3)(E)(i) of the PHS Act, clinical trial results information is due for an applicable clinical trial of an approved, licensed, or cleared product not later than 1 year after the completion date of the trial. Thus, if clinical trial results information is submitted after the effective date of the rule, consistent with this deadline, the responsible party would be required to submit the clinical trial results information required by proposed § 11.48.

Second, there may be situations consistent with proposed § 11.44(a)(2) in which an applicable clinical trial of an approved, licensed, or cleared product reaches its completion date prior to the effective date of the rule, has partial results information (i.e., primary outcome measures) submitted before the effective date of the rule, but has other partial results information (i.e., secondary outcome measures) that is neither due nor submitted until on or after the effective date of the rule. The Agency proposes to exercise its authority under section 402(j)(3)(D)(iv)(II) of the PHS Act in situations when partial results are due on or after the effective date of the rule to require the responsible party to submit clinical trial results information under proposed § 11.48 for all outcome measures, including primary outcome measures submitted prior to the effective date of the rule. We make this proposal so that, for any such trial, the data bank ultimately will contain the same required data elements for both primary and secondary outcome measures.

Third, as a result of modifications that would be made to the ClinicalTrials.gov data bank upon implementation of the final rule, the responsible party would be required to submit clinical trial results information as specified in proposed § 11.48 for any applicable clinical trial of an approved, licensed, or cleared product for which results information was required to be submitted under section 402(j)(3)(C) of the PHS Act prior to the effective date of the rule, but for which the responsible party failed to do so. Such responsible parties would be required to submit the clinical trial results information specified in § 11.48, even though only the clinical trial results information specified in section 402(j)(3)(C) of the PHS Act would have been required had results information been submitted on time. Accordingly, we are electing to exercise our authority under section 402(j)(3)(D)(iv)(II) of the PHS Act to require such responsible parties of applicable clinical trials of approved, licensed, or cleared products to submit the additional results data elements specified in proposed § 11.48. As discussed in section III.C.9 of this preamble, section 402(j)(3)(D)(iv)(II) of the PHS Act provides that the Secretary shall by regulation determine ''whether the clinical trial information described

in [section 402(j)(3)(D)(iii) of the PHS Act] should be required to be submitted for an applicable clinical trial for which the clinical trial information described in [section 402(j)(3)(C) of the PHS Act] is submitted to the registry and results data bank before the effective date of the regulations.'' We interpret the phrase ''is submitted'' to mean ''is required to be submitted,'' in order to make clear that this provision would also apply to those responsible parties who were required to submit results information under section 402(j)(3)(C) of the PHS Act, but failed to do so.

(c) Results information for applicable clinical trials that reach their completion dates prior to the effective date of the rule—unapproved, unlicensed, or uncleared products. With respect to applicable clinical trials of unapproved, unlicensed, or uncleared products that reach their completion dates prior to the effective date of the final rule, whether clinical trial results information is required under this proposed rule would depend on whether the product under study gets approved, licensed, or cleared. If the drug or device under study in an applicable clinical trial that reached its completion date prior to the effective date of the rule is never approved, licensed, or cleared by FDA, then submission of results information would not be required. However, if the drug or device under study is subsequently approved, licensed, or cleared after the effective date of the rule, then, consistent with section 402(j)(3)(E)(iv) of the PHS Act, clinical trial results information required by proposed § 11.48 would be due by the earlier of 1 year after the completion date or 30 calendar days after the date of initial FDA approval, licensure or clearance. In addition, the clinical trial results information under § 11.48 would be required if results were due and submitted after the effective date of this proposed rule.

5. Voluntary Submissions

If on or after the effective date, a responsible party voluntarily submits clinical trial information for a clinical trial that is not an applicable clinical trial, or that is an applicable clinical trial but is not required to register in ClinicalTrials.gov under section 402(j)(2)(C) of the PHS Act, the voluntary submissions provision of section 402(j)(4)(A) of the PHS Act and proposed § 11.60 apply to that submission, regardless of the completion date of such trial.

6. Updates and Corrections to Clinical Trial Information

With respect to clinical trial registration information or clinical trial results information that is due on or after the effective date of the rule, the Agency intends to require responsible parties to update such information, in accordance with proposed § 11.64.

With respect to clinical trial information that is due prior to the effective date of the rule, the Agency intends to continue requiring responsible parties to update such information in accordance with the requirements set forth in section 402(j)(4)(C) of the PHS Act. Because responsible parties that submitted clinical trial information to the data bank prior to the effective date of the final rule would have submitted only those data elements required under sections 402(j) of the PHS Act, which excludes any additional data elements required under the final rule, they would be required to update only that information that was required to be submitted prior to the effective date of the rule and only to the extent required under section 402(j)(4)(C) of the PHS Act.

In the event that a clinical trial reaches its completion date prior to the effective date of the rule but clinical trial results information is due after the effective date of the rule, the responsible party would be required to update the clinical trial registration information in accordance with the requirements of section 402(j)(4)(C) of the PHS Act, but it would be required to update the clinical trial results information submitted after the effective date in accordance with the requirements of proposed § 11.64(c). As discussed earlier in this section, a responsible party of a clinical trial that is registered but ongoing as of the effective date of the rule would be required to submit registration information consistent with proposed § 11.28 by the compliance date of the rule; consistent with this approach, responsible parties would be required to update the clinical trial registration information for such trials in accordance with the requirements of proposed § 11.64(c).

Notwithstanding the foregoing, if a responsible party becomes aware of previously submitted clinical trial information that contains errors that need to be corrected or that may have been falsified, the Agency proposes to require responsible parties to correct such previously submitted clinical trial information in accordance with proposed § 11.66(c), regardless of when such clinical trial information was submitted to data bank. We believe our proposed approaches outlined in this part balance the differing positions expressed in comments made at the public meeting. We invite public comment on the advantages and disadvantages of this proposed approach and on other approaches that might be considered by the Agency in establishing the effective date and the compliance date.

IV. Detailed Description of This Proposed Rule

Proposed Subpart A, General Provisions, sets forth the purpose of the regulations; to whom the regulations apply; the form and manner for submission of clinical trial information; the requirement that the submission of information under this part be truthful and not false or misleading; and the definitions applicable to this part.

Proposed Subpart B, Registration, sets forth the requirements related to clinical trial registration information. It delineates who must submit clinical trial registration information; which applicable clinical trials must be registered in ClinicalTrials.gov; when clinical trial registration information must be submitted; where clinical trial registration information must be submitted; what constitutes clinical trial registration information; and by when NIH will post submitted clinical trial registration information.

Proposed Subpart C, Results Submission, addresses the submission of clinical trial results information. It delineates who must submit clinical trial results information for applicable clinical trials; which applicable clinical trials are subject to the results submission requirement; when the clinical trial results information must be submitted; where and in what format clinical trial results information must be submitted; what constitutes clinical trial results information; by when NIH will post submitted clinical trial results information; and under what circumstances a waiver of the regulations will be granted.

Proposed Subpart D, Additional Submissions of Clinical Trial Information, sets forth the requirements and procedures for voluntary submissions of clinical trial information for clinical trials of FDA-regulated drugs and devices, submissions required to protect the public health, and updates to previously-submitted clinical trial registration and results information.

A detailed discussion of this proposed rule, its statutory basis, and the purpose of its provisions follows.

A. General Provisions—Subpart A

1. What is the purpose of this part—§ 11.2

As set forth in proposed § 11.2, the purpose of this part is to implement section 402(j) of the PHS Act [42 U.S.C. 282(j)], by providing requirements and procedures for the submission of clinical trial information for certain applicable clinical trials and other specified clinical trials to the Director of NIH to be made publicly available through ClinicalTrials.gov, the Internet-accessible clinical trial registry and results data bank established by NLM at *http://www.clinicaltrials.gov.*

2. To whom does this part apply?—§ 11.4

Proposed § 11.4(a) specifies that this proposed rule applies to any person or entity that is considered to be the ''responsible party'' for an applicable clinical trial that is required to be registered under § 11.22 or a clinical trial for which clinical trial information is submitted voluntarily under § 11.60. The responsible party would be either the sponsor of the clinical trial or a principal investigator who meets the criteria specified in proposed § 11.4(c)(2) and has been so designated by the sponsor. (See proposed § 11.4(c).) Proposed § 11.22 specifies which applicable clinical trials are required to submit registration information to ClinicalTrials.gov (i.e., applicable drug clinical trials and applicable device clinical trials that were initiated after September 27, 2007, or that were initiated on or before September 27, 2007, and ''ongoing'' (as such term is defined by this proposed rule) on December 26, 2007, consistent with section 402(j)(2)(C) of the PHS Act. Proposed § 11.60 specifies requirements for voluntary submissions of clinical trial information for applicable clinical trials that are not required to register under section 402(j) of the PHS Act (e.g., because they were completed prior to September 27, 2007), and for clinical trials that do not meet the definition of an applicable clinical trial. The voluntary submission of clinical trial registration or results information for such clinical trials, triggers a requirement to submit clinical trial registration or results information for certain other trials, as required by section 402(j)(4)(A) of the PHS Act. (*See* proposed § 11.60(a)(2)(ii)).)

In no case would this proposed rule apply to the sponsor or principal investigator or other individual or entity associated with a clinical trial of a health intervention that is not subject to FDA jurisdiction. Although section 402(j)(4)(A) of the PHS Act directs the NIH to permit ''[v]oluntary submissions'' of clinical trial information for ''a clinical trial that is not an applicable clinical trial or that is an applicable clinical trial that is not subject to'' the registration provisions of section 402(j)(2) of the PHS Act, we interpret section 402(j) of the PHS Act and thus this proposed rule as not applying to anyone who submits information to ClinicalTrials.gov about trials of interventions that are not subject to FDA jurisdiction under sections 505, 510(k), 515, 520(m), or 522 of the FD&C Act, or section 351 of the PHS Act. Moreover, we interpret section 402(j) of the PHS Act and thus this proposed rule as not applying to anyone who submits information to ClinicalTrials.gov for a study that is neither an interventional clinical trial nor a pediatric postmarket surveillance of a device as defined in this part (e.g., for a study that is an observational study), even if it involves a drug or device subject to sections 505, 510(k), 515, 520(m), or 522 of the FD&C Act, or section 351 of the PHS Act. Consistent with other statutory authorities of the NIH and long-standing practice, however, ClinicalTrials.gov may, and does, accept registration and results information on clinical studies and interventions that are not subject to the requirements of section 402(j) of the PHS Act and this proposed rule.

Proposed § 11.4(b) implements section 402(j)(1)(B) of the PHS Act, which provides that the Secretary ''shall develop a mechanism by which the responsible party for each applicable clinical trial shall submit the identity and contact information of such responsible party to the Secretary at the time of submission of clinical trial [registration] information.'' Proposed § 11.4(b) provides that the responsible party's identity and contact information must be included as part of the clinical trial information that is submitted in accordance with subpart B and updated in accordance with § 11.64(b)(1)(ix) and (x). We propose in § 11.28(a)(4)(vii), to require submission of a data element entitled Responsible Party Contact Information that, as specified in proposed § 11.10(b)(38) includes the name, official title, organizational affiliation, physical address (i.e., street address), mailing address, phone number, and email address of the responsible party. To minimize redundant data entry, we will provide a mechanism for the responsible party to indicate if the mailing address is the same as the physical address. In those cases in which the responsible party is an organization, as opposed to an individual, we would require the name and official title to correspond to a designated contact person for the organization. As described in section IV.B.4(a) of this preamble, if the responsible party is an individual, we intend to make the name of responsible party publicly available in the data bank, but we do not propose to make the other contact information publicly available (i.e., the physical address, mailing address, phone number, and email address). The other contact information will be used for internal administrative processes (e.g., for necessary communications). We note that the official title and organizational affiliation of the responsible party will also be made publicly available as part of the Responsible Party, By Official Title data element, which is required to be submitted to ClinicalTrials.gov at the time of registration. See section 402(j)(2)(A)(ii)(III)(bb) of the PHS Act.

Proposed § 11.4(c) outlines procedures for determining the responsible party for each applicable clinical trial or other clinical trial subject to this part. We believe that there must be one (and only one) responsible party for each applicable clinical trial or other clinical trial. Absent a responsible party, the objectives of registration and results submission cannot be met. Because the definition of responsible party under section 402(j) of the PHS Act specifies, first, that the sponsor will be the responsible party and, second, that the PI is the responsible party if delegated this role through a designation ''by a sponsor, grantee, contractor, or awardee,'' with regard to clinical trials, the Agency looks first to determine who is the sponsor of the clinical trial, consistent with the definition proposed in this part, and assumes that such individual or entity is the responsible party, unless the PI has been designated the responsible party in accordance with the procedure established in proposed § 11.4(c)(2). For a pediatric postmarket surveillance of a device that is not a clinical trial, the responsible party would be considered the entity whom FDA orders to conduct the pediatric postmarket surveillance of a device.

Proposed § 11.4(c)(1) specifies who will be considered the sponsor. The Agency believes that there must be a sponsor, as that term is used in section 402(j)(1)(A)(ix) of the PHS Act, for each clinical trial, and that there can be only one sponsor. Without a defined sponsor, there cannot be a responsible party for a clinical trial because responsible party is defined as either the sponsor or the

principal investigator who has been so designated by the sponsor. The proposed definition of sponsor in § 11.10(a), includes both a ''sponsor'' and a ''sponsor-investigator'' as those terms are defined in 21 CFR 50.3. Both definitions in 21 CFR 50.3 refer to the sponsor as, in part, the person or entity who ''initiates'' the clinical investigation. For purposes of this proposed rule, if a clinical trial is being conducted under an IND or IDE, the IND/IDE holder would be considered to be the individual or entity who initiated the clinical trial and, therefore, the sponsor, regardless of how the clinical trial is being funded. For clinical trials not conducted under an IND or IDE, the sponsor would be considered to be the person or entity who initiated the trial and would be identified as follows.

(1) Where the clinical trial is being conducted by an entity under a research assistance funding agreement such as a grant or sponsored research agreement, the funding recipient generally would be considered to be the initiator of the clinical trial, and therefore, the sponsor. This is because, as a general rule, when a clinical trial is funded in this manner, the funding recipient ''initiates'' the clinical trial process by, for example, submitting a funding proposal and designing the clinical trial.

(2) Where the clinical trial is being conducted by an entity under a procurement funding agreement such as a contract, the party obtaining the goods or services for its direct benefit or use (the funder) generally would be considered to be the initiator of the trial, and therefore, the sponsor. This is because, as a general rule, when a clinical trial is funded in this manner, it is the funder of the clinical trial that initiates the clinical trial process by, for example, contracting with another entity for that entity to conduct a clinical trial meeting the specifications of the funder.

(3) Where there is no funding agreement supporting the clinical trial, the person or entity who initiated the clinical trial by preparing and/or planning the clinical trial, and who has appropriate authority and control over the clinical trial to carry out the responsibilities under section 402(j) of the PHS Act and this proposed part would be the sponsor.

Proposed § 11.4(c)(2) establishes the procedures for designation of a principal investigator as the responsible party. Section 402(j)(1)(A)(ix) of the PHS Act defines the responsible party, as either ''the sponsor of the clinical trial (as defined in . . . 21 [CFR 50.3] (or any successor regulation);'' or, as ''the principal investigator of such clinical trial if so designated by the sponsor, grantee, contractor, or awardee. . .'' In order to give practical effect to this provision, we believe that, for any given applicable clinical trial, only one entity—the sponsor—can designate the PI as the responsible party. We believe that this interpretation is consistent with section 402(j) of the PHS Act because in many situations the sponsor of the clinical trial will also be a grantee, contractor, or awardee (e.g., in a situation in which there is no IND/IDE holder, and the sponsor is considered the ''initiator'' of the trial). In addition, interpreting this provision in a different manner could result in situations in which both a sponsor (e.g., an IND/IDE-holder) and a PI (designated by a separate grantee, contractor, or awardee) consider themselves the responsible party and submit information for the same clinical trial. This would not only increase the overall burden associated with registration, but more importantly would undermine the integrity of the data bank and potentially cause confusion to users of the system.

Section 402(j)(1)(A)(ix) of the PHS Act permits a PI to serve as a responsible party only if he or she ''is responsible for conducting the trial, has access to and control over the data from the clinical trial, has the right to publish the results of the trial, and has the ability to meet all of the requirements under [this proposed part] for the submission of clinical trial information.'' Accordingly, if the PI does not meet the specified conditions for serving as the responsible party, the sponsor cannot designate the PI as the responsible party, and the sponsor must remain the responsible party. In proposed § 11.10(a) we define, for purposes of this part, the term principal investigator (PI) to mean ''the individual who is responsible for the scientific and technical direction of the study.'' We note that under section 402(j)(1)(A)(ix) of the PHS Act, in order to be designated the responsible party, the PI must be responsible for ''conducting the trial'' and must have ''access to and control over the data from the clinical trial.'' We interpret ''the trial'' to mean ''the entire trial,'' and ''the data'' to mean ''all of the data'', including data collected at all sites of a multi-site trial.

We wish to clarify our understanding of section 402(j)(3)(C)(iv) of the PHS Act, as it relates to whether a PI would be eligible to serve as the responsible party under this proposed part. Section 402(j)(3)(C)(iv) of the PHS Act requires the responsible party to indicate, as an element of clinical trial results information, whether there exist ''certain agreements,'' which are described as ''an agreement . . . that restricts in any manner the ability of the principal investigator, after the completion date of the trial, to discuss the results of the trial at a scientific meeting or any other public or private forum, or to publish in a scientific or academic journal information concerning the results of the trial.'' We do not view the presence of such an agreement as necessarily disqualifying a PI from serving as the responsible party. Rather, we view only those agreements that prevent the PI from performing the functions described in section 402(j)(1)(A)(ix)(II) of the PHS Act or from submitting clinical trial information or any updates to such information required by section 402(j) of the PHS Act and this proposed part as preventing the PI from serving as the responsible party.

To provide for the orderly implementation of section 402(j)(1)(A)(ix)(II) of the PHS Act, pursuant to which the sponsor may designate a PI as responsible party, and ensure that the PI has notice of the designation, we have proposed a process in § 11.4(c)(2) for designating a PI, as follows: the sponsor shall provide notice of the designation to the PI and obtain acknowledgement of the PI's responsibilities under this proposed part. We intend to continue to provide mechanisms in the PRS for the sponsor and the PI to indicate the designation and the acknowledgement, respectively. The designation by the sponsor is currently reflected in ClinicalTrials.gov by having the PI submit clinical trial information via the sponsor's organizational account (the sponsor must provide an account for the PI within the sponsor's PRS organizational account). The acknowledgement is reflected by having the PI list his/her name as the responsible party and indicate that he/she was designated as responsible party by the sponsor. This approach has been implemented in ClinicalTrials.gov since 2011.

If and when a designated principal investigator becomes unable to meet all of the requirements of a responsible party, proposed § 11.04(c)(3) outlines the mechanisms by which the sponsor would become the responsible party. This might occur if, for example, a principal investigator dies, retires, changes jobs, or turns control of the clinical trial data over to the sponsor.

We note that even if a sponsor designates a principal investigator as the responsible party for an applicable clinical trial registered under proposed § 11.22, there may be times when the sponsor would need to provide the principal investigator with certain

information in order for the principal investigator to meet his or her obligations as responsible party under section 402(j) of the PHS Act and/or this proposed part. For example, the sponsor would likely have to provide the principal investigator with information to describe an expanded access program for which information is required to be submitted and updated pursuant to proposed §§ 11.28(a)(2)(viii) and 11.64. In some cases, a principal investigator who is the responsible party would rely upon the sponsor to obtain information necessary to determine if the applicable clinical trial meets the criteria for delayed submission of results information under proposed §§ 11.44(b) or (c). Although we would expect a principal investigator who is a responsible party to request such information from the sponsor, we also would expect a sponsor who has designated a principal investigator as the responsible party to provide such information. A principal investigator who is not provided the information necessary to enable him or her to meet all of the requirements for submitting and updating clinical trial information would not meet the criteria set forth in proposed § 11.4(c)(2)(i) to serve as the responsible party. If the sponsor does not provide the principal investigator with the requisite information to meet the criteria under proposed § 11.4(c)(2)(i), the principal investigator cannot be designated as a responsible party and the responsible party designation either would remain with or revert back to the sponsor.

3. What are the requirements for the submission of truthful information?—§ 11.6

Section 402(j)(5)(D) of the PHS Act specifies that ''clinical trial information submitted by a responsible party under this subsection shall not be false or misleading in any particular.'' In addition, it is a prohibited act under section 301(jj)(3) of the FD&C Act to submit clinical trial information under section 402(j) of the PHS Act that is false or misleading in any particular under section 402(j)(5)(D) of the PHS Act. Other Federal laws also govern the veracity of information or claims submitted to the Federal Government, such as 18 U.S.C. 1001 (making it a crime to make certain false statements to the executive, legislative, or judicial branch of the U.S. Government) and 31 U.S.C. 3802 (referencing civil and potential administrative liability of persons making certain false claims to the U.S. Government). Thus, we propose in § 11.6(a) to require that ''[t]he clinical trial information submitted by a responsible party under this part shall not be false or misleading in any particular.'' In addition, proposed § 11.6(b) provides that ''[s]ubmission of false and/or misleading information would subject the responsible party to civil, criminal, and/or administrative liability under U.S. law.'' Specifically, all information submitted by a responsible party to ClinicalTrials.gov must be truthful, including information submitted voluntarily and other information that may not fall under the definition of clinical trial information, such as certifications for delayed submission and requests for good-cause extensions. Note, however, that this part does not require inclusion of information from any source other than the applicable clinical trial or other clinical trial that is the subject of the submission.

To help ensure that responsible parties are aware of this requirement and to provide an opportunity for them to attest to the veracity of the information at the time of submission, we propose in § 11.6(b) to require the responsible party, each time he or she submits clinical trial information or other information to ClinicalTrials.gov, to ''certify that, to the best of his or her knowledge, the information submitted is truthful and not misleading and that he or she is aware that the submission of false and/or misleading information would subject the responsible party to civil, criminal, and/or administrative liability under U.S. law.'' This requirement is similar to requirements to certify to the truthfulness of information about FDA-regulated products submitted to FDA, and we believe is an important component of efforts to help ensure that submitted information is not false or misleading, as required by section 402(j)(5)(D) of the PHS Act, 18 U.S.C. 1001, and 31 U.S.C. 3802. We plan to implement this requirement in ClinicalTrials.gov by integrating a certification statement into the mechanism for submitting information electronically through the Protocol Registration System. The requirement of proposed § 11.6 would be met by the responsible party making an attestation such as the following: ''I certify that the information I have submitted is, to the best of my knowledge, truthful and not misleading, and I am aware that the submission of false and/or misleading information would subject me to civil, criminal, and/or administrative liability under U.S. law.''

4. In what form and manner must clinical trial information be submitted?—§ 11.8

Proposed § 11.8 sets forth requirements for the form and manner of submitting clinical trial information to ClinicalTrials.gov. It specifies that information submitted under this proposed part must be submitted electronically to ClinicalTrials.gov in the form and manner specified at *http://prsinfo.clinicaltrials.gov.* No other form or manner of submission will be accepted. Proposed §§ 11.10, 11.28 and 11.48, specify the individual data elements of clinical trial information that must be submitted to ClinicalTrials.gov at the time of registration and results submission (and updated in accordance with proposed § 11.64), including the subelements that are considered to be part of a data element (e.g., proposed § 11.10 specifies that the Study Design data element includes subelements of Interventional Study Model, Number of Arms, Arm Information, Allocation, Masking, and Single Arm Controlled).

Sections IV.B.4 and IV.C.4 of this preamble describe the specific form and manner in which data elements and subelements would be required to be submitted to ClinicalTrials.gov. For some data elements and subelements, responsible parties would be required to submit information in the form of free-text; for other data elements and subelements, responsible parties would be required to select the best response from menus of options presented in ClinicalTrials.gov. Some menus would offer a fixed set of options without an ''other'' option; others would offer a prespecified set of options plus an ''other'' option. In most cases, responsible parties selecting the ''other'' option would be required to provide an additional free-text response to elaborate on their other selections. Some data elements without an ''other'' option would also include an optional free-text field in which responsible parties could voluntarily provide additional information about the option selected. The use of menu options is intended to promote the entry of data in a structured manner that allows users to search ClinicalTrials.gov and retrieve comparable information, consistent with the requirements of sections 402(j)(2)(B) and (3)(D)(v)(I) of the PHS Act.

Menu options have been used in ClinicalTrials.gov since its launch. They are routinely used to improve the quality and help ensure the completeness of data submitted to information systems. Their use can reduce typographical errors in data

entry and minimize the data entry burden on responsible parties by providing a set of predefined options for common entries. By standardizing the set of available responses, they also promote the use of consistent terminology across entries and can improve the ability of users to search the data bank and compare entries easily across clinical trials, consistent with the requirements of sections 402(j)(2)(B)(iv) and (3)(D)(v)(I) of the PHS Act.

In describing the registration and results information to be submitted to ClinicalTrials.gov, the preamble specifies whether information would be submitted as free text or as menu selections. For data elements with menu options, the preamble specifies the complete set of options proposed, including whether or not an ''other'' option would be offered. The choice of providing menu options versus free-text fields and the set of menu options offered for specific data elements and subelements are based on our experience in operating ClinicalTrials.gov and on comments received from users of ClinicalTrials.gov, including those who commented on the draft guidance documents that were issued in 2002 and 2004 [Ref. 3, 4] (see section II.A of the preamble) and the preliminary version of the results database and adverse event module that were available for testing beginning in the spring of 2008 (see section II.B. of this preamble).

We anticipate that, from time to time, we might make minor changes to the specific form and manner in which responsible parties would submit individual data elements and subelements to ClinicalTrials.gov. Such changes would not require a responsible party to submit different or more clinical trial information than is specified in this proposed rule, but would alter the way in which the information is entered, with the general aim of making sure the menu options contain the most relevant, useful, and convenient options for responsible parties and users of the system. For example, if the research community develops a new type of clinical trial design, we might expand the list of menu options under the Interventional Study Model subelement of the Study Design data element to include it. If we find that many of the free-text entries for the Why Study Stopped data element fall into a small number of categories, we might offer them as menu options (in addition to accepting free-text for ''other'' reasons) to reduce the burden of data entry and improve the consistency and comparability of responses across registered clinical trials. We would provide prior notice and seek public comment on any proposed changes to the form and manner of submitting clinical trial information, and any changes would ultimately be reflected in the ClinicalTrials.gov data entry system at *http://prsinfo.clinicaltrials.gov*.

We invite comment on the specific form and manner described in this proposed rule for submitting data elements and subelements of proposed clinical trial information, including comment on the benefits and burden associated with providing proposed data elements and subelements, whether proposed menu options are sufficient to accommodate the range of potential entries (e.g., for different trial designs), and whether ''other'' options are needed for additional data elements. We also invite comment on the proposed approach described in this section for modifying the form and manner of submitting clinical trial information over time.

We further note that to reduce the burden on responsible parties related to the submission of information to the data bank, ClinicalTrials.gov accommodates both interactive, online entry of information for a specific clinical trial and automated uploading of information that is prepared in a specified electronic format. Responsible parties submitting information on multiple clinical trials may upload information that is prepared as a batch submission. We expect this feature will be of interest to large entities (e.g., drug and device manufacturers) who might be the responsible party for multiple clinical trials. Additional information about submitting information to ClinicalTrials.gov is available at *http://prsinfo.clinicaltrials.gov*.

5. What definitions apply to this part?—§ 11.10

Proposed § 11.10 defines certain terms and data elements used in this proposed part. The terms defined in proposed § 11.10(a) includes terms explicitly defined in section 402(j) of the PHS Act (e.g., ''applicable clinical trial'' and ''responsible party''); terms used but not defined in section 402(j) of the PHS Act (e.g., ''clinical trial''); and terms not specifically found in section 402(j) of the PHS Act but which are important for implementing the statutory provisions. With respect to terms not defined in the statute, we propose definitions to fit within the proposed framework for the expanded data bank and for purposes of satisfying the statutory goals, clarifying the application and operation of this proposed rule, in particular as related to information to be submitted to ClinicalTrials.gov, and/or for convenience. We also reference some terms defined under the PHS Act and the FD&C Act and implementing regulations, as necessary.

In March 2009 the Agency provided an elaboration of its then-current thinking about the definitions of the terms ''applicable clinical trial,'' ''applicable device clinical trial,'' ''applicable drug clinical trial,'' and ''responsible party'' in a document entitled ''Elaboration of the Definitions of Responsible Party and Applicable Clinical Trial'' that was posted on the ClinicalTrials.gov Web site. The posted document invites comments on the elaborations, but no written comments were received by the Agency. We discuss below a number of the proposed definitions.

Adverse event is a term used but not defined in section 402(j)(3)(I) of the PHS Act to describe a certain category of clinical trial results information. Current FDA regulations define the term ''adverse event'' with respect to drugs, but not to devices. (FDA regulations for devices include a different but related term, ''suspected adverse device effect,'' that is discussed below in the definition of the term ''serious adverse event''). FDA regulations for IND safety reporting requirements that were issued on September 29, 2010 (see 75 FR 59935, Sept. 29, 2010) and took effect on March 28, 2011 define an adverse event as ''any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related'' (21 CFR 312.32(a)). In addition to defining the term ''adverse event,'' those FDA regulations have the additional purpose of identifying circumstances in which certain adverse events (such as those that are serious and unexpected and that also meet the definition of a ''suspected adverse reaction,'' meaning the adverse event must have a reasonable possibility of being caused by the drug) must be reported in an expedited fashion while the trial is ongoing.

Because this proposed rule includes a requirement to submit to ClinicalTrials.gov summary information about anticipated and unanticipated adverse events observed during a clinical trial (as well as a requirement to submit information about serious adverse events), regardless of attribution (i.e., whether or not the investigator believes they are related to the intervention(s)), our proposed definition cannot be limited to adverse events that are anticipated, are likely to have been caused by the drug or device (or other type of intervention used in the clinical

trial), or that have a reasonable possibility of being related to the intervention under study. Instead, the proposed definition of adverse event must include all adverse events regardless of possible attribution and regardless of whether they were anticipated.

The HHS Office for Human Research Protections (OHRP) has a definition of adverse event that covers drug, device, and other interventions and has the same scope of adverse events addressed by section 402(j) of the PHS Act, i.e., it includes both anticipated and unanticipated event(s) regardless of whether they are attributed to the intervention(s) studied in the clinical trial. As discussed in OHRP's ''Guidance on Reviewing and Reporting Unanticipated Problems Involving Risks to Subjects or Others and Adverse Events'' (January 2007), an adverse event means ''[a]ny untoward or unfavorable medical occurrence in a human subject, including any abnormal sign (for example, abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the subject's participation in the research, whether or not considered related to the subject's participation in the research'' [Ref. 39]. The OHRP definition was adapted from the definition used by the International Conference on Harmonization (ICH) Guideline E6, Good Clinical Practice: Consolidated Guidance [Ref. 40], which was published by FDA as a guidance document in the **Federal Register** in 1997 (62 FR 25692, May 9, 1997). The definition, therefore, is consistent with international norms. Although the ICH Guidelines are intended to apply to pharmaceutical products, the OHRP definition is intended to apply broadly to research in humans that involves any type of intervention.

Our proposed definition of adverse event derives from the OHRP definition. We propose to define an adverse event as ''any untoward or unfavorable medical occurrence in a human subject, including any abnormal sign (for example, abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the subject's participation in the research, whether or not considered related to the subject's participation in the research.'' This interpretation helps improve consistency in the submission of adverse event information for applicable device clinical trials and applicable drug clinical trials. It is consistent with, although not identical to, the definition of adverse event included in FDA's IND regulations. We invite public comment on this proposed definition.

Applicable clinical trial is the term used in section 402(j)(1)(A)(i) of the PHS Act to designate the scope of clinical trials that may be subject to the requirements to submit clinical trial registration and results information as specified in this proposed part. Not all applicable clinical trials are subject to clinical trial registration and results submission requirements. For example, an applicable clinical trial that reached its completion date on or before September 27, 2007, is not subject to registration under section 402(j) of the PHS Act, nor is an applicable clinical trial that was ongoing as of September 27, 2007, and reached its completion date prior to December 26, 2007. This proposed rule adopts the definition of applicable clinical trial from section 402(j)(1)(A)(i) of the PHS Act, which relies on two other terms defined in that section of the PHS Act and this proposed rule, namely applicable device clinical trial and applicable drug clinical trial. In addition, in proposed § 11.22(b), we propose an approach for determining whether a clinical study or trial meets the definition of an applicable clinical trial.

Applicable device clinical trial is the term used in section 402(j)(1)(A) of the PHS Act to designate the clinical trial of a device and FDA-ordered pediatric postmarket surveillance of a device for which clinical trial information must be submitted to ClinicalTrials.gov under section 402(j) of the PHS Act. The term ''device'' is defined in section 402(j)(1)(A)(vi) as ''a device as defined in section 201(h) of the [FD&C] Act.'' We have adopted this definition of ''device'' in proposed § 11.10. In addition, this proposed rule adopts, in § 11.10, the definition of applicable device clinical trial, as provided in section 402(j)(1)(A)(ii) of the PHS Act: ''(I) a prospective clinical study of health outcomes comparing an intervention with a device subject to section 510(k), 515, or 520(m) of the [FD&C] Act against a control in human subjects (other than a small clinical trial to determine the feasibility of a device, or a clinical trial to test prototype devices where the primary outcome measure relates to feasibility and not to health outcomes); and (II) a pediatric postmarket surveillance as required under section 522 of the [FD&C] Act.''

The first part of the definition in section 402(j)(1)(A)(ii)(I) defines a clinical study as an applicable device clinical trial if it meets the following four criteria: (1) It is a prospective clinical study of health outcomes; (2) it compares an intervention with a device against a control in human subjects; (3) the studied device is subject to section 510(k), 515, or 520(m) of the FD&C Act; and (4) it is other than a small clinical trial to determine the feasibility of a device or a clinical trial to test prototype devices where the primary outcome measure relates to feasibility and not to health outcomes. Except as described below with regard to pediatric postmarket surveillances of a device, if a clinical investigation fails to meet one or more of these criteria, it would not be considered an applicable device clinical trial. We have considered the meaning of these criteria carefully and our interpretation follows.

(1) ''Prospective clinical study of health outcomes.'' First, we interpret the term ''clinical study,'' with respect to a device. We interpret ''clinical study'' with respect to a device to mean an investigation in which a device is used in one or more human subjects. For purposes of interpreting the term ''clinical study,'' we consider the term ''human subject'' to have the same meaning as the term ''subject,'' which is defined in FDA regulations as a ''human who participates in an investigation, either as an individual on whom or on whose specimen an investigational device is used or as a control. A subject may be in normal health or may have a medical condition or disease.'' (See 21 CFR 812.3(p).) For purposes only of the requirements under section 402(j) of the PHS Act and this proposed rule, the term ''human subject'' does not include de-identified human specimens (see [Ref. 41]). Note that we use the term ''participant'' interchangeably with ''human subject'' in this document.

The term ''study'' is often used interchangeably with the term ''investigation.'' As pertaining to devices, ''investigation'' is defined as ''a clinical investigation or research involving one or more subjects to determine the safety or effectiveness of a device.'' (See 21 CFR 812.3(h).) Although FDA regulations pertaining to devices do not specifically define the term ''clinical investigation,'' that term is defined in FDA regulations pertaining to clinical investigations of drugs and biological products as ''any experiment in which a drug is administered or dispensed to, or used involving, one or more human subjects,'' where ''experiment'' is defined as ''any use of a drug except for the use of a marketed drug in the course of medical practice.'' (See 21 CFR 312.3.) In our view, these definitions can be applied to device trials by defining a ''clinical study of a device'' as ''any experiment in which a device is administered, dispensed to, or used involving, one or more human subjects,'' defining an ''experiment'' as ''any use of a device except for the use

of a marketed device in the course of medical practice,'' and using the definition of ''subject'' described above (from 21 CFR 812.3(p)). This interpretation helps improve consistency between definitions of the terms applicable device clinical trial and applicable drug clinical trial. In addition, our proposed interpretation of a ''clinical study'' of a device would include studies in which subjects are assigned to specific interventions according to a study protocol. Studies in which a device is used on a patient as part of routine medical care and not because of a study or protocol would not be considered ''clinical studies'' for purposes of this rulemaking. An example of studies that would not be considered clinical investigations include situations in which, after a device has been administered to a patient in the course of routine medical practice by a healthcare provider, a researcher not associated with the administration of the device reviews the records of the patients in order to assess certain effects, interviews the patients to assess certain impacts, or collects longitudinal data to assess health outcomes.

Second, turning to our interpretation of ''prospective,'' we consider a ''prospective'' clinical study to be any study that is not retrospective or, in other words, one in which subjects are followed forward in time from a well-defined point (i.e., the baseline of the study) or are assessed at the time the study intervention is provided. A ''prospective clinical study'' also may have non-concurrent (e.g., historical) control groups. An example of a retrospective study, and thus not an applicable device clinical trial, is a study in which subjects are selected based on the presence or absence of a particular event or outcome of interest (e.g., from hospital records or other data sources) and their past exposure to a device is then studied.

Third, we interpret ''of health outcomes.'' For purposes of the definition of applicable device clinical trial, a ''prospective clinical study of health outcomes'' is a clinical study in which the primary objective is to evaluate a defined clinical outcome directly related to human health. For example, a clinical study of a diagnostic device (such as an in vitro diagnostic (IVD)) in which the primary purpose is to evaluate the ability of the device to make a diagnosis of a disease or condition is related directly to human health and, therefore, would be considered a clinical study ''of health outcomes'' for purposes of this proposed rule.

(2) ''Comparing an intervention with a device against a control in human subjects.'' We interpret an ''intervention with a device'' to be one in which a device is used on a human subject in the course of a study. As stated above, the meaning of the term ''human subject'' is consistent with the definition of ''subject'' in 21 CFR 812.3(p), except that for purposes only of the requirements under this part, the term ''human subject'' does not include de-identified human specimens. We interpret the term ''intervention'' broadly, to include various techniques of using the device such as, among other things, device regimens and procedures and use of prophylactic, diagnostic, or therapeutic agents.

A clinical study is considered to ''compare an intervention with a device against a control in human subjects'' when it compares differences in the clinical outcomes, or diagnosis, between human subjects who received an intervention that included a device and human subjects who received other interventions, or no intervention (i.e., the control group). The intervention under study may be with a device that has never been cleared or approved or with a device that has been cleared or approved, regardless of whether the clearance or approval is for the indication being studied. Such controlled clinical studies include not only concurrent control groups, but also non-concurrent controls such as historical controls (e.g., literature, patient records, human subjects as their own control) or validated objective outcomes using objective performance criteria, by which we mean performance criteria based on broad sets of data from historical databases (e.g., literature or registries) that are generally recognized as acceptable values.

Expanded access protocols under section 561 of the FD&C Act, under which investigational devices are made available to individuals under certain conditions, generally are not controlled clinical investigations and therefore generally are not applicable device clinical trials. In those instances in which use of an investigational device in an expanded access program is controlled and the program otherwise meets the definition of an applicable device clinical trial, the expanded access program would be considered an applicable clinical trial and would be registered as such. Similarly, continued access protocols, under which an investigational device continues to be made available after completion of a controlled trial while a marketing application is being prepared or reviewed, are, by definition, not controlled clinical investigations and, therefore, not applicable device clinical trials.

(3) ''A device subject to section 510(k), 515, or 520(m)'' of the FD&C Act. A device is considered to be subject to section 510(k), 515, or 520(m) of the FD&C Act if any of the following is required before it may be legally marketed in the U.S.: (1) a finding of substantial equivalence under section 510(k) permitting the device to be marketed; (2) an order under section 515 of the FD&C Act approving a pre-market approval application for the device; or (3) a humanitarian device exemption under section 520(m) of the FD&C Act. Such devices that are considered to be subject to section 510(k), 515, or 520(m) of the FD&C Act include significant risk devices for which approval of an investigational device exemption (IDE) is required under section 520(g) of the FD&C Act; non-significant risk devices that are considered to have an approved IDE in accordance with 21 CFR 812.2(b); or devices that are exempt from the submission requirements of 21 CFR 812.

If a clinical study of a device (1) includes sites both within the U.S. (including any territory of the U.S.) and outside of the U.S., and (2) any of those sites is using (for purposes of the clinical study) a device that is subject to section 510(k), 515, or 520(m) of the FD&C Act, we would consider the entire clinical study to be an applicable device clinical trial, provided that it meets all of the other criteria of the definition under this part. However, a clinical study of a device that is being conducted entirely outside of the U.S. (i.e., does not have any sites in the U.S. or in any territory of the U.S.) and is not conducted under an IDE may not be a clinical study of a device subject to section 510(k), 515, or 520(m) of the FD&C Act, and thus not an applicable device clinical trial, depending on where the device being used in the clinical study is manufactured. If the device is manufactured in the U.S. or any territory of the U.S., and is exported for study in another country (whether it is exported under section 801(e) or section 802 of the FD&C Act), then the device is considered to be subject to section 510(k), 515, or 520(m) of the FD&C Act. If the device is manufactured outside of the U.S. or its territories, and the clinical study sites are all outside of the U.S. and/or its territories, then the device would not be considered to be subject to section 510(k), 515, or 520(m) of the FD&C Act.

(4) ''Other than a small clinical trial to determine the feasibility of a device, or a clinical trial to test prototype devices where the primary outcome

measure relates to feasibility and not to health outcomes.'' Clinical studies designed primarily to determine the feasibility of a device or to test a prototype device are considered by the Agency to be clinical studies conducted to confirm the design and operating specifications of a device before beginning a full clinical trial. Feasibility studies are sometimes referred to as phase 1 studies, pilot studies, prototype studies, or introductory trials. Feasibility studies are not considered applicable device clinical trials under this proposed part.

The second part of the definition in section 402(j)(1)(A)(ii)(II) specifies that an applicable device clinical trial includes ''pediatric postmarket surveillance as required under section 522 of the Federal Food, Drug, and Cosmetic Act.'' Postmarket surveillances can take many forms, from literature reviews to controlled clinical trials. Based on the statutory language, any pediatric postmarket surveillance under section 522 of the FD&C Act, regardless of its design, is an applicable device clinical trial.

Applicable drug clinical trial is the term used in section 402(j) of the PHS Act to designate a clinical trial involving a drug (including a biological product) for which clinical trial information must be submitted to ClinicalTrials.gov, if the trial is subject to the registration and results submission requirements under section 402(j) of the PHS Act. Section 402(j)(1)(A)(iii)(I) of the PHS Act provides the following detailed definition of the term applicable drug clinical trial: ''a controlled clinical investigation, other than a phase I clinical investigation, of a drug subject to section 505 of the Federal Food, Drug, and Cosmetic Act or to section 351 of th[e] [PHS] Act.'' Sections 402(j)(1)(A)(iii)(II) and (III) of the PHS Act further clarify that the term ''clinical investigation'' has the meaning given in 21 CFR 312.3 (or any successor regulation) and ''phase I'' has the meaning given in 21 CFR 312.21 (or any successor regulation). We propose to adopt the statutory definition of this term, replacing ''phase I'' with ''phase 1,'' to be consistent with the numbering scheme used in FDA regulations (21 CFR 312.21). We provide additional elaboration of the interpretation of applicable clinical trial below.

We interpret the definition of applicable drug clinical trial under section 402(j)(1)(A)(iii) of the PHS Act as having four operative elements: (1) ''controlled''; (2) ''clinical investigation''; (3) ''other than a phase [1] clinical investigation''; and (4) ''drug subject to section 505 of the Federal Food, Drug, and Cosmetic Act or section 351 of th[e] [Public Health Service] Act.'' A clinical investigation that meets all four elements is considered to be an ''applicable drug clinical trial.'' Conversely, a clinical investigation that does not meet one or more of these criteria would not be considered an applicable drug clinical trial. We have carefully considered these four criteria, and our interpretation follows in an order that facilitates the explanation.

(1) First, with regard to a ''drug subject to section 505 of the Federal Food, Drug, and Cosmetic Act or section 351 of th[e] [Public Health Service] Act,'' proposed § 11.10 adopts the definition of the term ''drug'' in section 402(j)(1)(A)(vii) of the PHS Act as follows: ''drug as defined in section 201(g) of the [FD&C Act] or a biological product as defined in section 351 of th[e] [PHS] Act.'' In keeping with the requirements of the FD&C Act and section 351 of the PHS Act, a drug or a biological product is considered to be ''subject to section 505 of the [FD&C] Act or section 351 of th[e] [PHS] Act,'' as applicable, if it is the subject of an approved new drug application (NDA) or licensed biologics license application (BLA), or if an approved NDA or licensed BLA would be required in order for that drug or biological product to be legally marketed. A non-prescription drug that is or could be marketed under an existing over-the-counter (OTC) drug monograph (See 21 CFR 330–358) is not considered ''subject to section 505 of the [FD&C] Act.''

A drug or a biological product that is subject to section 505 of the FD&C Act or to section 351 of the PHS Act, and therefore would require an approved NDA or licensed BLA in order to be marketed legally, can be shipped for the purpose of conducting a clinical investigation of that product if an investigational new drug application (IND) is in effect. Drugs (including biological products) that are being studied under an IND are considered ''subject to section 505'' both because (in most situations) the drug being studied would need an approved NDA or licensed BLA to be marketed legally, and because INDs are issued by FDA pursuant to the authority in section 505(i) of the FD&C Act. However, whether a drug or biological product is subject to section 505 of the FD&C Act or section 351 of the PHS Act is a different question from whether a clinical investigator would need to obtain an IND from FDA before beginning to enroll human subjects in that clinical investigation. Therefore, a drug (or biological product) being studied in a clinical investigation can be subject to section 505 of the FD&C Act or section 351 of the PHS Act, even if a clinical investigation of that drug or biological product is ''IND exempt'' (i.e., does not require an IND because that clinical investigation falls within 21 CFR 312.2(b)). Hence, provided it meets all other criteria of the definition, a clinical investigation of a drug (including a biological product) can be an applicable drug clinical trial under section 402(j) of the PHS Act and this part, even if it does not require an IND. Furthermore, if a sponsor chooses to obtain an IND (issued under section 505 of the FD&C Act) for a clinical investigation of a drug (including a biological product) that is not otherwise subject to section 505 or to section 351 of the PHS Act, the sponsor, in so doing, agrees to regulation under section 505 of the FD&C Act, and that clinical investigation thus will be considered an applicable drug clinical trial, provided that it meets all other criteria of the definition under this part.

If a clinical investigation of a drug (including a biological product) (1) includes sites both within the U.S. (including any territory of the U.S.) and outside of the U.S., and (2) any of those sites is using (for purposes of the clinical investigation) a drug or biological product that is subject to section 505 of the FD&C Act or section 351 of the PHS Act, we would consider the entire clinical investigation to be an applicable drug clinical trial, provided that it meets all other criteria of the definition under this part. However, a clinical investigation of a drug (including a biological product) that is being conducted entirely outside of the U.S. (i.e., does not have any sites in the U.S. or in any territory of the U.S.) may or may not be a clinical investigation of a drug or biological product subject to section 505 of the FD&C Act or section 351 of the PHS Act, and thus not an applicable drug clinical trial, depending on where the drug (including biological product) being used in the clinical investigation is manufactured. If the drug (including a biological product) is manufactured in the U.S. or any territory of the U.S., and is exported for study in another country under an IND (whether pursuant to 21 CFR 312.110 or section 802 of the FD&C Act), the drug or biological product is considered to be subject to section 505 of the FD&C Act or section 351 of the PHS Act (as applicable), and the clinical investigation may be an applicable drug clinical trial, provided that it meets all other criteria of the definition under this part. If the drug (including a biological

product) is manufactured outside of the U.S. or its territories, the clinical investigation sites are all outside of the U.S., and the clinical investigation is not being conducted under an IND, the drug or biological product would not be considered to be subject to section 505 of the FD&C Act or section 351 of the PHS Act, and the clinical investigation would not be an applicable drug clinical trial.

(2) Second, with regard to ''clinical investigation,'' section 402(j)(1)(A)(iii)(II) of the PHS Act provides that ''clinical investigation'' has the meaning given that term in 21 CFR 312.3, which defines ''[c]linical investigation'' as ''any experiment in which a drug is administered or dispensed to, or used involving, one or more human subjects.'' The regulation further defines an ''experiment'' as ''any use of a drug except for the use of a marketed drug in the course of medical practice.''

The FDA definition of ''clinical investigation'' of a drug includes studies in which human subjects are assigned to specific interventions according to a protocol. However, a situation in which a drug is administered or provided to a patient as part of routine medical care and not under a study or protocol would not be considered a ''clinical investigation'' for purposes of this rulemaking. Examples of studies that might fall under this description include situations in which, after a drug has been administered to a patient in the course of routine medical practice by a healthcare provider, a researcher not associated with the administration of the drug reviews the records of the patients to assess certain effects, interviews the patients to assess certain impacts, or collects longitudinal data to track health outcomes. Similarly, a situation in which a healthcare provider only observes and records the effects of the use of a marketed drug in the course of his or her routine medical practice would not be considered a ''clinical investigation'' under this definition. Because these activities would not be considered ''clinical investigations'' under 21 CFR 312.3, they would not be considered applicable drug clinical trials under section 402(j) of the PHS Act and this proposed part. Accordingly, in the approach described below in § 11.22(b)(2), we consider an ''interventional'' study (or investigation) of a drug to be an applicable drug clinical trial.

(3) Third, with regard to ''controlled,'' we consider a controlled clinical investigation to be one that is designed to permit a comparison of a test intervention with a control to provide a quantitative assessment of the drug effect. The purpose of the control is to distinguish the effect of a drug from other influences, such as the spontaneous change in the course of the diseases, placebo effect, or biased observation. The control will provide data about what happens to human subjects who have not received the test intervention or who have received a different intervention. Generally, the types of controls that are used in clinical investigations are: (1) Placebo concurrent control; (2) dose-comparison control; (3) no intervention concurrent control; (4) active intervention concurrent control; and (5) historical control. (See 21 CFR 314.126(b).)

In our view, a clinical investigation designed to demonstrate that an investigational drug product is bioequivalent to a previously approved drug product, or to demonstrate comparative bioavailability of two products (such as for purposes of submitting an abbreviated new drug application under 21 U.S.C. 355(j) or a new drug application as described in 21 U.S.C. 355(b)(2)) is considered to be a controlled clinical investigation. In this case, the control generally would be the previously approved drug product. However, as discussed below, bioequivalent or comparative bioanalysis studies that fall within the scope of studies described in 21 CFR 320.24(b)(1), (2), and (3) share many of the characteristics of a phase 1 study and would be considered phase 1 trials (and thus not applicable clinical trials) in this proposed rule.

Similar to expanded access to investigational devices, as discussed above in the definition of applicable device clinical trial, the use of an investigational drug in an expanded access program under section 561 of the FD&C Act is generally not ''controlled,'' and generally does not meet the definition of a ''controlled clinical investigation.'' In those instances in which use of an investigational drug in an expanded access program is controlled and the program otherwise meets the definition of an applicable drug clinical trial, the expanded access program would be considered an applicable clinical trial.

(4) Fourth, with regard to the ''other than a phase [1] clinical investigation'' element, an applicable drug clinical trial is defined in section 402(j)(1)(A)(iii) of the PHS Act to exclude phase 1 clinical investigations, consistent with 21 CFR 312.21. Under 21 CFR 312.21(a)(1), a phase 1 study ''includes the initial introduction of an investigational new drug into humans. Phase 1 studies are typically closely monitored and may be conducted in patients or normal volunteer subjects. These studies are designed to determine the metabolism and pharmacologic actions of the drug in humans, the side effects associated with increasing doses, and, if possible, to gain early evidence on effectiveness. During phase 1, sufficient information about the drug's pharmacokinetics and pharmacological effects should be obtained to permit the design of well-controlled, scientifically valid, phase 2 studies. The total number of subjects and patients included in phase 1 studies varies with the drug, but is generally in the range of 20 to 80.'' Under 21 CFR 312.21(a)(2), ''[p]hase 1 studies also include studies of drug metabolism, structure-activity relationships, and mechanism of action in humans, as well as studies in which investigational drugs are used as research tools to explore biological phenomena or disease processes.'' Studies that are phase 1 studies under 21 CFR 312.21 are not applicable drug clinical trials. Studies that are phase 1/phase 2 studies are not considered phase 1 studies and may be applicable drug clinical trial if they meet the other specified criteria.

Under certain circumstances, a clinical investigation designed to demonstrate that an investigational drug product is bioequivalent to a previously approved drug product, or to demonstrate comparative bioavailability of two products (such as for purposes of submitting an abbreviated new drug application under 21 U.S.C. 355(j) or a new drug application as described in 21 U.S.C. 355(b)(2)) will be considered to be a phase 1 clinical investigation under 21 CFR 312.21 for purposes of determining whether a particular clinical trial is an applicable drug clinical trial under section 402(j)(1)(A)(iii) of the PHS Act. Although phase 1 clinical investigations are generally designed to fit sequentially within the development plan for a particular drug, and to develop the data that will support beginning phase 2 studies, 21 CFR 312.21(a) does not limit phase 1 trials to that situation. Bioequivalence or comparative bioavailability studies that fall within the scope of the studies described in 21 CFR 320.24(b)(1), (2), and (3) share many of the characteristics of phase 1 clinical investigations as described in 21 CFR 312.21(a), and therefore will be considered to be phase 1 trials for purposes of section 402(j) of the PHS Act. However, bioequivalence or comparative bioavailability trials that fall within the scope of 21 CFR 320.24(b)(4) do not share the characteristics of phase 1 trials as

described in 21 CFR 312.21(a), and thus would not be considered to be phase 1 trials for purposes of section 402(j) of this proposed part.

In addition, for purposes of implementing this proposed rule, we propose to treat certain clinical trials of combination products as applicable drug clinical trials. Combination products are defined in 21 CFR 3.2(e). A combination product is comprised of a drug and device; a biological product and device; a drug and biological product; or a drug, biological product, and device that, for example, are physically, chemically, or otherwise combined or mixed and produced as a single entity or are separate products packaged together in a single package or as a unit. (See 21 CFR 3.2(e)(1) and (2)). Because the definition of drug in proposed § 11.10 includes a biological product, a combination product under this proposed rule would always consist, in part, of a drug. For this reason, we propose to treat clinical trials of combination products that meet the definition in 21 CFR 3.2(e) as applicable drug clinical trials, for purposes of implementing this proposed rule, so long as the clinical trial of the combination product is a controlled clinical investigation, other than a phase 1 clinical investigation (as described in above), and the combination product is subject to sections 505 of the FD&C Act and/or section 351 of the PHS Act (as described above) and/or section 510(k), 515, or 520(m) of the FD&C Act (as described in the definition of an applicable device clinical trial). Such clinical trials of combination products would therefore be subject to the registration and results submission requirements, including requirements for posting clinical trial information, for applicable drug clinical trials as described in this proposed part. We believe this approach will provide clarity to responsible parties conducting clinical trials of combination products.

Approved drug is defined to mean ''a drug that is approved for any indication under section 505 of the FD&C Act or a biological product licensed for any indication under section 351 of the PHS Act.''

Approved or cleared device. Section 402(j)(2)(D)(ii)(II) of the PHS Act uses the phrase ''a device that was previously cleared or approved'' to refer to a subset of devices that, if studied in an applicable device clinical trial, would trigger certain requirements under this proposed part with respect to the submission and public posting of clinical trial information. Accordingly, we believe that it is helpful to define the term ''approved or cleared device.'' Specifically, we want to clarify that our definition of approved or cleared device refers to any device that has been approved or cleared under the applicable section of the FD&C Act for any indication, even if the applicable device clinical trial studies the device for an unapproved or uncleared use. Consistent with the reference in section 402(j)(2)(D)(ii) of the PHS Act to approval or clearance of a device under the designated sections of the FD&C Act, we propose to define an approved or cleared device as ''a device that is cleared under section 510(k) of the FD&C Act or approved under section 515 or 520(m) of the FD&C Act for any indication.''

Arm is defined to mean ''a pre-specified group or subgroup of human subjects in a clinical trial assigned to receive specific intervention(s) (or no intervention) according to a protocol.''

Clinical trial is defined to mean ''a clinical investigation or a clinical study in which human subjects are prospectively assigned, according to a protocol, to one or more interventions (or no intervention) to evaluate the effects of the interventions on biomedical or health-related outcomes.'' The proposed definition explicitly includes ''biomedical'' in addition to ''health-related'' outcomes because we have defined the term ''clinical trial'' to include phase 1 studies, which may measure physiological changes that are biomedical in nature but may not be related to health effects. We have defined the term ''clinical trial'' to include phase 1 studies, in part, because phase 1 studies may be voluntarily submitted under section 402(j)(4)(A) of the PHS Act. The restriction of the scope of this definition to clinical investigations or studies in which human subjects are prospectively assigned to interventions is intended to distinguish clinical trials (interventional studies) from observational studies, in which the investigator does not assign human subjects to interventions, but, for example, observes patients who have been given interventions in the course of routine clinical care. Observational studies may also include retrospective reviews of patient medical records or relevant literature.

Further, in terms of defining the scope of a clinical trial, we recognize that it is sometimes difficult to determine the boundaries of a single clinical trial when there are two or more closely related clinical trials. In general, a clinical trial has an explicit group of human subjects who are assigned to interventions based on a protocol. The data from these human subjects are assessed and analyzed based on a protocol. However, when two different clinical trials share the same protocol, but the groups of human subjects are different and the outcomes will be analyzed separately, then they should be considered separate clinical trials. This is distinct from a situation in which multiple sites of the same clinical trial follow the same protocol with different groups of human subjects, but the intention is to analyze the primary outcome measure(s) with pooled data from all of the study sites. When some (or all) human subjects from a clinical trial are offered the opportunity to participate in an additional clinical trial that was not part of the original protocol (e.g., a follow-on study), and that requires a separate consent process, it would be considered a separate clinical trial.

Clinical trial information is the term defined in section 402(j) of the PHS Act to designate those data elements that the responsible party is required to submit to ClinicalTrials.gov when registering or submitting results information for a clinical trial, as described in §§ 11.28 and 11.48 of this proposed rule, respectively. Section 402(j)(1)(A)(iv) of the PHS Act expressly provides that ''[c]linical trial information'' means ''those data elements that the responsible party is required to submit under paragraph (2) or under paragraph (3)'' of section 402(j) of the PHS Act. Paragraph (2) refers to registration requirements and paragraph (3) refers to results submission requirements. Section 402(j)(3)(I)(v) of the PHS Act also expressly provides that adverse event information included in the data bank pursuant to the paragraph (3)(I) ''is deemed to be clinical trial information included in such data bank pursuant to subparagraph (C).'' Therefore, for purposes of this proposed rule, clinical trial information means ''the data elements, including clinical trial registration information and clinical trial results information that the responsible party is required to submit to ClinicalTrials.gov under this part.''

Clinical trial registration information is defined to mean ''the data elements that the responsible party is required to submit to ClinicalTrials.gov under § 11.28.'' The full set of data elements under § 11.28 must be submitted in order to register under proposed subpart B.

Clinical trial results information is defined to mean ''the data elements that the responsible party is required to submit to ClinicalTrials.gov under § 11.48 or, if applicable, § 11.60(a)(2)(i)(B).'' The full set of data elements under § 11.48 must be submitted when providing results

information under proposed subpart C. Clinical trial results information includes the adverse event information set forth in proposed § 11.48(a)(4). We include adverse event information as part of clinical trial results information pursuant to section 402(j)(3)(I)(v) of the PHS Act, which indicates that the adverse event information included in the registry and results data bank under section 402(j)(3)(I) of the PHS Act ''is deemed to be clinical trial information included in [the] data bank pursuant to [section 402(j)(3)(C) of the PHS Act].'' As discussed in greater detail in section IV.D.1 of this preamble, if, under proposed § 11.60, a responsible party seeks to submit clinical trial results information voluntarily for a clinical trial for which clinical trial registration information specified in § 11.28(a) is not submitted, clinical trial results information is defined to include the data elements in proposed § 11.48(a) and the data elements set forth in proposed § 11.60(a)(2)(i)(B).

Comparison group is defined in this proposed rule to mean ''a grouping of human subjects in a clinical trial, other than an arm, that is used in analyzing the results data collected during the clinical trial.'' In some trials, results data are not analyzed according to the arms to which human subjects were assigned; the data may be combined into other groupings for analysis. For example, in a cross-over study, human subjects in one arm of a trial may receive intervention X for a period of time followed by intervention Y, while human subjects in another arm of the trial may receive intervention Y for a period of time followed by intervention X. In such studies, results data are often analyzed by intervention (e.g., results for human subjects when receiving intervention X versus results for human subjects when taking intervention Y), rather than by arm. When submitting results information to ClinicalTrials.gov under proposed § 11.48, we believe responsible parties should submit the data in the same way in which it was analyzed, whether by arm (as defined above) or by comparison group. We do expect that the set of comparison groups for a particular trial would account for all of the participants in the analysis.

Completion date is defined in section 402(j)(1)(A)(v) of the PHS Act 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, whether the clinical trial concluded according to the pre-specified protocol or was terminated.'' This term has particular significance because the responsible party is required to submit ''the expected completion date'' to ClinicalTrials.gov upon registration (See section 402(j)(2)(A)(ii)(I)(jj) of the PHS Act) and to submit clinical trial results information for certain applicable clinical trials not later than 1 year after the earlier of the estimated or the actual completion date, See sections 402(j)(3)(E)(i)(I)&(II) of the PHS Act (unless the deadline is delayed or extended using one of the mechanisms described in proposed § 11.44). For purposes of this proposed rule, we interpret ''expected completion date'' to be synonymous with ''estimated completion date.''

This proposed rule adopts the statutory definition of completion date with respect to applicable clinical trials that are clinical trials with one modification. If a clinical trial has multiple primary outcome measures, each with a different date on which the final human subject is examined or receives an intervention for purposes of final data collection, the ''completion date'' refers to the date upon which data collection is completed for all of the primary outcomes. While this approach may delay somewhat the submission and public availability of clinical trial results information for the earliest primary outcomes, we expect any such delays to be minimal. Most clinical trials registered at ClinicalTrials.gov to date specify only a single primary outcome, and those with multiple primary outcomes have measurement time frames that are relatively close in time. Moreover, the proposed approach avoids cases in which the submission of clinical trial results information would be required before data collection has been completed for all of the primary outcomes in a clinical trial and before all of the results data for the primary outcomes have been ''unblinded,'' a situation that could threaten the scientific integrity of the clinical trial. While a responsible party could request a good-cause extension of the results submission deadline in such a situation under proposed § 11.44(e), the proposed definition should reduce the number of good-cause extension requests that responsible parties might be expected to file. Submission of results data for all primary outcomes at the same time will also aid in the interpretation of clinical trial results information by providing users of ClinicalTrials.gov with a more comprehensive set of data from the clinical trial, rather than data for only some of the primary outcomes. Thus, for purposes of this proposed rule, completion date means ''for a clinical trial, 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 pre-specified protocol or was terminated. In the case of clinical trials with more than one primary outcome measure with different completion dates, this term refers to the date upon which data collection is completed for all of the primary outcomes.''

We note that the current implementation of ClinicalTrials.gov uses the term ''primary completion date'' to refer to ''completion date,'' as defined in section 402(j)(1)(A)(v) of the PHS Act. This was done to alert those submitting data to ClinicalTrials.gov under section 402(j) of the PHS Act that the definition of completion date differs from that of the term, ''study completion date,'' which refers to the date on which the last subject makes the last visit as part of the clinical trial (commonly referred to as ''last patient, last visit'' or LPLV) and is also collected by ClinicalTrials.gov. To improve concordance with section 402(j) of the PHS Act and to be consistent with our proposed definition, ClinicalTrials.gov will begin to use the term completion date once the final regulations take effect. We will include a notice in ClinicalTrials.gov to alert responsible parties to this change in data element name.

For a pediatric postmarket surveillance of a device that is not a clinical trial, completion date means ''the date on which the final report summarizing the results of the pediatric postmarket surveillance is submitted to FDA.'' (See proposed § 11.10.)

Control or Controlled are terms used in sections 402(j)(1)(A)(ii)(I) and (iii)(I) of the PHS Act as part of the definitions of ''applicable device clinical trial'' and ''applicable drug clinical trial,'' respectively. For purposes of this proposed rule, the term ''controlled'' means, ''with respect to a clinical trial, that data collected on human subjects in the clinical trial will be compared to concurrently collected data or to non-concurrently collected data (e.g., historical controls, including a human subject's baseline data), as reflected in the pre-specified primary or secondary outcome measures.'' This is consistent with FDA regulations that define the related concepts of ''adequate and well-controlled studies'' for drugs (21 CFR 314.126(b)(1) and (2)) and ''a well-controlled clinical investigation'' for devices (21 CFR 860.7(f)). FDA has also adopted as guidance the International Conference on Harmonization E10: Choice of Control Group and Related Issues in Clinical Trials (ICH E10), which describes considerations to be

used in choosing a control group. In FDA regulations, the critical attribute of a well-controlled clinical trial, which is the intent of any controlled trial, is ''a design that permits a valid comparison with a control to provide a quantitative assessment'' of the effect of the investigational intervention. (See 21 CFR 314.126(b)(2).) The FDA regulations recognize several types of concurrent controls (e.g., active control) and the non-concurrent, historical control. This can refer to a control group for which data were collected at a different time or place but can also refer to a clinical trial in which subjects serve as their own controls (e.g., the clinical trial measures change from baseline).

Our proposed definition of controlled is consistent with the types of controls recognized by FDA and the ICH E10 guidance, but is potentially broader in that it does not require that the study be ''adequate,'' i.e., that the control allows a valid comparison of the two treatments. It is consistent in that it explicitly recognizes both concurrent and non-concurrent controls. We recognize that this interpretation may differ from common use of the term ''controlled'' by some researchers, who may consider only studies with concurrent controls to be ''controlled,'' but we believe it is important to maintain consistency with the approach of the FDA and ICH E10 and to include non-concurrent controls. Our definition of controlled is broader than that of ''well-controlled'' used by FDA and ICH E10 because FDA regulations and the ICH E10 guidance describe the more limited circumstances in which use of a non-concurrent control constitutes a ''well-controlled'' clinical trial, i.e., one that might serve to support marketing. Although FDA regulations state that historical controls are usually reserved for special circumstances, such as studies of a disease with ''high and predictable mortality'' (e.g., certain malignancies) or in which the effect of the drug is ''self-evident'' (e.g., anesthesia, cardioversion), our proposed definition of controlled would include all studies using an historical control, regardless of whether the study is of a disease with a ''high and predictable mortality'' or in which the effect of the drug is self-evident. Our proposed definition would encompass all studies and investigations with a placebo concurrent control, dose-comparison concurrent control, no treatment concurrent control, active treatment concurrent control, and historical control, but it would not reflect a consideration of the adequacy or appropriateness of the control or the adequacy of the study design, e.g., whether adequate steps were taken to minimize bias. Hence it would cover all trials that are controlled, using concurrent or non-concurrent controls, regardless of whether they would be considered ''well-controlled.''

Under our proposed definition, any clinical trial with two or more arms would be considered controlled because it would involve the comparison of data collected concurrently from different arms of the study. Some single-arm trials that meet the other components of the definition of an applicable clinical trial, e.g., not phase 1 or a feasibility study, could also meet this definition of controlled. These include the single-arm trials of FDA-regulated products that have as a stated objective in their protocol to evaluate a response rate to an intervention, to measure effectiveness of an intervention at specific endpoints, and/or to compare the effect of an intervention against an identified baseline. Thus, single-arm clinical trials that explicitly identify primary or secondary outcomes in the protocol that involve comparisons to historical data (including baseline data) would be considered controlled.

Enroll or Enrolled is a term used in section 402(j)(1)(A)(viii)(I) of the PHS Act as part of the definition of ''[o]ngoing'' and in 402(j)(2)(C)(ii) of the PHS Act as one of the criteria used to establish the deadline by which a responsible party is required to submit clinical trial registration information. For purposes of this proposed rule, the term ''enrolled'' means ''a human subject's agreement to participate in a clinical trial, as indicated by the signing of the informed consent document(s).'' (See proposed § 11.10.)

Human subjects protection review board is defined in § 11.10 of this proposed rule to mean an ''institutional review board (IRB) as defined in 21 CFR 50.3 and 45 CFR 46.102 (or any successor regulation), as applicable, or equivalent independent ethics committee that is responsible for ensuring the protection of the rights, safety, and well-being of human subjects involved in a clinical investigation and is adequately constituted to provide assurance of that protection.'' We propose to include this definition to clarify the scope of the review boards for which Human Subjects Protection Review Board Status must be submitted under proposed § 11.28 (see section IV.B.4(a)(4) of this preamble). For clinical trials conducted in the U.S. or under an IND or IDE, the term human subjects protection review board would mean an institutional review board, as defined in the cited regulations issued by the FDA and OHRP within HHS. For clinical trials conducted outside the United States or otherwise outside the scope of the regulations for institutional review boards, the term would refer to other independent ethics committees that are responsible for ensuring the protection of the rights, safety, and well-being of human subjects involved in a clinical investigation and are adequately constituted to provide assurance of that protection. This phrasing is consistent with, but not identical to, the definition of the term ''independent ethics committee,'' in FDA regulations for INDs (See 21 CFR 312.3). It is also consistent with longstanding use of the term ''human subjects protection review board'' at ClinicalTrials.gov, which instructed registrants to provide information about ''[a]ppropriate review boards[, including] an Institutional Review Board, an ethics committee or an equivalent group that is responsible for review and monitoring of this protocol to protect the rights and welfare of human research subjects.'' [Ref 50]

Interventional is defined in this proposed rule to mean, ''with respect to a clinical study or a clinical investigation that 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.'' We propose to define this term to distinguish interventional studies from observational studies, as those terms are used in the clinical research community. Observational studies include those in which a patient receives an intervention as part of routine medical care, and a researcher studies the effect of the intervention. They also include retrospective reviews of patient medical records or relevant literature, as may occur in a pediatric postmarket surveillance of a device. Interventional studies are those in which a researcher assigns subjects to specific interventions (or to no intervention) according to a study protocol for purposes of the investigation. For purposes of this part, we use the term ''clinical trial'' to refer to interventional studies to the exclusion of observational studies. (See the proposed definition of clinical trial). The term ''interventional'' is one of the responses that can be submitted as part of the Study Type data element that is included as clinical trial registration information under proposed § 11.28 and defined in § 11.10. Responsible parties must indicate whether a study being registered is ''interventional'' or

''observational,'' or is an expanded access program that does not meet the definition of an applicable clinical trial. A study that is designated as ''interventional'' can be an applicable clinical trial if it meets the other criteria for an applicable clinical trial that are specified in this part. (See the proposed definitions of applicable device clinical trial and applicable drug clinical trial). A study should be designated interventional if it meets the proposed definition even if the medical products being studied are being used in a manner considered to be the standard of care. A study that is designated ''observational'' can be an applicable clinical trial only if it is a pediatric postmarket surveillance of a device as defined in this part. (See the proposed definition of pediatric postmarket surveillance of a device).

NCT number is the term used in this proposed part to refer to the term ''National Clinical Trial number[,]'' which is used in section 402(j)(2)(B)(i)(VIII) of the PHS Act. Since its launch in 2000, ClinicalTrials.gov has assigned each submitted clinical trial record a unique identifier once the information has completed quality review procedures. While the identifier originally was called a National Clinical Trial number, that nomenclature was soon changed to ''NCT number'' in recognition of the fact that ClinicalTrials.gov also receives clinical trial information about trials being conducted in countries other than the United States. We propose to maintain the term ''NCT number'' in this part. NCT numbers are used in many contexts to refer to clinical trial records or other types of records (e.g., observational studies, expanded access programs) that are accepted by ClinicalTrials.gov. Under the ICMJE registration policy, for example, journals publishing original papers on the results of clinical trials require their authors to include in their manuscripts a unique identification number assigned by a recognized clinical trial registry as evidence that the trial has been registered in compliance with the ICMJE policy [Ref. 10]. For trials registered in ClinicalTrials.gov, this unique identifier is the NCT number. When published in journal articles, NCT numbers are also included in MEDLINE records and are searchable through PubMed [Ref. 42]. For purposes of this proposed rule, NCT number means ''the unique identification code assigned to each record in ClinicalTrials.gov, including a record for an applicable clinical trial, a clinical trial, or an expanded access program.'' The NCT number is assigned to clinical trials and expanded access records once registration information has been submitted to the Director and the Director's quality control process has been completed, with the exception that if a responsible party voluntarily submits only clinical trial results information under § 11.60(a)(2)(i)(B), the NCT number is assigned once complete clinical trial results information has been submitted to the Director and the Director's quality control process has been completed.

Ongoing is defined in this proposed rule in § 11.10 to mean, ''with respect to a clinical trial of a drug or a device and to a date, that one or more human subjects is enrolled in the clinical trial, and the date is before the completion date of the clinical trial.'' This definition is the same as the statutory definition except the term ''human subjects'' has been substituted for the term ''patients'' that is used in section 402(j)(1)(A)(viii) of the PHS Act. The reason for this change is that clinical trials may include healthy volunteers as well as human subjects who might be considered ''patients.''

With respect to a pediatric postmarket surveillance of a device, we define the term ''ongoing'' to mean ''a date between the date on which FDA approves the plan for conducting the surveillance and the date on which the final report is submitted to FDA.''

Outcome measure is defined in this proposed rule to mean ''a pre-specified measurement that will be used to determine the effect of experimental variables on the human subjects in a clinical trial.'' The experimental variables may be the specific intervention(s) used in the clinical trial or other elements of the clinical trial that vary between arms, e.g., diagnostic or other procedures provided to participants in different arms. In this proposed part, outcome measure refers to measurements taken on those human subjects who are enrolled in the clinical trial of interest. Although it is not uncommon to compare data derived from human subjects enrolled in a clinical trial with data derived from other sources (e.g., literature, other clinical trials), we believe that only measurements taken from participants in the clinical trial of interest should be submitted as results information to ClinicalTrials.gov. In our view, comparisons of such data with results data derived from other sources are more appropriately described in forums other than ClinicalTrials.gov (e.g., journal articles) where the other comparator can be explained in detail. Clinical trial information submitted for a clinical trial of interest would not describe the human subjects studied in another clinical trial (i.e., the clinical trial record would not contain baseline and demographic information about them, nor would it describe how they were allocated to arms of the clinical trial to receive interventions). See the definitions of primary outcome, measure and secondary outcome measure below.

Pediatric postmarket surveillance of a device is a term used in section 402(j)(1)(A)(ii)(II) of the PHS Act to describe a type of applicable device clinical trial. The term ''[a]pplicable device clinical trial'' includes ''a pediatric postmarket surveillance as required under . . . [section 522 of the FD&C Act].'' Pursuant to section 522, FDA defines the term ''postmarket surveillance'' as ''the active, systematic, scientifically valid collection, analysis, and interpretation of data or other information about a marketed device.'' (See 21 CFR 822.3(h).) In Title III of FDAAA, Congress directed that the term ''pediatric,'' when used with respect to devices, refers to patients 21 and younger. (See Title III of FDAAA (''Pediatric Medical Device Safety and Improvement Act of 2007''), amending section 520(m) of the FD&C Act). Thus, for purposes of this proposed rule, the term pediatric postmarket surveillance of a device is defined to mean ''the active, systematic, scientifically valid collection, analysis, and interpretation of data or other information conducted under section 522 of the [FD&C] Act about a marketed device that is expected to have significant use in patients who are 21 years of age or younger at the time of diagnosis or treatment. A pediatric postmarket surveillance of a device may be, but is not always, a clinical trial.'' (See proposed § 11.10.)

Primary outcome measure(s) is a term used, but not defined, in section 402(j) of the PHS Act. Section 402(j)(2)(A)(ii)(I)(ll) of the PHS Act expressly requires primary outcome measures to be submitted as a clinical trial registration information data element. In addition, section 402(j)(1)(A)(v) of the PHS Act defines the completion date in relation to the ''final collection of data for the primary outcome.'' Primary outcome measure(s) also expressly is required as a clinical trial results information data element by section 402(j)(3)(C)(ii) of the PHS Act. We believe this enables users of ClinicalTrials.gov to identify the pre-specified primary outcome measure(s) for the clinical trial submitted as part of the clinical trial registration information and to examine the results data collected for those outcome measures and submitted to the data bank as part

of clinical trial results information. We propose to define primary outcome measure to mean ''the outcome measure(s) of greatest importance specified in the protocol, usually the one(s) used in the power calculation. Most clinical trials have one primary outcome measure, but a clinical trial may have more than one . . .'' (See proposed § 11.10.) We note that for the purpose of this proposed rule, ''primary outcome'' has the same meaning as ''primary outcome measure.'' (See proposed § 11.10.) See also the discussion in part IV of this preamble regarding primary outcome measure as a clinical trial registration information data element in proposed § 11.28(a)(1)(xix) and as a clinical trial results information data element in proposed § 11.48(a)(3).

Principal Investigator (PI) is a term used in the definition of responsible party in section 402(j)(1)(A)(ix) of the PHS Act. For purposes of this proposed rule, principal investigator means ''the individual who is responsible for the scientific and technical direction of the study.'' (See proposed § 11.10.) This proposed definition uses terminology derived from 42 CFR 52.2, which defines principal investigator in the context of an NIH grant as ''the individual(s) judged by the applicant organization to have the appropriate level of authority and responsibility to direct the project or program supported by the grant and who is or are responsible for the scientific and technical direction of the project.'' We have modified that definition to remove references to ''applicant organization'' and ''project or program supported by the grant'' that are specific to NIH-funded grants and would not necessarily apply to applicable clinical trials that are funded by industry or other non-governmental organizations. We use the term ''study'' in place of ''project'' because the projects of relevance to this rule would be clinical studies, whether clinical trials or pediatric postmarket surveillances of a device. We have also modified the definition in order to indicate that it applies to only a single individual. This is consistent with our interpretation that there cannot be more than one responsible party for a clinical trial. We would expect a principal investigator to have full responsibility for the treatment and evaluation of human subjects in the study and for the integrity of the research data for the full study. In keeping with this approach, an investigator for an individual site in a multi-site clinical trial would not be considered the PI unless he or she also has overall responsibility for the clinical trial at all sites at which it is being conducted. This interpretation is consistent with the requirement in section 402(j)(1)(A)(ix) of the PHS Act that a principal investigator may be a responsible party only if he or she is responsible for conducting the trial, has access to and control over the data from the clinical trial, has the right to publish the clinical trial results, and has the ability to meet all the requirements for the submission of clinical trial information under section 402(j) of the PHS Act and this proposed part.

We note that the PI of a grant awarded by a Federal Government agency that funds a clinical trial may not necessarily be the PI for that clinical trial for purposes of this proposed rulemaking. For example, the PI on a federal grant who has responsibility for only one site of a multi-site clinical trial (See, e.g., 42 CFR 52.2.) would neither have the requisite responsibility for conducting the entire trial nor the requisite access to data from all sites involved in the clinical trial, both of which are required by section 402(j) of the PHS Act and this proposed part in order to meet the definition of responsible party. Accordingly, the PI on such a grant would not be considered to be the responsible party for purposes of registering and submitting clinical trial results information under section 402(j) of the PHS Act and this proposed part.

Protocol is the document that describes the design of a clinical trial. It may be, and frequently is, amended after a clinical trial has begun. For purposes of this proposed rule, protocol means ''the written description of the clinical trial, including objective(s), design, and methods. It may also include relevant scientific background and statistical considerations.'' This proposed definition is derived from ICH E6(R1): Good Clinical Practice: Consolidated Guideline [Ref. 40], which defines the term as ''[a] document that describes the objective(s), design, methodology, statistical considerations, and organization of a trial. The protocol usually also gives the background and rationale for the trial, but these could be provided in other protocol referenced documents.'' The protocol generally addresses major statistical considerations, such as the number of human subjects required to provide adequate statistical power, but it may or may not include detailed information about the specific statistical analyses to be performed as part of the clinical trial. Such information may be contained in a separate statistical analysis plan.

Responsible party is the term used in section 402(j) of the PHS Act in order to refer to the entity or individual who is responsible for registering a clinical trial or a pediatric postmarket surveillance of a device that is not a clinical trial and for submitting clinical trial information to ClinicalTrials.gov. Consistent with the definition provided in section 402(j)(1)(A)(ix) of the PHS Act, this proposed rule defines the term ''responsible party'' to mean, ''with respect to a clinical trial, (i) the sponsor of the clinical trial, as defined in 21 CFR 50.3 (or any successor regulation); or (ii) the principal investigator of such clinical trial if so designated by a sponsor, grantee, contractor, or awardee, so long as the principal investigator is responsible for conducting the trial, has access to and control over the data from the clinical trial, has the right to publish the results of the trial, and has the ability to meet all of the requirements under this part for the submission of clinical trial information. For a pediatric postmarket surveillance of a device that is not a clinical trial, the responsible party is the entity whom FDA orders to conduct the pediatric postmarket surveillance of a device.'' Proposed procedures for determining which individual or entity meets the definition of responsible party are specified in § 11.4(c) and described in section IV.A.2 of this preamble.

Secondary outcome measure(s) is a term used, but not defined, in section 402(j) of the PHS Act. Section 402(j)(2)(A)(ii)(I)(ll) of the PHS Act expressly requires secondary outcome measures to be submitted as a clinical trial registration information data element, as a component of the outcome measures data element. In addition, secondary outcome measure(s) also is expressly required as a clinical trial results information data element by section 402(j)(3)(C)(ii) of the PHS Act. We believe this structure enables users of ClinicalTrials.gov to identify the pre-specified secondary outcome measures for the clinical trial submitted as part of the clinical trial registration information and to examine the results data collected for those outcome measures and submitted to the data bank as part of clinical trial results information. Our proposed definition of ''secondary outcome measure'' means ''an outcome measure that is of lesser importance than a primary outcome measure, but is part of a pre-specified plan for evaluating the effects of the intervention or interventions under investigation in a clinical trial. A clinical trial may have more than one secondary outcome measure.'' This definition is consistent with the WHO Trial Registration standard and ICMJE registration policies

[Ref. 10, 13]. We note that for the purpose of this proposed rule, ''secondary outcome'' has the same meaning as ''secondary outcome measure.''

The specification in proposed § 11.10 that a secondary outcome measure is ''specifically planned to be analyzed as part of the clinical trial'' is intended to help responsible parties differentiate between secondary outcome measures and tertiary or other lesser outcome measures that are more exploratory in nature. We consider secondary outcome measures to be those outcome measures (other than the primary outcome measures) that are not considered exploratory and for which there is a specific analysis plan. In general, the analysis plan would be specified in the protocol or statistical analysis plan, but protocols do not always contain detailed information about statistical analysis, and statistical analysis plans may not be complete at the time a trial is registered. Hence, the plan to analyze the secondary outcome measure may be expressed only in other formal trial documentation (e.g., a grant application, contract, or published journal article). We view outcomes measures that are not part of an analysis plan or are indicated to be exploratory as tertiary or lower level outcome measures that do not need to be submitted to ClinicalTrials.gov, but for which information may be submitted voluntarily. See discussion in sections IV.B.4 and IV.C.4 of this preamble, respectively, regarding secondary outcome measure(s) as a clinical trial information data element to be submitted at the time of registration following proposed § 11.28(a)(1)(xx) and at the time of results submission, following proposed § 11.48(a)(3).

Serious adverse event is a term used but not defined in section 402(j)(3)(I) of the PHS Act. Section 402(j)(3)(I)(iii)(I) of the PHS Act requires the submission to ClinicalTrials.gov of specific information about ''anticipated and unanticipated serious adverse events'' for applicable clinical trials of drugs as well as devices. In defining the term ''serious adverse event'' in its IND Safety Reporting regulations at 21 CFR 312.32(a), FDA considers an adverse event to be ''serious'' when, in the view of either the sponsor or the investigator, it ''results in any of the following outcomes: Death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.'' A ''serious adverse event'', as defined in 21 CFR 312.32(a), applies only in the context of drugs (including biological products). No fully equivalent term is defined in FDA regulations for medical devices. In 21 CFR 812.3(s), FDA defines an ''unanticipated adverse device effect'' as, in part, ''any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device'' that ''was not previously identified . . . in the investigational plan or application . . . or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.'' However, because it is restricted to unanticipated effects, we do not consider this definition sufficient to meet the statutory requirement in section 402(j)(3)(I)(iii) of the PHS Act for submission of serious adverse event information that encompasses both anticipated and unanticipated events. Although we are relying on an FDA drug regulation, we emphasize that ''serious adverse event,'' as defined for purposes of this proposed rulemaking, applies to both drugs and devices.

Therefore, for purposes of this rulemaking, we draw upon the FDA definition of ''serious adverse event'' in 21 CFR 312.32(a), because it more fully characterizes the criteria for ''other serious problems'' as well as ''any life-threatening problem'' or ''[d]eath.'' Our proposed rule defines serious adverse event to mean ''an adverse event that results in any of the following outcomes: death, a life-threatening adverse event as defined in 21 CFR 312.32 (or any successor regulation), inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the human subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of a substance use disorder.'' We use the phrase ''a substance use disorder'' instead of the phrase ''drug dependency or drug abuse,'' which is used in the FDA definition, for consistency with the latest version (fifth edition) of the Diagnostic and Statistical Manual of Mental Disorders (DSM V). By referring to adverse events (and thus the definition of that term in this proposed part), our proposed definition of serious adverse event is broader than the FDA definition of serious adverse event in 21 CFR 312.32(a) because it encompasses any untoward or unfavorable medical occurrences associated with any intervention included in a clinical trial (not just the use of the FDA-regulated product), including any intervention(s) in any arm of the clinical trial that does not involve FDA-regulated products. In addition, as with our proposed definition of adverse event, our proposed definition of serious adverse event encompasses both anticipated and unanticipated effects regardless of attribution or association with the intervention.

Sponsor is a term used in section 402(j) of the PHS Act to define responsible party. Section 402(j)(1)(A)(ix)(I) of the PHS Act explicitly defines ''sponsor'' as such term is defined at 21 CFR 50.3 or any successor regulation. There are two types of sponsors defined in 21 CFR 50.3, both of which meet the definition of sponsor for purposes of this proposed rule. The first type is a ''sponsor,'' which is defined as ''a person who initiates a clinical investigation but who does not actually conduct the investigation, i.e., the test article is administered or dispensed to or used involving, a subject under the immediate direction of another individual. A person other than an individual (e.g., corporation or agency) that uses one or more of its own employees to conduct a clinical investigation it has initiated is considered to be a sponsor (not a sponsor-investigator), and the employees are considered to be investigators.'' The second is a ''sponsor-investigator,'' which is defined as ''an individual who both

initiates and actually conducts, alone or with others, a clinical investigation, i.e., under whose immediate direction the test article is administered or dispensed to, or used involving, a subject. The term does not include any person other than an individual, e.g., corporation or agency.'' We believe that the definition of sponsor used in this proposed rule, must encompass both a sponsor and a sponsor-investigator because both terms are relevant in determining who initiates the clinical trial. Hence, we propose to define sponsor as ''either a 'sponsor' or 'sponsor-investigator', as each is defined 21 CFR 50.3 or any successor regulation.'' Procedures for determining which individual or entity would be considered the sponsor of a applicable clinical trial or other clinical trial subject to this part are specified in proposed § 11.4(c) and described in section IV.A.2 of this preamble. As those sections explain, the individual or entity that is the sponsor will be considered to be the responsible party of an applicable clinical trial or other clinical trial, unless and until that responsibility is delegated to the PI, consistent with the requirements of section 402(j)(1)(A)(ix) of the PHS and this proposed part.

Proposed § 11.10(b) defines certain data elements that are part of the clinical trial information that must be submitted to ClinicalTrials.gov under this proposed part.

B. Registration—Subpart B

Proposed subpart B sets forth the requirements for registration. It identifies who must submit clinical trial registration information; which applicable clinical trials must be registered in ClinicalTrials.gov; when clinical trial registration information must be submitted; where clinical trial registration information must be submitted; what constitutes clinical trial registration information; and by when NIH will post submitted clinical trial registration information.

1. Who must submit clinical trial registration information?—§ 11.20

Proposed § 11.20 requires that ''[t]he responsible party for an applicable clinical trial specified in § 11.22 must register the applicable clinical trial [. . .] .'' This approach is consistent with section 402(j)(2)(C) of the PHS Act, which states that the ''responsible party for an applicable clinical trial . . . shall submit to the Director of NIH for inclusion in the registry data bank the [clinical trial registration information].''

2. Which applicable clinical trials must be registered?—§ 11.22

(a) General specification. Proposed §§ 11.22(a)(1) and (2) specify which applicable clinical trials must be registered with ClinicalTrials.gov. They state that registration is required for: (1) ''[a]ny applicable clinical trial that is initiated after September 27, 2007;'' and (2) [a]ny applicable clinical trial that is initiated on or before September 27, 2007 and is ongoing on December 26, 2007 [. . .] .'' This is consistent with section 402(j)(2)(C) of the PHS Act. We note that under section 402(j)(2)(C)(iii) of the PHS Act, in the case of an applicable clinical trial for a non-serious or non-life-threatening disease or condition that was ongoing as of September 27, 2007, clinical trial registration information was not required to be submitted until September 27, 2008. However, this distinction is no longer relevant because any such trial already should have been registered in the data bank.

We note that this proposal differs from guidance that the Agency originally provided regarding its interpretation of section 402(j)(2)(C) of the PHS Act. The original interpretation may have resulted in some responsible parties registering applicable clinical trials that we no longer believe are subject to the registration requirement of section 402(j)(2)(C) of the PHS Act and this proposed part (i.e., applicable clinical trials for non-serious or non-life-threatening diseases or conditions that were ongoing as of September 27, 2007, but not as of December 26, 2007). We believe that our revised, proposed interpretation more accurately implements the text of section 402(j)(2)(C) of the PHS Act. This revised interpretation was announced to the public in October 2009 through the NIH Guide [Ref. 43], the ClinicalTrials.gov Listserv [Ref. 44], and ClinicalTrials.gov. Although there is no legal requirement for responsible parties to keep clinical trial information for such previously-registered applicable clinical trials in ClinicalTrials.gov, we anticipate that many responsible parties will want to continue to make clinical trial information for such applicable clinical trials available to the public through the data bank. We do not intend to remove these clinical trial records from ClinicalTrials.gov, but we note that the clinical trial information for such clinical trials would be considered voluntary submissions of clinical trial information under section 402(j)(4)(A) of the PHS Act and would be subject to all of the requirements applicable to voluntarily-submitted clinical trial information under section 402(j)(4)(A) of the PHS Act, including but not limited to the requirements that such information be truthful and not misleading in accordance with proposed § 11.6 and updated in accordance with proposed § 11.64. The Agency recognizes that some responsible parties for applicable clinical trials described in this paragraph may not want to be subject to the requirements that apply to clinical trial information submitted under 402(j)(4)(A) of the PHS Act or proposed § 11.60. To address this situation, any responsible party who wishes to remove an active clinical trial record from ClinicalTrials.gov for such an applicable clinical trial must submit an electronic request to the Agency at *register@clinicaltrials.gov* to have the record removed from the data bank. We note that if the Agency removes a clinical trial record from ClinicalTrials.gov as a result of such a request, the clinical trial record would continue to be available to the public in the ClinicalTrials.gov archives; however, the responsible party for such an applicable clinical trial would not be subject to the requirements of section 402(j) of the PHS Act or this proposed part. For example, clinical trial results information is not required to be submitted for these clinical trials.

Proposed § 11.22(a)(3) provides clarification for determining the date on which an applicable clinical trial is initiated. This date is important for determining if an applicable clinical trial is required to register in ClinicalTrials.gov, because, as described above, the registration requirements of section 402(j) of the PHS Act and this proposed part apply only to applicable clinical trials initiated after September 27, 2007, and to applicable clinical trials that were initiated prior to September 27, 2007 and ongoing on December 26, 2007. However, section 402(j) of the PHS Act does not define how to determine when an applicable clinical trial is ''initiated.'' We considered several possibilities for determining the date of initiation, including our longstanding practice for ClinicalTrials.gov which was to consider the date of initiation to be the date that an applicable clinical trial is open to recruitment. In order to be consistent with the definitions of ''ongoing'' and ''enrolled'' and these proposed regulations, we propose instead that for any applicable clinical trial, other than a pediatric postmarket surveillance of a device that is not a clinical trial, the date of initiation means the date on which the first human subject is enrolled in the clinical

trial. For any pediatric postmarket surveillance of a device that is not a clinical trial, we propose that the date of initiation be the date on which FDA approves the plan for conducting the surveillance. This date will be well-documented in correspondence with FDA and represents the first date on which the pediatric postmarket surveillance of a device could be started in accordance with an approved plan.

(b) Determination of applicable clinical trial. Proposed § 11.22(b) sets forth an approach for determining whether or not a clinical trial or study meets the definition of an applicable clinical trial. By relying on certain aspects of the detailed discussions in section IV.A.5 regarding the definitions of applicable device clinical trial and applicable drug clinical trial, this approach outlines specific data elements that would be submitted as part of the registration process. For clinical trials and studies that are registered with ClinicalTrials.gov, it would provide a simple mechanism for determining whether or not the clinical trial or study is an applicable clinical trial that is subject to section 402(j) of the PHS Act and this part, and we could indicate such status in ClinicalTrials.gov. The order in which the data elements are considered would not influence the outcome: A clinical trial for which the submitted information meets the criteria specified below would be considered an applicable clinical trial.

Other than situations where a clinical trial that is not an applicable clinical trial is registered voluntarily (see proposed § 11.60), there is no requirement under section 402(j) of the PHS Act or this proposed part for a responsible party to submit clinical trial registration information to ClinicalTrials.gov for a clinical trial or study that does not meet the definition of an applicable clinical trial. Algorithms following the approach outlined here could be developed to allow potential registrants to determine a priori whether their clinical trial or study meets the definition of an applicable clinical trial, without having to go through the registration process. To this end, we would make such algorithms accessible on ClinicalTrials.gov outside of the registration system.

The proposed approach of using specified data elements to determine whether a clinical trial or study meets the definition of an applicable clinical trial is intended to amend and replace the approach currently implemented in ClinicalTrials.gov, which asks potential registrants to indicate whether their trial is an applicable clinical trial. We believe our proposed approach accurately reflects the proposed definitions of the terms applicable device clinical trial and applicable drug clinical trial. We invite public comment on this proposed approach and on whether there are any types of clinical trials or studies which might be errantly classified as applicable clinical trials that do not in fact meet the definitions of applicable device clinical trial or applicable drug clinical trial, or, conversely, any types of clinical trials or studies that do in fact meet the definitions of applicable device clinical trial or applicable drug clinical trial that might fail to be classified as applicable clinical trials.

Consistent with the elaboration provided in section IV.A.5 of this preamble for the proposed definition of applicable device clinical trial, under proposed § 11.22(b)(1), a study would meet the definition of an applicable device clinical trial if (1) it is a Pediatric Postmarket Surveillance of a Device required by FDA under section 522 of the FD&C Act (regardless of whether the pediatric postmarket surveillance is a clinical trial), (2) it meets all of the following criteria for the submitted data elements: (a) The Study Type is interventional; (b) the Primary Purpose selected is other than feasibility; (c) either the Number of Arms is two or more, or the Number of Arms is one and Single Arm Controlled is selected; (d) the Intervention Type selected is something other than a combination product; (e) the clinical trial Studies an FDA-regulated Device; and (f) one or more of the following applies: At least one Facility Location is within the U.S. or one of its territories, the device under investigation is a Product Manufactured in the U.S. or one of its territories and is exported for study in another country, or the clinical trial has a U.S. Food and Drug Administration IDE Number.

Taking a similar approach for applicable drug clinical trials, and consistent with the elaboration provided in section IV.A.5 of this preamble for the proposed definition of applicable drug clinical trial, proposed § 11.22(b)(2) states that a clinical trial meets the definition of an applicable drug clinical trial if it meets all of the following criteria for the submitted data elements: (1) The Study Type is interventional; (2) the Study Phase is other than phase 1; (3) either the Number of Arms is two or more, or the Number of Arms is one and Single Arm Controlled is selected; (4) the clinical trial Studies an FDA-regulated Drug; and (5) one or more of the following applies: At least one Facility Location is within the U.S. or one of its territories, the drug under investigation is a Product Manufactured in the U.S. and is exported for study in another country, or the clinical trial has a U.S. Food and Drug Administration IND Number.

With respect to Study Phase, we do not consider a phase 1/phase 2 study to be a phase 1 study; therefore, a clinical trial that is indicated to be phase 1/phase 2 would be considered an applicable drug clinical trial if it meets the other conditions listed in (1) through (5) above and would be required to register at ClinicalTrials.gov if it also meets the conditions specified in proposed § 11.22(a). If a clinical trial is registered as phase 1/phase 2, and the trial subsequently proceeds through only the phase 1 stage and/or is terminated before reaching phase 2, the Study Phase data element may be updated to indicate that the trial is a phase 1 trial, in which case it would not be considered an applicable drug clinical trial and would not be subject to the requirements for results submission specified in subpart C. However, submitted registration information would continue to be posted in ClinicalTrials.gov.

While most applicable clinical trials will meet the definition of either an applicable device clinical trial or an applicable drug clinical trial, some applicable clinical trials that study multiple intervention types (e.g., in different arms of the clinical trial) could meet both definitions. For example, a clinical trial with facility locations in the U.S. that studies an FDA-regulated drug in one arm and studies an FDA-regulated device in another arm and compares outcomes of the two arms would meet both definitions. If the device studied in such an applicable clinical trial is not approved or cleared by FDA for any use and is not a component of a combination product, it would be treated as an applicable device clinical trial in that we would not post clinical trial registration information for that clinical trial prior to the date of approval or clearance of the device, consistent with proposed § 11.35(b)(2). We consider this situation to differ from that of an applicable clinical trial in which a studied device is part of a combination product. As explained in the discussion of the definition of an applicable drug clinical trial in section IV.A.5 of this preamble, any applicable clinical trial that studies a combination product would be treated as an applicable drug clinical trial under this proposed rule.

3. When must clinical trial registration information be submitted?—§ 11.24

Proposed § 11.24 specifies the deadlines by which a responsible party must submit clinical trial registration information to register an applicable clinical trial in ClinicalTrials.gov. Consistent with section 402(j)(2)(C) of the PHS Act, proposed § 11.24(a) requires that clinical trial registration information be submitted on the later of December 26, 2007, or 21 calendar days after the first human subject is enrolled in the clinical trial. However, section 402(j)(2)(C)(iii) of the PHS Act provides an exception to this deadline. For any applicable clinical trial that was not for a serious or life-threatening disease or condition (e.g., was not for indications such as acquired immunodeficiency syndrome (AIDS), all other stages of human immunodeficiency virus (HIV), Alzheimer disease, cancer, or heart failure; See [Ref. 4]), was initiated on or before September 27, 2007, and was still ongoing on December 26, 2007, the responsible party must submit clinical trial registration information by the later of September 27, 2008, or 21 calendar days after the first human subject is enrolled in the clinical trial. This proposed rule mirrors this standard in § 11.24(b)(1).

With regard to registering a pediatric postmarket surveillance of a device that is not a clinical trial, the submission deadlines described above may not be applicable because such surveillances may not entail formal recruitment of human subjects. We propose in § 11.24(b)(2), therefore, that registrations of pediatric postmarket surveillances of a device that are not clinical trials be submitted ''not later than December 26, 2007, or 21 calendar days after FDA approves the postmarket surveillance plan, whichever date is later.'' This provides a clear deadline for submission of clinical trial registration information, and the 21-day period is consistent with the requirement in section 402(j)(2)(C)(ii) of the PHS Act that clinical trials be registered 21 days after enrollment of the first human subject.

4. What constitutes clinical trial registration information?—§ 11.28

Proposed § 11.28 identifies the structured information, or data elements, that constitute clinical trial information that a responsible party must submit in order to register an applicable clinical trial. Section 402(j)(2)(A)(ii) of the PHS Act specifies a number of data elements that must be submitted to ClinicalTrials.gov for registration. In general, the proposed data elements in § 11.28 conform to the items enumerated in section 402(j)(2)(A)(ii) of the PHS Act. In many instances, the Agency, through this proposed rulemaking has restated or clarified the registration data elements required by section 402(j)(2)(A)(ii) of the PHS Act. In addition, section 402(j)(2)(A)(iii) of the PHS Act expressly authorizes the Secretary to modify the registration data elements, by regulation, if a rationale is provided as to why such a modification ''improves and does not reduce'' such information. In developing the proposed set of data elements for registration, we carefully considered the items enumerated in section 402(j)(2)(A)(ii) of the PHS Act, the mandate in section 402(j)(2)(A)(i) to ''expand'' the existing registration data bank, and the intent to expand the data bank ''to enhance patient enrollment and provide a mechanism to track subsequent progress of clinical trials.'' (*See* section 402(j)(2)(A)(i) of the PHS Act). We have also taken into consideration the WHO trial registration standards and have sought to maintain consistency with the clinical trial registration requirements of the ICMJE [Ref. 13, 10].

Careful consideration was given to the data elements that were part of the data bank prior to passage in 2007 of section 402(j) of the PHS Act, some of which are not expressly required under section 402(j)(2)(A)(ii) of the PHS Act, but which we consider necessary to fulfill both the purpose of the expansion of registration information contained in ClinicalTrials.gov and certain other requirements of section 402(j) of the PHS Act. We believe, in general, that maintaining consistency with the pre-existing data elements for ClinicalTrials.gov is consistent with the intent of section 402(j) of the PHS Act. Not only do we presume that Congress was familiar with those existing definitions when it developed and passed section 402(j) of the PHS Act, but also we believe that maintaining consistency will minimize confusion for those who submitted registration information previously to ClinicalTrials.gov prior to enactment of section 402(j) of the PHS Act. It will also minimize the level of effort required by those who previously established automated computer-based processes for submitting and updating registration data in ClinicalTrials.gov, rather than entering the data manually into the data bank. It will serve the public by facilitating cross-comparison of entries made before and after enactment of section 402(j) of the PHS Act. It also will ensure that the proposed clinical trial registration information requirements would not have the effect of reducing the amount of information available for newly-registered clinical trials as compared to those registered prior to the passage in 2007 of section 402(j) of the PHS Act, a result that we believe would be contrary to the intent of section 402(j) of the PHS Act. For these reasons, we believe that requiring the submission of data elements that were expected to be submitted to ClinicalTrials.gov prior to the passage in 2007 of section 402(j) of the PHS Act in order to register a clinical trial would improve and not reduce the clinical trial information submitted to ClinicalTrials.gov.

As further discussed in section III.C.2 of this preamble, in developing our proposed set of data elements for clinical trial registration information, we have decided to exercise our authority under section 402(j)(2)(A)(iii) of the PHS Act to modify the section 402(j)(2)(A)(ii) requirements for registration information in order to achieve the following objectives:

(1) Specify a particular structure for submitting certain clinical trial registration information in order to: (a) Help the public use the data bank more easily and be able to compare entries, consistent with section 402(j)(2)(B)(iv) of the PHS Act; (b) enable searching of the data bank using criteria listed in sections 402(j)(2)(B)(i) and (ii) of the PHS Act; and (c) facilitate the submission of complete and accurate information by responsible parties;

(2) Enable effective implementation of, or compliance with, other provisions of section 402(j) of the PHS Act and this part, e.g., proposing to add data elements to indicate whether a product under study in a clinical trial in manufactured in the U.S. and whether a study is a pediatric postmarket surveillance of a device, both of which are important to help determine whether a study meets the definition of an applicable clinical trial;

(3) Improve the quality and consistency of clinical trial registration information, e.g., proposing to add Other Intervention Name(s) and Intervention Description to help users identify and differentiate among similar interventions studied in registered clinical trials; or

(4) Demonstrate whether clinical trials registered in the data bank have complied with ethical and scientific review procedures in accordance with applicable statutes and regulations, e.g., proposing to add Human Subjects Protection Review Board Status to indicate to potential human subjects and other users whether an applicable clinical trial has received needed

approvals or is not subject to such requirements.

(a) Registration data elements for applicable clinical trials other than pediatric postmarket surveillances of a device that are not clinical trials. Proposed § 11.28(a) specifies the data elements that a responsible party would be required to submit to ClinicalTrials.gov to register an applicable clinical trial other than a pediatric postmarket surveillance of a device that is not a clinical trial. A pediatric postmarket surveillance of a device that does not take the form of a clinical trial would be registered by submitting the clinical trial information specified in § 11.28(b). The clinical trial registration information data elements in § 11.28(a) are grouped into the four categories used in section 402(j)(2)(A)(ii) of the PHS Act: (1) Descriptive information, (2) recruitment information, (3) location and contact information, and (4) administrative data. Additional data elements that the Agency proposes via this rule are listed in the categories in which they best fit. The clinical trial registration information data elements, grouped by category, are as follows.

(1) Descriptive Information

Brief Title. Section 402(j)(2)(A)(ii)(I)(aa) of the PHS Act specifically requires the submission of a brief title as part of the clinical trial information submitted at registration, but does not define the term, other than to indicate that the title is ''intended for the lay public.'' We interpret this requirement to mean that potential human subjects should be able to understand, from the brief title, the general purpose of the clinical trial and distinguish it from others listed in the data bank. Prior to FDAAA, those submitting information to the ClinicalTrials.gov registry pursuant to FDAMA, were requested to include a ''brief title'' of the trial [Ref. 2]. This term was defined to mean a ''protocol title intended for the lay public'' [Ref. 2]. This definition of ''brief title'' also is consistent with ''public title'' (data item #9) of the WHO Trial Registration standard and ICMJE registration policies [Ref. 13, 10].

Based on our experience to date with ClinicalTrials.gov, we recognize that acronyms are frequently used to refer to clinical trials (e.g., ''ACCORD'' for the Action to Control Cardiovascular Risk in Diabetes trial or ''STAR*D'' for the Sequenced Treatment Alternatives to Relieve Depression trial), and believe it is important for such acronyms to be included in the registry to enable users of the data bank to identify clinical trials that they might see referenced in other media (e.g., news reports, journal articles). As such, we consider an acronym used to identify a clinical trial to be part of the brief title. Therefore, in proposed § 11.10(b)(1), Brief Title is described as ''a short title of the clinical trial written in language intended for the lay public, including any acronym or abbreviation used publicly to identify the clinical trial.'' Although we do not specify what type of information must be conveyed by the Brief Title, we believe that a Brief Title intended for the lay public should include, where possible, information on the participants, condition being evaluated, and intervention(s) studied.

Official Title. Using the authority in section 402(j)(2)(A)(iii) of the PHS Act we propose to require a responsible party to submit an ''official title'' as part of clinical trial information when registering an applicable clinical trial at ClinicalTrials.gov. In proposed § 11.10(b)(2), we define Official Title as: ''The title of the clinical trial, corresponding to the title of the protocol.'' We believe that the official title will complement the Brief Title that is intended for the lay public, by providing a technical title that will help researchers understand the general purpose of the study. The official title would also be helpful in associating the clinical trial in ClinicalTrials.gov with information about the clinical trial that is contained in other sources, such as scientific publications, regulatory submissions, and media reports, which often use the official title of the study protocol. Those who learn about a clinical trial from one of these other sources could more easily search for the trial in ClinicalTrials.gov using the Official Title. Prior to passage of FDAAA, those submitting information to ClinicalTrials.gov were able to submit an ''official title'' as an optional data element, defined to mean ''Official name of the protocol provided by the study principal investigator or sponsor'' [Ref. 2]. This submission of an official title is also consistent with the WHO Trial Registration standard and ICMJE registration policies, which require the submission of a ''scientific title'' (data item #10) [Ref. 13, 10].

Brief Summary. Section 402(j)(2)(A)(ii)(I)(bb) of the PHS Act expressly requires a ''brief summary'' to be submitted as clinical trial registration information, but it does not define the term other than to indicate that the brief summary is ''intended for the lay public.'' Prior to FDAAA, those submitting information to the ClinicalTrials.gov registry pursuant to FDAMA were requested to include a ''brief summary'' of the clinical trial [Ref. 4]. This term was defined to mean a ''short description of the protocol intended for the lay public, including a brief statement of the study hypothesis'' [Ref. 2]. We propose to continue to use that definition. Accordingly, in proposed § 11.10(b)(3), Brief Summary is described as ''a short description of the clinical trial, including a brief statement of the clinical trial's hypothesis, written in language intended for the lay public.''

Primary Purpose. Section 402(j)(2)(A)(ii)(I)(cc) of the PHS Act expressly requires the ''primary purpose'' of the intervention(s) to be submitted as clinical trial registration information, but it does not define the term. Prior to passage of section 402(j) of the PHS Act in 2007, those submitting information to the registry were requested to indicate the primary purpose of the clinical trial. This term was defined to mean the ''reason for the protocol'' [Ref. 2], and those submitting information were given a choice of selections, including ''treatment,'' ''prevention,'' ''diagnostic,'' ''supportive care,'' ''screening,'' ''health services research,'' and ''basic science.'' Data submitters could also indicate ''other'' and include a description of the purpose in the detailed description portion of the clinical trial record. We found this approach effective for indicating the primary purpose of the intervention(s) studied in the clinical trials registered with ClinicalTrials.gov and believe this approach would apply well to clinical trials being registered pursuant to this proposed part. Therefore, under proposed § 11.10(b)(4), Primary Purpose refers to ''the main objective of the intervention(s) being evaluated by the clinical trial.'' We would require a responsible party to provide a response selected from the following set of options: ''treatment'' (for a protocol designed to evaluate one or more interventions for treating a disease, syndrome or condition), ''prevention'' (for a protocol designed to assess one or more interventions aimed at preventing the development of a specific disease or health condition), ''diagnostic'' (for a protocol designed to evaluate one or more interventions aimed at identifying a disease or health condition), ''supportive care'' (for a protocol designed to evaluate one or more interventions where the primary intent is to maximize comfort, minimize side effects or mitigate against a decline in the subject's health or function), ''screening'' (for a protocol designed to assess or examine methods of identifying a condition, or risk factors

for a condition, in people who are not yet known to have the condition or risk factor), ''health services research'' (for a protocol designed to evaluate the delivery, processes, management, organization or financing of health care), ''basic science'' (for a protocol designed to examine the basic mechanism of action, e.g., physiology or biomechanics, of an intervention), ''feasibility'' (for a protocol designed to determine the feasibility of a device or test prototype devices where the primary outcome measure relates to feasibility and not to health outcomes), or ''other''. The inclusion of ''feasibility'' on the list of options is intended to permit the responsible party for a clinical trial of a device to indicate whether such clinical trial is a feasibility study. Feasibility studies do not meet the definition of an applicable device clinical trial as specified in section 402(j)(1)(A)(ii) of the PHS Act and § 11.10(a) of this proposed part. A responsible party may nevertheless voluntarily register a clinical trial that is a feasibility study of a device. Such registration would be a voluntary submission of clinical trial information under section 402(j)(4)(A) of the PHS Act and proposed § 11.60.

Study Design. Section 402(j)(2)(A)(ii)(I)(dd) of the PHS Act expressly requires ''study design'' to be submitted as part of clinical trial registration information, but does not define the term. There are many important aspects of a study design, and information about each is relevant to ensuring that the descriptions of study designs are complete and comparable across clinical trials. Hence, we propose to require that several components of study design be submitted. Prior to FDAAA, those submitting information to ClinicalTrials.gov pursuant to FDAMA were requested to include the interventional study characteristics of the trial [Ref. 4]. This term was defined to mean the ''[p]rimary investigative techniques used in the protocol,'' and data submitters were instructed to provide information describing several key attributes of the study design, including the study model, number of arms, masking, and allocation [Ref. 2]. This definition of study design, including the key attributes, conforms to ICH Guidelines [Ref. 23] and is consistent with ''study type'' (data item #15) of the WHO Trial Registration standard (version 1.0) and ICMJE registration policies [Ref. 13, 10]. Consistent with this approach, proposed § 11.10(b)(5) requires that Study Design include information about several important aspects of a clinical trial: interventional study model, number of arms, arm information, allocation, masking, and whether a single-armed clinical trial is controlled. None of these terms is used in section 402(j) of the PHS Act, but we believe each is key component of study design. We propose the following meanings for these terms.

(a) *Interventional Study Model* characterizes the approach used for assigning groups of human subjects to interventions during the clinical trial. In proposed § 11.10(b)(5)(i), the data item is defined as ''[t]he strategy for assigning interventions to human subjects.'' In ClinicalTrials.gov, responsible parties would be required to select an entry from the following limited set of proposed options: ''single group'' (i.e., clinical trials with a single arm), ''parallel'' (i.e., participants are assigned to one of two or more groups in parallel for the duration of the study), ''cross-over'' (i.e., participants receive one of two alternative interventions during the initial phase of the study and receive the other intervention during the second phase of the study), or ''factorial'' (i.e., two or more interventions, each alone and in combination, are evaluated in parallel against a control group). No ''other'' option is proposed. To address those situations in which a clinical trial might use a modified version of one of these models or the responsible party might wish to provide more information about the specific implementation of the model, responsible parties would also be able to provide voluntarily additional free-text description containing more specific details about the interventional study model. We invite public comment on whether the proposed set of options adequately addresses existing and emerging interventional study models, including dose escalation study designs, and whether it would provide suitable selections, without an ''other'' option for all types of applicable clinical trials and voluntarily registered trials that are subject to this proposed regulation.

(b) *Number of Arms* specifies the total number of arms in a clinical trial. We define the term ''arm'' in proposed § 11.10(a). Some clinical trials contain multiple periods or phases, each of which might use different numbers of arms. Hence, in proposed § 11.10(b)(5)(ii), the data element is defined as ''[t]he number of arms in the clinical trial. For a trial with multiple periods or phases that have different numbers of arms, the maximum number of arms during any period or phase.'' We note that historical controls are not considered to be an ''arm'' of a clinical trial and thus are not counted in the number of arms.

(c) *Arm Information* provides key information about each arm in the clinical trial. In proposed § 11.10(b)(5)(iii), the data element is defined as ''[a] description of each arm of the clinical trial that indicates its role in the clinical trial, provides an informative title, and, if necessary, additional descriptive information to differentiate each arm from other arms in the clinical trial.'' Responsible parties would be required to select from the following list of options for describing the role of each arm in the clinical trial: ''experimental,'' ''active comparator,'' ''placebo comparator,'' ''sham comparator,'' ''no intervention,'' or ''other.'' The informative title would consist of a label or short name to identify the arm in the clinical trial record (e.g., the name of the experimental intervention used in the arm or placebo). Additional descriptive information would be required if the informative title does not sufficiently differentiate among arms in the clinical trial (e.g., in a clinical trial that compares two different dosages of the same investigational drug, the descriptive information would have to indicate which is the higher dose arm versus the lower dose arm). Even if the informative title and/or additional descriptive information vary sufficiently among the arms of the clinical trial, responsible parties may voluntarily include additional details about the interventions or the arms in this field.

(d) *Allocation* describes how human subjects are assigned to interventions. In proposed § 11.10(b)(5)(iv), the data item is defined as ''[t]he method by which human subjects are assigned to arms in a clinical trial.'' Responsible parties would be required to select from the following limited set of options: ''randomized'' (participants are assigned to intervention groups by chance), or ''nonrandomized'' (participants are expressly assigned to intervention groups through a non-random method, such as physician choice), or ''not applicable'' (for a single arm study). No ''other'' option is proposed. We invite public comment on whether this limited set of options would provide suitable selections for all types of applicable clinical trials and voluntarily registered clinical trials that are subject to this proposed rule.

(e) *Masking* specifies which entities, if any, involved in the clinical trial are not informed of the intervention assignments (i.e., who is ''blinded'' in the clinical trial). In proposed § 11.10(b)(5)(v), the data item is defined as ''[t]he party or parties, if any, involved in the clinical trial who are prevented from having knowledge of the interventions assigned to individual human subjects.'' In the data bank,

responsible parties would be required to select from the following limited menu of choices for describing which party(ies) is/are blinded: ''human subject,'' ''care provider,'' ''investigator,'' and/or an ''outcomes assessor'' (i.e., another individual who evaluates the outcome(s) of interest). No ''other'' option is proposed, but responsible parties would have the ability to voluntarily provide additional, free-text, information about other parties who might be blinded in clinical trial.

(f) *Single Arm Controlled*? is not a data element that is explicitly listed in section 402(j) of the PHS Act as part of clinical trial information, but we propose it as a sub-element part of Study Design to enable the Agency to determine whether a registered clinical trial is an applicable clinical trial when such a determination cannot be made based on other submitted registration data elements. This data element, which is described in proposed § 11.10(b)(5)(vi) as ''[f]or a single-armed clinical trial only, whether or not the clinical trial is controlled, as specified by the protocol or statistical analysis plan,'' would assist the Agency, responsible parties, and users of the data bank in determining whether a clinical trial with only one arm meets the definition of an applicable clinical trial. As explained in section IV.A.5 of this preamble, a study of a device that is not a pediatric postmarket surveillance of a device can meet the definition of an applicable device clinical trial only if it ''compar[es] an intervention with a device . . . against a control in human subjects.'' (See 402(j)(1)(A)(ii)(I) of the PHS Act.) Similarly, a clinical trial of a drug can meet the definition of an applicable drug clinical trial only if it is ''a controlled clinical investigation . . .'' (See 402(j)(1)(A)(iii)(I)).

As explained in the definition of the term ''controlled'' in section IV.A.5 of this preamble, we consider any clinical trial with two or more arms to be controlled and/or to compare an intervention against a control. A clinical trial with only one arm (a single-armed study) may or may not be controlled and/or compare an intervention against a control, depending on whether or not the data collected on human subjects in the clinical trial will be compared to non-concurrently collected data. To determine whether a clinical trial with only one arm meets this criterion, we propose to require the responsible party for a single-armed study to indicate whether the clinical trial is controlled, as defined in this part. In doing so, the responsible party would consider whether the protocol or statistical analysis plan for the clinical trial indicates that data collected in the single-arm clinical trial will be compared to non-concurrently collected data, such as an historical control group. To reduce the burden on responsible parties, we would require this element of Study Design to be submitted only if the other clinical trial information submitted by the responsible party indicates that the clinical trial has one arm and otherwise meets the criteria for an applicable clinical trial, as listed in proposed § 11.22(b) (section IV.B.2(b) of this preamble). If other submitted registration data elements demonstrate that the clinical trial is not an applicable clinical trial or that it includes two or more arms, the Single Arm Controlled? data element would not need to be submitted.

Study Phase. Section 402(j)(2)(A)(ii)(I)(ee) of the PHS Act expressly requires, for an applicable drug clinical trial, the ''study phase'' to be submitted as a clinical trial registration information data element, but it does not define the term. Prior to FDAAA, those submitting registration information to ClinicalTrials.gov pursuant to FDAMA were requested to include the study phase of the clinical trial [Ref. 4]. This term was interpreted to mean ''phase of investigation, as defined by FDA for trials involving investigational new drugs'' [Ref. 2]. In proposed § 11.10(b)(6), the data item is defined as ''for a clinical trial of a drug, the numerical phase of such clinical trial, consistent with terminology in 21 CFR 312.21, or any successor regulation, such as phase 2 or phase 3, and in 21 CFR 312.85, or any successor regulation, for phase 4 studies.'' Responsible parties would be required to select one response from a limited list of options that includes phases 1, 2, 3, and 4, consistent with the terminology in 21 CFR 312.21 and 21 CFR 312.85. In addition, they would be able to select from other options that are commonly used in practice: Phase 1/phase 2 (for trials that are a combination of phases 1 and 2; as discussed previously, phase 1/phase 2 studies are not considered phase 1 studies and may be applicable drug clinical trials); and phase 2/phase 3 (for trials that are a combination of phases 2 and 3). No ''other'' option is proposed. Although we are aware that the term ''phase 0'' is used in practice (e.g., to refer to clinical trials that are exploratory in nature and are not designed to evaluate therapeutic or diagnostic intent), any trial that would be referred to as ''phase 0'' meets the definition of a phase 1 trial under FDA's regulations (21 CFR 312.21). Therefore, we do not propose to include ''phase 0'' as an option for the Study Phase data element, and responsible parties registering a clinical trial that might be referred to as ''phase 0'' should indicate the Study Phase as ''phase 1''. Study phases are not intended for use in describing clinical trials of devices, and therefore, consistent with section 402(j)(2)(A)(ii)(I)(ee) of the PHS Act, responsible parties for applicable device clinical trials would not be required to submit this data element.

Study Type. Section 402(j)(2)(A)(ii)(I)(ff) of the PHS Act expressly requires ''study type'' to be submitted as clinical trial information at the time of registration, but it does not define the term. Prior to FDAAA, those submitting information to the registry pursuant to FDAMA were requested to include the study type of the record being submitted to the registry by indicating whether the record corresponded to an interventional study (i.e., a clinical trial), an observational study, or an expanded access program. The study type selected would determine which other data elements to submit [Ref. 4]. Consistent with prior practice, proposed § 11.10(b)(7) defines the Study Type date element as ''the type of study for which clinical trial information is being submitted.'' Responsible parties would be required to select one of the following limited set of options: ''interventional,'' ''observational,'' or ''expanded access program.'' No ''other'' option is proposed. We believe that all applicable clinical trials and all other clinical studies that might be registered voluntarily with ClinicalTrials.gov can be characterized accurately as either ''interventional'' or ''observational,'' depending on whether human subjects studied are assigned to interventions based on a study protocol (interventional) or patients receive interventions as part of routine medical care, and a researcher studies the effect of the intervention (observational). We would consider observational studies to include a wide range of non-interventional studies, including retrospective reviews of patient records or relevant literature. (*See* the elaboration of the terms applicable device clinical trial and applicable drug clinical trial in section IV.A.5 of this preamble). A study that is designated as ''interventional,'' as that term is defined in this proposed part, may or may not be an applicable clinical trial, depending on whether it meets the other criteria for an applicable clinical trial that are specified in this part. A study that is designated ''observational''

would be an applicable clinical trial only if it is a pediatric postmarket surveillance of a device as defined in this part. (*See* the proposed definition of pediatric postmarket surveillance of a device in § 11.10, the discussion of proposed § 11.28(b), and the discussion of observational studies in section IV.A.5 of this preamble). Conversely, any applicable clinical trial other than a pediatric postmarket surveillance of a device must always have a Study Type of ''interventional.'' An applicable clinical trial that is a pediatric postmarket surveillance of a device could have a Study Type of ''interventional'' or ''observational.'' The term, ''expanded access program,'' is proposed as an option for Study Type because responsible parties are required to enter the data elements describing an expanded access program that is not an applicable clinical trial by creating an expanded access record if there is an expanded access program for the drug or biological product under study in the clinical trial being registered, consistent with section 402(j)(2)(A)(ii)(II)(gg) of the PHS Act, and if such a record does not already exist. As discussed in section IV.A.5 of this preamble, we expect that most expanded access programs will not meet the definition of an applicable clinical trial. The appropriate Study Type for expanded access programs that do not meet the definition of applicable clinical trial would be ''expanded access program.'' The appropriate Study Type for an expanded access program that does meet the definition of applicable clinical trial would be ''interventional.'' An expanded access program must be registered under only one Study Type. (See discussion of proposed § 11.28(c)). We invite public comment on our proposal for Study Type, including whether the limited set of options proposed would provide suitable selections for all types of applicable clinical trials and voluntarily registered clinical trials that are subject to this proposed rule.

Whether the Study is a Pediatric Postmarket Surveillance of a Device. We propose, in § 11.28(a)(1)(viii), to add a requirement for responsible parties of a study of a device to indicate if the study is a pediatric postmarket surveillance of a device. As we stated previously, the term ''applicable device clinical trial'' is defined, in part, as ''a pediatric postmarket surveillance as required under section 522 of the Federal Food, Drug, and Cosmetic Act.'' (See section 402(j)(1)(A)(ii)(II) of the PHS Act). A responsible party would be required to provide this data element only if the study is a pediatric postmarket surveillance of a device; a responsible party would not be required to submit this data element if the device study is not a pediatric postmarket surveillance of a device.

By indicating that a study is a pediatric postmarket surveillance of a device, users of the data bank and the Agency would be able to confirm that the study is an applicable device clinical trial. In addition, by combining this information with other submitted clinical trial registration information, e.g., the Study Type data element (interventional, observational), the Agency could confirm whether the pediatric postmarket surveillance of a device is a clinical trial and indicate which other data elements must be submitted at the time of registration. If a pediatric postmarket surveillance of a device is a clinical trial, the clinical trial registration information data elements set forth at proposed § 11.28(a) are required to be submitted. If a pediatric postmarket surveillance of a device is not a clinical trial (i.e. it is a form of observational study, including a retrospective review of patient records or relevant literature), the clinical trial registration information data elements set forth in § 11.28(b) are required to be submitted.

Primary Disease or Condition Being Studied in the Trial, or the Focus of the Study. Section 402(j)(2)(A)(ii)(I)(gg) of the PHS Act expressly requires ''the primary disease or condition being studied, or the focus of the study'' to be submitted as part of clinical trial registration information, but it does not define the term. Section 402(j)(2)(B)(i)(I) of the PHS Act further requires the data bank to be searchable by one or more of eight listed criteria, including ''the disease or condition being studied in the clinical trial, using Medical Subject Headers (MeSH) descriptors.'' To support searching using MeSH descriptors, the primary disease or condition being studied in the clinical trial, or the focus of the study, must be described using either MeSH terminology (*http://www.nlm.nih.gov/mesh/*) or another terminology that has been mapped to MeSH, when possible (if the other terminology is mapped to MeSH, the data bank can be searched using MeSH terms and retrieve the correct record(s)). SNOMED CT (Systematized Nomenclature of Medicine—Clinical Terms) (*http://www.ihtsdo.org/snomed-ct/*) meets the criteria of having been mapped to MeSH and has been designated as a U.S. standard for certified electronic health records that meet specified criteria for meaningful use of health information technology. (*See http://www.gpo.gov/fdsys/pkg/FR-2012-09-04/pdf/2012-20982.pdf*). Other vocabularies have also been mapped to MeSH within the NLM's Unified Medical Language System® (UMLS®) Metathesaurus. While it is possible that not all primary diseases or conditions or study foci can be expressed using MeSH, SNOMED CT, or another vocabulary that is mapped to MeSH within the UMLS Metathesaurus, we believe such terminology would accommodate most clinical trials and must be used when available. When a suitable term is unavailable in MeSH, SNOMED CT, or another vocabulary that is included in the UMLS Metathesaurus, ClinicalTrials.gov can accept another English language entry that accurately describes the primary disease or condition being studied, or the focus of the study. ClinicalTrials.gov could then use the information to enable searching by MeSH terms. Therefore, under proposed § 11.10(b)(9), we define Primary Disease or Condition Being Studied in the Trial, or the Focus of the Study as ''the name(s) of the disease(s) or condition(s) studied in the clinical trial, or the focus of the clinical trial, using, if available, appropriate descriptors from the National Library of Medicine's Medical Subject Headings (MeSH) controlled vocabulary thesaurus *http://www.nlm.nih.gov/mesh/,* or terms from another vocabulary, such as the Systematized Nomenclature of Medicine—Clinical Terms (SNOMED CT), that has been mapped to MeSH within the Unified Medical Language System (UMLS) Metathesaurus (*https://uts.nlm.nih.gov*).'' This definition is consistent with ''health condition(s) or problem(s) studied'' (data item #12) of the WHO Trial Registration standard (version 1.0) and ICMJE registration policies [Ref. 13, 10]. It is also consistent with the terminology used in ClinicalTrials.gov prior to FDAAA when those submitting information to the registry in response to FDAMA were requested to include ''conditions or focus of study,'' which were described as the ''primary disease or condition being studied, or focus of the study,'' and submitters were directed to describe the diseases or conditions using MeSH controlled vocabulary when possible [Ref. 2, 4].

Intervention Name(s). Section 402(j)(2)(A)(ii)(I)(hh) of the PHS Act expressly requires ''intervention name'' to be submitted as part of clinical trial information at the time of registration, but it does not define the term. We believe the purpose of this data element is to enable interested parties to readily identify the intervention(s) being studied in each arm of a clinical trial

and compare clinical trials by intervention. While some clinical trials compare a single intervention against a placebo (which would not need to be listed as a separate intervention), many compare multiple interventions (e.g., a new drug versus standard treatment, or different dosages of the same drug). We believe it is important for the names of all interventions studied in a clinical trial to be submitted to the data bank. Based on our previous experience in operating ClinicalTrials.gov, we recognize that there are inherent difficulties in determining the level of detail that should be required for naming interventions, especially those without non-proprietary (i.e., generic) names [Ref. 4]. We believe that non-proprietary names must be provided for interventions (e.g., drugs, biological products, and devices) when available. For interventions for which a non-proprietary name is not available, our prior experience suggests that a brief descriptive name can suffice. In either case, additional descriptive information is often needed to distinguish the intervention(s) under study from other similar interventions used in practice or studied in the same or other clinical trials. Therefore, under proposed § 11.10(b)(10), Intervention Name(s) is specified as ''a brief descriptive name used to refer to the intervention(s) studied in each arm of the clinical trial. A non-proprietary name of the intervention must be used, if available. If a non-proprietary name is not available, a brief descriptive name or identifier must be used.'' Examples of a brief descriptive name or identifier include a chemical name, company code or serial number. This description of Intervention Name is consistent with the ''intervention(s)'' (data item #13) of the WHO Trial Registration standard (version 1.0) and ICMJE registration policies [Ref. 13, 10]. It is also consistent with use of the term in ClinicalTrials.gov prior to FDAAA when those submitting information to the ClinicalTrials.gov registry pursuant to FDAMA were requested to include the intervention name for each intervention involved in the trial [Ref. 4], and the term was defined to mean the ''generic name of the precise intervention being studied. For investigational new drugs that do not yet have a generic name, a chemical name, company code or serial number may be used on a temporary basis.'' Our current proposal is consistent with this approach.

Other Intervention Name(s) is a term that is not used in section 402(j) of the PHS Act, but is proposed as a data element that responsible parties must submit if the sponsor has used more than one name publicly to identify the intervention under study in a clinical trial. Based on our prior experience operating ClinicalTrials.gov, we are aware that interventions often have multiple names, including, for example, a sponsor code name, brand name(s), or a name or identifier from a standard vocabulary, such as RxNorm for drugs (*http://www.nlm.nih.gov/research/umls/rxnorm/index.html*). Accordingly, providing only a single name for each intervention (as is required under the Intervention Name(s) data element) does not necessarily provide enough information to allow users to find and compare all clinical trials in ClinicalTrials.gov that involve a specific intervention, as a different clinical trial with the same intervention may have been registered by another responsible party under a different intervention name. Therefore, we believe that adding a requirement to submit Other Intervention Name(s) improves and does not reduce the clinical trial information available in the data bank. Under proposed § 11.10(b)(11), this term is defined as ''other current and former name(s) or alias(es), if any, different from the Intervention Name(s), that the sponsor has used publicly to identify the intervention, including, but not limited to, past or present names such as brand name(s), serial numbers, or chemical descriptions.'' This requirement could mean that, in some circumstances (e.g., when the responsible party is a designated principal investigator), the responsible party would need to communicate with the sponsor or the manufacturer of the intervention(s) to determine whether another name has been used publicly. We do not believe such additional communication would be frequent or onerous. This proposal would not require a responsible party to submit names that have not been used publicly because users of ClinicalTrials.gov would be unlikely to search for a clinical trial using such names. We seek comment on this approach.

Intervention Description. The term ''intervention description'' is not used in section 402(j) of the PHS Act, but we propose it as an additional data element to be submitted as clinical trial information at the time of registration. Based on prior experience, we recognize that the Intervention Name(s) and Other Intervention Name(s) data elements, whether providing information on brand or non-proprietary names, do not always provide enough information to allow potential human subjects or other users to differentiate among similar interventions used in different arms of a clinical trial, or to distinguish the intervention used in one clinical trial from a similar intervention used in another clinical trial, or to understand the differences between interventions studied in a clinical trial and those used in routine medical practice. For example, a clinical trial might compare two or more dosages of the same drug or two different clinical trials might examine drug-eluting stents that are similar to those used in standard medical practice. To reduce this ambiguity, additional descriptive information is needed about the intervention, such as information about the dosage, dosage form, frequency of administration, route of administration, and/or duration of administration of a drug, or a general description of the device, including how the device functions, the scientific concepts that form the basis for the device, and the significant physical and performance characteristics of the device, such as its key components and general types of materials used. The submission of such information will enable users (whether subjects, patients, physicians, researchers, or others) to understand key elements of a clinical trial, and compare information among clinical trials. For these reasons, requiring submission of an Intervention Description would improve but not reduce the clinical trial information available in the data bank. Under proposed § 11.10(b)(12), the term is defined to mean ''details that can be made public about the intervention, other than the Intervention Name and Other Intervention Name(s), sufficient to distinguish it from other, similar interventions studied in the same or another clinical trial.'' The information should be sufficiently detailed to differentiate the specified intervention from other similar interventions, but should not include information that the responsible party cannot make public. For example, if the specific dosage of a drug being studied cannot be divulged, a responsible party could instead indicate if the dosage is higher or lower than that used in an approved or licensed drug or in another arm of the study. If an experimental device uses different material than previous versions of the device, or than other marketed devices, the responsible party could provide a general description of the new material without including its specific formulation.

Intervention Type. Section 402(j)(2)(A)(ii)(I)(hh) of the PHS Act expressly requires ''intervention type'' to be submitted as part of clinical trial information at the time of registration,

but it does not define the term. Prior to FDAAA, those submitting information to the ClinicalTrials.gov registry were requested to specify the intervention type for each intervention studied in the clinical trial. Under proposed § 11.10(b)(13) Intervention Type would be defined as ''for each intervention studied in the clinical trial, the general type of intervention.'' When submitting this information, responsible parties would be required to select one of the following options for each intervention studied: ''drug'' (including placebo), ''device'' (including sham), ''biological/vaccine,'' ''procedure/surgery,'' ''radiation,'' ''behavioral'' (e.g., psychotherapy, lifestyle counseling), ''genetic'' (including gene transfer, stem cell and recombinant DNA), ''dietary supplement'' (e.g., vitamins, minerals), ''combination product'' (combining a drug and device, a biological product and device; a drug and biological product; or a drug, biological product, and device), ''diagnostic test'' (e.g., imaging in-vitro), and ''other.'' Note that when the intervention used is a combination product (e.g., drug-eluting stent), the responsible party must select ''combination product'' as the Intervention Type. As specified in proposed § 11.28(a)(1)(xiii), selection of an Intervention Type would be required for each intervention studied in each arm of the clinical trial. Some clinical trials will therefore include multiple Intervention Types. As discussed in section IV.B.2(b) of this preamble, a clinical trial that studies a drug and a device as separate, independent interventions would list both ''drug'' and ''device'' as Intervention Types and may meet the definitions of both an applicable device clinical trial and an applicable drug clinical trial.

Studies an FDA-Regulated Device. Section 402(j) of the PHS Act does not explicitly require submission of a clinical trial registration information data element to indicate whether or not a clinical trial studies an FDA-regulated device. We propose to require such a data element using our authority under section 402(j)(2)(A)(iii) of the PHS Act to assist responsible parties, users of ClinicalTrials.gov, and the Agency in determining whether or not a clinical trial is an applicable device clinical trial, using the approach specified in proposed § 11.22(b)(1). As specified in the elaboration of the definition of an applicable device clinical trial in section IV.A.5 of this preamble, one criterion for an applicable device clinical trial is that the clinical trial studies a device ''subject to section 510(k), 515, or 520(m) of the [FD&C Act].'' It is possible that a clinical trial with an Intervention Type of ''device'' would not be an applicable device clinical trial because the device is not subject to section 510(k), 515, or 520(m) of the FD&C Act. Conversely, it is possible that a clinical trial could be an applicable device clinical trial even if none of the specified Intervention Types is ''device.'' For example, a clinical trial for which a responsible party indicates the Intervention Type is ''radiation,'' ''genetic,'' or ''procedure'' could in fact be an applicable device clinical trial studying a device subject to section 510(k), 515, or 520(m) of the FD&C Act (e.g., an x-ray device, a genetic test, or a surgical device). If the responsible party has obtained an IDE and submitted an IDE number to ClinicalTrials.gov, it would be clear that the clinical trial is an applicable device clinical trial as defined in this part (assuming, as discussed previously, that the clinical trial is not a clinical trial of a combination product). If the responsible party does not submit an IDE number, however, ambiguity would arise because the lack of an IDE number (or an IDE) does not per se indicate that a clinical trial is not an applicable device clinical trial.

To avoid this ambiguity and help ensure that applicable clinical trials can be properly identified, we propose to require a responsible party to specifically indicate whether or not a clinical trial studies an FDA-regulated device by submitting the Studies an FDA-regulated Device data element. The data element is defined in proposed § 11.10(b)(39) to mean that ''a clinical trial studies a device that is subject to section 510(k), 515, or 520(m) of the Federal Food, Drug, and Cosmetic Act.'' Consistent with the elaboration of the term applicable device clinical trial in section IV.A.4 of this preamble, we interpret this definition to mean that the clinical trial studies a device that would require any of the following before it may be legally marketed in the U.S.: (1) A finding of substantial equivalence under section 510(k) of the FD&C Act; (2) an order under section 515 of the FD&C Act approving a premarket approval application for the device, or (3) a humanitarian device exemption under section 520(m) of the FD&C Act. We believe that submission of this information would improve and not reduce the clinical trial information submitted at the time of registration by making it clear to the responsible party, the Agency, and users of ClinicalTrials.gov whether or not a clinical trial without an IDE studies an FDA-regulated device. This information would, in turn, be used in determining whether a clinical trial meets the definition of an applicable device clinical trial, following the approach specified in proposed § 11.22(b)(1). To reduce the data entry burden on responsible parties, ClinicalTrials.gov could automatically pre-populate this data field to indicate ''yes'' if a responsible party submits an IDE number as part of the FDA IND or IDE Number data element specified in proposed § 11.10(b)(35).

We are aware that devices may be used in clinical trials even though they are not the intervention studied in the clinical trial or the experimental variable of interest in the study. For example, clinical trials of procedures involving surgical devices may not be designed to study the effect of these devices. Therefore, when considering whether a clinical trial Studies an FDA-regulated Device a responsible party should consider whether: (a) The study is designed to examine the effect or performance of an FDA-regulated device, or differences in the intended use, e.g., variations in frequency of use, method of administration, design specifications, and other characteristics (e.g., used in one or more, but not all, arms in a multi-arm study); and/or (b) at least one pre-specified primary or secondary outcome measure reflects a characteristic, effect, or performance of an FDA-regulated device (e.g., need for replacement or maintenance of the device).

Studies an FDA-Regulated Drug. Section 402(j) of the PHS Act does not explicitly require submission of a clinical trial registration information data element to indicate whether or not a clinical trial studies an FDA-regulated drug. We propose to require such a data element using our authority under section 402(j)(2)(A)(iii) of the PHS Act to assist responsible parties, users of ClinicalTrials.gov, and the Agency in determining whether or not a clinical trial is an applicable drug clinical trial using the approach specified in proposed § 11.22(b)(1). As specified in the elaboration of the definition of an applicable drug clinical trial in section IV.A.5 of this preamble, one criterion for an applicable drug clinical trial is that the clinical trial studies a drug ''subject to section 505 of the [FD&C] Act or [a biological product subject] to section 351 of [the PHS] Act.'' It is possible that a clinical trial with an Intervention Type of ''drug'' or ''biological product'' would not be an applicable drug clinical trial because the drug is not subject to section 505 FD&C Act (e.g., a non-prescription drug that is marketed under an over-the-counter drug monograph)

and/or the biological product is not subject to section 351 of the PHS Act. Conversely, it is possible that a clinical trial could be an applicable drug clinical trial even if none of the specified Intervention Types is ''drug'' or ''biological product.'' A clinical trial for which the responsible party indicates the Intervention Type to be ''dietary supplement'' or ''genetic'' or ''procedure'' could in fact be an applicable drug clinical trial studying a drug subject to section 505 of the FD&C Act or a biological product subject to section 351 of the PHS Act. For example, a dietary supplement could be studied for treatment of cancer, or a genetic trial could study a gene therapy. If the responsible party has obtained an IND and submitted an IND number to ClinicalTrials.gov, then it would be clear (assuming, as discussed previously, that the clinical trial is not a clinical trial of a combination product) that the clinical trial is an applicable drug clinical trial as defined in this part. If the responsible party does not submit an IND number, however, ambiguity would arise because the lack of an IND number (or an IND) does not per se indicate that a trial is not an applicable drug clinical trial. To avoid this ambiguity and help ensure that applicable clinical trials can be properly identified, we propose to require a responsible party to specifically indicate whether or not a clinical trial studies an FDA-regulated drug by submitting the Studies an FDA-regulated Drug data element. The data element is defined in proposed § 11.10(b)(40) to mean that ''a clinical trial studies a drug that is subject to section 505 of the Federal Food, Drug, and Cosmetic Act or section 351 of the Public Health Service Act.'' Consistent with the elaboration of the term applicable drug clinical trial in section IV.A.4 of this preamble, we interpret this definition to mean that the clinical trial studies a drug that is the subject of an approved new drug application (NDA) or biologics license application (BLA) or that would require an approved NDA or BLA to be legally marketed in the U.S. We believe that submission of this information would improve and not reduce the clinical trial information submitted at the time of registration by making it clear to the responsible party, the Agency, and users of ClinicalTrials.gov whether or not a clinical trial without an IND studies an FDA-regulated drug or biological product. This information would, in turn, be used in determining whether a clinical trial meets the definition of an applicable drug clinical trial, following the approach specified in proposed § 11.22(b)(2). To reduce the data entry burden on responsible parties, ClinicalTrials.gov could automatically pre-populate this data field to indicate ''yes'' if a responsible party submits an IND number as part of the FDA IND or IDE Number data element specified in proposed § 11.10(b)(35).

We are aware that a clinical trial may include an FDA-regulated drug even though the drug is not a variable of interest. For example, a clinical trial of a device may involve the surgical insertion of the device under anesthesia, but the anesthesia drug is not studied in the clinical trial. In determining whether a clinical trial Studies an FDA-regulated Drug a responsible party should consider whether: (a) The clinical trial is designed to examine the effect of the FDA-regulated drug(s), or of differences in the intended use, including differences in dosing, frequency of use, or route of administration; and/or (b) at least one of the pre-specified primary or secondary outcome measures reflects a characteristic or effect of the FDA-regulated drug(s).

U.S. FDA Approval, Licensure, or Clearance Status. We propose U.S. FDA Approval, Licensure, or Clearance Status to be submitted as clinical trial information to indicate whether any intervention regulated by FDA and studied in the clinical trial has been approved, licensed, or cleared for any use. Such information would help in ensuring that the data bank operates in compliance with statutory requirements. For example, knowledge of the approval or clearance status of a device is necessary to determine when clinical trial registration information submitted for an applicable device clinical trial may be posted publicly in the data bank. (See section 402(j)(2)(D)(ii) of the PHS Act.) This information also would be helpful for users of ClinicalTrials.gov, including potential participants, who might wish to know whether or not the product(s) under study have been approved, licensed, or cleared for the use studied in the clinical trial. Requiring submission of the approval, licensure, or clearance status for each drug or device studied in an applicable clinical trial would therefore improve and not reduce the clinical trial information available in the data bank, consistent with section 402(j)(2)(A)(iii) of the PHS Act for proposed modifications to clinical trial registration information. We propose referring explicitly to the ''U.S.'' FDA to provide clarification for those submitting information about foreign clinical trials to ClinicalTrials.gov. In proposed § 11.10(b)(14), we therefore define U.S. FDA Approval, Licensure, or Clearance Status, to mean, ''for each drug or device studied in the clinical trial, whether that drug or device is approved, licensed, or cleared by the U.S. Food and Drug Administration for any use.'' We would require responsible parties to select a response from the following limited list of choices: ''for studied use(s)'' (the drug, biological product, or device is approved, licensed, or cleared for the use studied in the clinical trial; ''for other use(s)'' (the drug, biological product, or device is approved, licensed, or cleared for use(s) other than those studied in the clinical trial, e.g., the clinical trial studies a new use of the product); ''No'' (the product has not been approved, licensed, or cleared for any use). No ''other'' option is proposed, but a responsible party would also be able to provide voluntarily additional free-text information to further describe the approval, licensure, or clearance status, e.g., to indicate that the product has been approved in another dose or dosage form, or to list the indications for which it has been approved. We invite public comment on whether the set of proposed options is sufficient to describe the approval, licensure, or clearance status of FDA-regulated drugs or devices that would be studied in applicable clinical trials or voluntarily registered clinical trials that are subject to this proposed rule.

Product Manufactured in the U.S. Section 402(j) of the PHS Act does not explicitly require a data element to be submitted as part of clinical trial information to indicate whether a product under study is manufactured in the U.S, but we propose to include it using our authority under section 402(j)(2)(A)(iii) of the PHS Act to allow users to determine whether a registered clinical trial is an applicable clinical trial. This data element, which is defined in § 11.10(b)(15) as ''for a drug or device studied in a clinical trial, whether or not the drug or device is manufactured in the U.S. or one of its territories,'' will assist the Agency in determining whether a clinical trial meets the definition of an applicable clinical trial. As explained above in the definitions of ''applicable device clinical trial'' and ''applicable drug clinical trial,'' even if a clinical trial is being conducted entirely outside of the U.S. or one of its territories, it may be considered an applicable clinical trial where the drug or device is subject to regulation under the FD&C Act. A drug or device is considered to be subject to regulation under the FD&C Act if the product under investigation is

manufactured in the U.S. or one of its territories and is exported for study in another country, either under an IND, pursuant to 21 CFR 312.110, or any successor regulation, or under section 801(e) or 802 of the FD&C Act. Thus, information indicating whether each intervention studied in a clinical trial is manufactured in the U.S. or one of its territories would be essential in some situations to determine whether such trial is subject to FDA jurisdiction and meets the definition of an applicable clinical trial.

To reduce data submission burden, this data element would need to be submitted to ClinicalTrials.gov only if the entry submitted for the U.S. Food and Drug Administration IND or IDE Number data element indicates that there is no IND or IDE for the clinical trial, and the entry(ies) for the Facility Information data element include no facility locations in the U.S. or its territories. In those situations in which a responsible party would be required to submit information about whether the product(s) under study is manufactured in the U.S., including this information in the data bank would improve and not reduce clinical trial information by publicly providing data necessary to determine whether or not such trial is an applicable clinical trial. Accordingly, we propose the addition of this data element as clinical trial registration information pursuant to our authority to modify the requirements for clinical trial registration information under section 402(j)(2)(A)(iii) of the PHS Act.

Study Start Date. Section 402(j)(2)(A)(ii)(I)(ii) of the PHS Act expressly requires ''study start date'' to be submitted as clinical trial information at the time of registration, but it does not define this term. Prior to passage in 2007 of section 402(j) of the PHS Act, those submitting information to ClinicalTrials.gov were requested to include the study start date of the trial, which was defined as the ''date that enrollment to the protocol begins'' [Ref. 2], meaning the date on which the clinical trial is open to enrollment, even if no subjects are enrolled on that date. The WHO Trial Registration standard (version 1.0) and ICMJE registration policies, in contrast, define the term study start date (data item #16) as the ''date of first enrollment'' [Ref. 13, 10].

Section 402(j)(2)(C)(ii) of the PHS Act and proposed § 11.24(a) generally require that clinical trial registration information be submitted to ClinicalTrials.gov not later than 21 calendar days after the first human subject is enrolled in the clinical trial. In practice, however, many responsible parties submit clinical trial registration information to ClinicalTrials.gov before the first subject is enrolled. In some cases, at the time the clinical trial is registered, the responsible party might not have information about when the first subject will be enrolled or when the first subject was enrolled (for example, in a large multi-site trial) but might know only when the clinical trial was or will be opened for enrollment. To account for these potential scenarios, we propose that responsible parties be required to provide an estimated study start date (i.e., the estimated date on which the clinical trial will be open to enrollment of human subjects), unless and until the responsible party knows the actual study start date (i.e., the actual date on which the first human subject is enrolled). Not later than 21 days after the first human subject is enrolled, the responsible party would be required to update the Study Start Date data element to reflect the actual study start date, consistent with proposed § 11.64. Providing the estimated study start date to the public, even before the first subject is enrolled, has important benefits to potential human subjects because it will allow them to know when a clinical trial likely will be open to enrollment. Hence, in proposed § 11.10(b)(16) we define Study Start Date to mean: ''the estimated date on which the clinical trial will be open to enrollment of human subjects. If the clinical trial has enrolled the first human subject, the actual date on which the first human subject was enrolled.'' The Study Start Date must include the day, month, and year. We note that if a clinical trial is registered with an estimated study start date but the clinical trial then is halted before enrolling the first subject (e.g., because of difficulties in recruitment, loss of funding, etc.), the responsible party would not be expected to update the study start date; rather, responsible party would be expected to update the Overall Recruitment Status data element specified in proposed § 11.10(b)(25) to indicate that the clinical trial has been ''withdrawn,'' as such term is used for the purpose of this regulation, and to update the Why Study Stopped data element specified in proposed § 11.10(b)(26).

Completion Date. Section 402(j)(2)(A)(ii)(I)(jj) of the PHS Act requires the responsible party to submit information on the ''expected completion date'' of an applicable clinical trial when registering a clinical trial. The public availability of information about the expected completion date is important for an ongoing clinical trial because it provides an indication of the relative progress of the clinical trial and the expected date on which results information may be submitted to the data bank because section 402(j)(3)(E)(i) of the PHS Act requires that, in general, clinical trial results information be submitted not later than 1 year after the earlier of the estimated completion date of the applicable clinical trial or the actual completion date of the applicable clinical trial. We note, as described in the discussion of proposed § 11.44, that certain exceptions apply to this general deadline for the submission of clinical trial results information. In addition, we note that we interpret the phrase ''estimated completion date,'' as such term is used in section 402(j)(3)(E)(i)(I) of the PHS Act, to have the same meaning as ''expected completion date,'' as such term is used in section 402(j)(2)(A)(ii)(I)(jj) of the PHS Act, because both indicate the date on which the responsible party anticipates that the clinical trial will be completed.

In addition, we believe it is important for users to have information about the actual completion date of a clinical trial, so that they can know when clinical trial results information ordinarily would be due under section 402(j)(3)(E)(i) of the PHS Act and proposed § 11.44(a), absent certain specified circumstances in which submission of clinical trial results information may be delayed. Because clinical trial results information generally is required under section 402(j)(3)(E)(i) of the PHS Act and proposed § 11.44 to be submitted not later than 1 year after the estimated or actual completion date, whichever is earlier, we believe it is important for the Completion Date data element to be updated promptly after the completion date is reached. We therefore propose in § 11.28(a)(1)(xvii) that when registering a clinical trial, a responsible party must submit the Completion Date for the clinical trial, which is defined in § 11.10(b)(17) to mean: ''the estimated completion date. Once the clinical trial has reached the completion date, the responsible party must update the Completion Date data element to reflect the actual completion date.'' The Completion Date must include the day, month, and year. We would require the responsible party to take the following steps with regard to the Completion Date data element: (1) Provide a reasonable estimated completion date at the time of registration; (2) update the estimated completion date at least once every 12 months during the course of the clinical trial, in accordance with proposed § 11.64(b)(1)(viii)(A), if the

estimate changes; and (3) update the Completion Date information to indicate the actual completion date not later than 30 days after the clinical trial reaches its completion date, in accordance with proposed § 11.64(b)(1)(viii)(B). Finally, we note that, consistent with the requirement in section 402(j)(4)(C)(ii) of the PHS Act, ClinicalTrials.gov will maintain an archive of all of the updates made to the Completion Date data element.

Enrollment. Section 402(j)(2)(A)(ii)(I)(kk) of the PHS Act expressly requires submission of ''the target number of subjects'' to be enrolled in an applicable clinical trial, but this phrase is not defined. We believe this data element is intended to describe the intended or estimated size of the clinical trial, in terms of the estimated total number of human subjects (including healthy volunteers) or target number of human subjects who will be enrolled in the clinical trial. We therefore propose in § 11.28(a)(1)(xviii) to require the submission of enrollment information at the time of registration, which is described in proposed § 11.10(b)(18) as ''the estimated total number of human subjects to be enrolled or target number of human subjects in the clinical trial.''

We expect that the estimated or target enrollment in a clinical trial might change either before or during the clinical trial, e.g., as recruitment continues. Consistent with section 402(j)(4)(C) of the PHS Act and proposed § 11.64(a)(1), a responsible party would be required to update the Enrollment data element not less than once every 12 months, if the anticipated or target enrollment in the clinical trial changes. This update would be in addition to the requirement in proposed § 11.64(b) that a responsible party submit the Actual Enrollment data element when recruitment for a clinical trial has ended, i.e., when the Overall Recruitment Status of the trial is changed to ''active, no longer recruiting'' or ''terminated.'' This latter requirement is intended to provide users of ClinicalTrials.gov with additional information about the total number of participants enrolled in the clinical trial, which may differ from the target enrollment. (See proposed § 11.64(b) and the discussion below of ''Overall Recruitment Status'' for a discussion of this requirement.) Our proposal for Enrollment is similar to procedures in place for ClinicalTrials.gov prior to FDAAA.

Primary Outcome Measures and *Secondary Outcome Measures* are data elements expressly required by section 402(j)(2)(A)(ii)(I)(ll) of the PHS Act to be submitted as part of clinical trial information at the time of registration. Definitions of the terms Outcome Measure, Primary Outcome Measure, and Secondary Outcome Measure are provided and elaborated upon earlier in this preamble and in proposed subpart A.

Section 402(j) of the PHS Act does not specify what specific information about primary and secondary outcome measures must be submitted to ClinicalTrials.gov at the time of registration. We therefore have attempted to develop requirements that are consistent with what we believe to be the intent of section 402(j) of the PHS Act, with data submission standards for ClinicalTrials.gov prior to passage in 2007 of section 402(j) of the PHS Act, and with our understanding of common practice in the clinical trials community.

Under proposed §§ 11.28(a)(1)(xix) and (xx), responsible parties would be required to submit the information specified in §§ 11.10(b)(19) and (20) for each primary or secondary outcome measure in their clinical trials, namely: (1) The name of the specific outcome measure (e.g., systolic blood pressure); (2) a description of the metric used to characterize the specific outcome measure (e.g., mean value of systolic blood pressure); and (3) the time point(s) at which the measurement is assessed for the specific metric used (e.g., 24 weeks after initiation of treatment). These requirements are consistent with the WHO Data Elements Version 1.2.1, which specifies that each outcome include the name of the outcome, the metric or method of measurement used, and the time point(s) of primary interest. Furthermore, based on our experience in operating ClinicalTrials.gov, we believe these three elements are key attributes of an outcome measure. Not only might certain outcome measures can be assessed in different ways (e.g., systolic blood pressure can be measured as a mean value or as a change from baseline), but also a single clinical trial may assess a single attribute at multiple points in time, e.g., systolic blood pressure may be measured 3 months, 6 months, and 12 months after beginning treatment. Each of these would be considered a different outcome measure. Ensuring that the primary and secondary outcome measures include descriptions of the measures and the time points of assessment is therefore necessary for differentiating between similar measures and for subsequently ensuring that results information is provided for all of them and in a manner that is consistent with the way in which they were pre-specified in the registry. It also ensures that any changes in the outcome measure are recorded as updates to the registration information, consistent with the purpose of the data bank ''to track subsequent progress of clinical trials,'' section 402(j)(2)(A)(i) of the PHS Act. Defining Primary Outcome Measure Information and Secondary Outcome Measure Information to include these three pieces of information also retains consistency with data submission prior to FDAAA, when those submitting information to ClinicalTrials.gov were requested to provide ''the specific measure that will be used to determine the effect of the intervention(s), along with the timeframe for taking measurements'' [Ref. 2].

(2) Recruitment Information

Eligibility criteria. Section 402(j)(2)(A)(ii)(II)(aa) of the PHS Act expressly requires ''eligibility criteria'' to be submitted for registration in ClinicalTrials.gov, but it does not define the term. We believe the purpose of this data element is to enable users of the data bank to determine key characteristics of potential participants in the clinical trial and to assist prospective participants in identifying clinical trials that may be of interest. Consistent with the stated objective of section 402(j)(2)(A)(i) of the PHS Act to ''enhance patient enrollment,'' we interpret the requirement to include an ''eligibility criteria'' data element as part of clinical trial registration information to refer to information that can be of practical use to prospective participants who wish to determine if they potentially qualify to participate in a clinical trial and who might be interested in seeking additional information about a clinical trial.

Clinical trial protocols typically contain lengthy, detailed descriptions of inclusion and exclusion requirements for participants, including, for example, specific laboratory test result values. The requirements are often complex and must be assessed by a clinician or researcher involved in the clinical trial. We believe the submission of all eligibility criteria would be burdensome for responsible parties and, instead of helping prospective participants, would instead prove confusing or overwhelming. We believe that prospective participants would be better served by including a more limited list of inclusion and exclusion criteria in the data bank, in order to assist prospective participants in identifying clinical trials of possible interest. Prospective participants who believe they meet the criteria listed in the data

bank could discuss the clinical trial with their physician or other healthcare advisor and contact the facility-specific contact or central contact for the clinical trial for more information and a more complete assessment of eligibility. While there may be other users of the data bank who wish to have more detailed information about eligibility criteria for purposes of interpreting clinical trial results information and better understanding the population of human subjects studied, they could request such information from the Results Point of Contact, whose information would be submitted under proposed § 11.48(a)(5), and/or request a copy of the protocol.

Therefore, in proposed § 11.10(b)(21), Eligibility Criteria is described as ''a limited list of criteria for selection of human subjects to participate in the clinical trial, provided in terms of inclusion and exclusion criteria and suitable for assisting potential human subjects in identifying clinical trials of interest.'' For entry of eligibility criteria information, we would prefer that responsible parties list inclusion and exclusion criteria (e.g., inclusion criteria: Clinical diagnosis of Alzheimer's Disease, and must be able to swallow tablets; exclusion criteria: Insulin dependent diabetes and thyroid disease).

Our proposed definition of ''eligibility criteria'' is consistent with ''key inclusion and exclusion criteria'' (data item #14) of the WHO Trial Registration standard (version 1.0) and ICMJE registration policies [Ref. 13, 10]. This proposed interpretation is also consistent with longstanding practice in ClinicalTrials.gov and the international clinical trial community. Prior to FDAAA, those submitting information to the ClinicalTrials.gov registry pursuant to FDAMA were requested to include ''key eligibility criteria'' for the trial [Ref. 4]. This term was defined to mean ''summary criteria for participant selection'' including inclusion and exclusion criteria [Ref. 2].

Gender. Section 402(j)(2)(A)(ii)(II)(bb) of the PHS Act expressly requires ''gender'' to be submitted as clinical trial information at the time of registration, but it does not define this term. In proposed § 11.10(b)(22) we define the term to mean, ''the biological sex of the human subjects who may participate in the clinical trial.'' This is consistent with practice prior to FDAAA, when those submitting information to the ClinicalTrials.gov registry were requested to include the gender of participants of the trial [Ref. 4], which was defined to mean, ''physical gender of individuals who may participate in the protocol'' [Ref. 2]. Responsible parties would select from the following limited set of choices: ''male,'' ''female,'' or ''both.'' No ''other'' option is proposed, but responsible parties would be able to provide voluntarily additional, free-text information about the gender of participants who may participate in the clinical trial.

Age limits. Section 402(j)(2)(A)(ii)(II)(cc) of the PHS Act expressly requires ''age limits'' to be submitted as a clinical trial information at the time of registration, but it does not define the term. In proposed § 11.10(b)(23) we define the term to mean, ''the minimum and maximum age of human subjects who may participate in the clinical trial, provided in relevant units of time.'' Examples of ''relevant units of time'' include but are not limited to years, months, or weeks. This description of age limits is consistent with that used prior to FDAAA, when those submitting information to the ClinicalTrials.gov registry were requested to include the age limits for participants in the trial [Ref. 4]. At that time, the term was defined to mean a ''minimum age'' and ''maximum age of participants'' using ''a number and a unit of time (years, months, weeks, days, hours or minutes)'' [Ref. 2].

Accepts Healthy Volunteers? Section 402(j)(2)(A)(ii)(II)(dd) of the PHS Act requires the submission of information about ''whether the trial accepts healthy volunteers.'' In proposed § 11.10(b)(24), we define a data element called Accepts Healthy Volunteers to mean ''whether human subjects who do not have a disease or condition, or related conditions or symptoms, under study in the clinical trial are permitted to participate in the clinical trial.'' This definition is consistent with practice prior to FDAAA, when those submitting information to the ClinicalTrials.gov registry were required to indicate ''if persons who have not had the condition(s) being studied or otherwise related conditions or symptoms, as specified in the eligibility requirements, may participate in the study'' [Ref. 4]. Note that we consider any human participant in a clinical trial to be a human subject regardless of whether he or she is a healthy volunteer.

Overall Recruitment Status. Section 402(j)(2)(A)(ii)(II)(ee) of the PHS Act requires ''overall recruitment status'' to be submitted as clinical trial information at the time of registration, but it does not define this term. Prior to FDAAA, those submitting registration information to ClinicalTrials.gov were requested to indicate the overall recruitment status of the trial [Ref. 4]. This term was defined to mean ''overall accrual activity for the protocol'' [Ref. 2]. This definition of overall recruitment status is consistent with ''recruitment status'' (data item #18) of the WHO Trial Registration standard (version 1.0) and ICMJE registration policies [Ref. 13, 10]. Therefore, under proposed § 11.10(b)(25) we define the Overall Recruitment Status data element as ''the recruitment status for the clinical trial as a whole, based upon the status of the individual sites. If at least one facility in a multi-site clinical trial has an individual site status of 'recruiting,' then the overall recruitment status for the trial must be 'recruiting.'

To facilitate user searching by recruitment status and allow information to be compared across clinical trials, responsible parties would be required to select from the following limited set of choices: ''Not yet recruiting'' (participants are not yet being recruited); ''Recruiting'' (participants are currently being recruited); ''Enrolling by invitation'' (participants are being, or will be selected from a predetermined population); ''Active, not recruiting'' (study is ongoing, meaning participants are being treated or examined, but new participants are not currently being recruited or enrolled); ''Completed'' (the study has concluded normally; participants are no longer being examined or treated, i.e., last patient's last visit has occurred); ''Suspended'' (recruiting or enrolling participants has halted prematurely but potentially will resume), ''Terminated'' (recruiting or enrolling participants has halted prematurely and will not resume; participants are no longer being examined or treated), and ''Withdrawn'' (study halted prematurely, prior to enrollment of first participant). No ''other'' option is proposed. We believe this list includes all relevant choices for Overall Recruitment Status, but we invite public comment on whether the proposed options are sufficient to accurately describe the Overall Recruitment Status of applicable clinical trials and other voluntarily registered clinical trials that would be subject to this proposed rule.

If a clinical trial is registered before it is open to enrollment, we would expect the Overall Recruitment Status to be listed as ''Not yet recruiting.'' When the clinical trial opens for enrollment, we would expect the Overall Recruitment Status to be listed as ''Enrolling by invitation'' if human subjects are selected from a predetermined population, or as ''Recruiting'' if the study is open to volunteers who meet the study's eligibility criteria. As

indicated in the discussion of the Study Start Date data element, in the context of this rulemaking, if a clinical trial is registered prior to enrollment of the first subject and the clinical trial is subsequently halted before the first subject is enrolled, we would expect the responsible party to update the Overall Recruitment Status data element to ''Withdrawn.''

When indicating that recruitment to a clinical trial has stopped, we believe it is important to distinguish between several different situations: (1) ''Active, not recruiting,'' in which enrollment has closed, but enrolled human subjects are continuing to be examined or treated according to the study protocol; (2) ''Completed,'' in which the clinical trial has concluded according to its protocol and human subjects are no longer being enrolled, treated, or examined; (3) ''Suspended,' in which the clinical trial is temporarily halted after one or more human subjects is enrolled but may potentially resume enrollment and in which enrolled human subjects may continue to be treated or examined; and (4) ''Terminated,'' in which the study is permanently halted after one or more subjects is enrolled in the clinical trial but before the trial is completed as anticipated in the protocol. We would therefore require responsible parties to provide such information. We believe that updating the Overall Recruitment Status data element would provide users of ClinicalTrials.gov with an effective means of tracking the progress of clinical trials, as the data bank is intended to do (section 402(j)(2)(A)(i) of the PHS Act). In the case of a clinical trial that is halted before the first subject is enrolled (i.e., withdrawn), this information would explain why no results information is to be expected or is required to be submitted. In the case of a clinical trial for which recruitment is prematurely halted (i.e., suspended or terminated), this information would allow potential human subjects to determine whether enrollment is likely to resume. Such information would also assist in the interpretation of results information, for example, by providing an explanation of why some clinical trial outcomes were not achieved and/or enrollment was significantly below the target.

Why Study Stopped? In situations in which a clinical trial is suspended, terminated, or withdrawn prior to its completion as anticipated by the protocol, we propose to require that responsible parties not only submit or update the Overall Recruitment Status data element but also provide a brief explanation for why the clinical trial was stopped. While this information is not required for submission by section 402(j) of the PHS Act, we believe it is important to communicate to users of the data bank why a clinical trial was suspended, terminated, or withdrawn, e.g., because of safety concerns, difficulties in recruitment, or for financial reasons. Such information also furthers the statutory objective stated in section 402(j)(2)(A)(i) of the PHS Act to enable users ''to track subsequent progress of clinical trials.'' For these reasons, requiring this information improves and does not reduce the clinical trial information available in the data bank, consistent with section 402(j)(2)(A)(iii) of the PHS Act.

In our experience operating ClinicalTrials.gov, we have found that users often wish to have information describing why a clinical trial stopped prematurely and that clinical trial sponsors often wish to submit such information voluntarily so they may explain why a clinical trial was prematurely stopped. We are concerned that if submission of this information is not required then some responsible parties might submit it selectively, resulting in users having information about why clinical trials are stopped for only some registered clinical trials. In order to reduce confusion and inconsistencies in the information available for registered clinical trials, we believe that submission of such information should be required in each instance in which a clinical trial is stopped prematurely (i.e., not according to the protocol). Accordingly, proposed §§ 11. 28(a)(2)(vi) and 11.64(b) specify that a brief explanation for why the clinical trial was stopped must be submitted if the overall recruitment status is ''suspended'' or ''terminated,'' or ''withdrawn.'' In most cases, the overall recruitment status of a clinical trial would be other than ''suspended,'' ''terminated,'' or ''withdrawn'' at the time of registration (e.g., ''not yet recruiting'' or ''recruiting''). The responsible party would not be required to complete the ''why study stopped'' data element unless and until there is a change in overall recruitment status to ''suspended,'' ''terminated,'' or ''withdrawn.'' (The Why Study Stopped data element would be presented neither to a responsible party during the registration process nor to the public in the posted clinical trial record, unless and until the overall recruitment status indicates that the clinical trial is ''suspended,'' ''terminated,'' or ''withdrawn''). However, we note that if a clinical trial is ''suspended,'' ''terminated,'' or ''withdrawn,'' the responsible party would be required to update the Overall Recruitment Status data element and, consistent with proposed § 11.64(b), submit the Why Study Stopped data element not later than 30 calendar days after the date of such suspension, termination, or withdrawal, to explain why the study stopped. We propose to allow responsible parties to enter this information as free-text, to provide them with the flexibility to explain the reason(s) why a clinical trial stopped prematurely. We define the data to be submitted in proposed § 11.1(b)(26) as ''for a clinical trial that is suspended or terminated or withdrawn prior to its completion as anticipated by the protocol, a brief explanation of the reason(s) why such clinical trial was stopped.''

Actual Enrollment. When enrollment of human subjects to a clinical trial ends because recruitment was completed in accordance with the protocol or because the clinical trial was terminated prior to its completion as anticipated by the protocol, we propose to require responsible parties to submit the actual number of human subjects enrolled in the clinical trial by completing the Actual Enrollment data element. The actual enrollment data element does not need to be completed until such time as the overall recruitment status data element is updated to ''active, not recruiting'' or ''terminated.'' See proposed § 11.64(b). (The Actual Enrollment data element would be presented neither to a responsible party during the registration process nor to the public in the posted clinical trial record, unless and until the overall recruitment status indicates that the clinical trial is ''active, not recruiting'' or ''terminated.'') We believe submission of actual enrollment information is consistent with the objective of the expanded registry data bank to ''provide a mechanism to track subsequent progress of clinical trials'' (section 402(j)(2)(A)(i) of the PHS Act). It would offer a means of measuring how actual enrollment compares with the target or estimated enrollment in the clinical trial (collected under proposed § 11.28(a)(1)(xviii)).

Our proposal would require a responsible party to submit the actual enrollment figure only after enrollment is closed. Although requiring more frequent updates while recruitment is ongoing would allow tracking of enrollment progress, we believe it would be burdensome for responsible parties, especially for clinical trials with multiple sites, and provide limited value to users. The data could become quickly outdated as enrollment for the clinical trial continues, potentially

leading users to believe that enrollment is lower than is the case. We believe that providing the actual enrollment figure once, at the time recruitment ends, would provide an effective means for tracking the progress of clinical trials registered in ClinicalTrials.gov. When combined with information about target enrollment, the actual enrollment data would indicate the degree to which the clinical trial met its enrollment target. By requiring the submission of actual enrollment data when enrollment closes, rather than when results information is submitted (which could be several years after enrollment closed), users would be able to gauge in advance their level of interest in the results of the clinical trial: The results of a clinical trial for which actual enrollment is substantially below the target enrollment might be of less interest than one in which recruitment targets were met. In proposed § 11.10(b)(27) we define Actual Enrollment as ''for a clinical trial for which recruitment of human subjects has terminated or completed, the actual number of human subjects enrolled in the clinical trial.''

Individual Site Status. Section 402(j)(2)(A)(ii)(II)(ff) of the PHS Act expressly requires ''individual site status'' to be submitted as a clinical trial information at the time of registration, but it does not define this term. Prior to FDAAA, those submitting information to the ClinicalTrials.gov registry were requested to include a recruitment status for each site of the trial [Ref. 4]. This term was defined to mean ''protocol accrual activity at a facility'' [Ref. 2]. In proposed § 11.28(a)(2)(viii), we would require the submission of Individual Site Status, which is defined in § 11.10(b)(28) as ''the recruitment status of each participating facility in a clinical trial.'' Consistent with the proposed Overall Recruitment Status data element, responsible parties would be required to indicate individual site status by selecting from the following limited set of choices: ''Not yet recruiting,'' ''Recruiting,'' ''Enrolling by invitation,'' ''Active, not recruiting,'' ''Completed,'' ''Suspended,'' ''Terminated,'' and ''Withdrawn.'' No ''other'' option is proposed, but we invite public comment on whether the proposed options are sufficient to accurately describe the Individual Site Status of applicable clinical trials and other voluntarily registered clinical trials that would be subject to this proposed rule. (See the discussion of Overall Recruitment Status for a description of these categories.)

Availability of Expanded Access. Section 402(j)(2)(A)(ii)(II)(gg) of the PHS Act specifies that, if a drug (including a biological product) being investigated in an applicable clinical trial is not approved under section 505 of the FD&C Act or licensed under section 351 of the PHS Act, the responsible party must specify: (1) ''whether or not there is expanded access to the drug under section 561 of the Federal Food, Drug, and Cosmetic Act for those who do not qualify for enrollment in the clinical trial''; and, if so, (2) ''how to obtain information about such access.'' We believe the purpose of this requirement is to allow prospective human subjects and other users of the data bank to readily identify unapproved drugs that are available through an expanded access program under section 561 of the FD&C Act and to be directed to additional information about the expanded access program. Therefore, we propose that responsible parties meet the requirements of section 402(j)(2)(A)(ii)(II)(gg) by indicating in the clinical trial record whether expanded access is available for the drug under study (i.e., ''yes'' or ''no'') and, if so, submitting the additional information about the expanded access in the form of an expanded access record under proposed § 11.28(c) and including the NCT number for the expanded access record in the record of a clinical trial that studies the drug.

We propose to require the submission of information to create an Expanded Access record using the statutory authority at section 402(j)(2)(A)(iii) of the PHS Act, which allows the Secretary by regulation to modify the requirements for clinical trial registration information if the Secretary provides a rationale for why such a modification ''improves and does not reduce such clinical trial information.'' Information about the availability of expanded access is a data element that a responsible party is required to submit under section 402(j)(2)(A)(ii)(II) and thus meets the definition of ''clinical trial information'' in section 402(j)(1)(A)(iv). We believe the additional data elements describing expanded access would improve and not reduce this clinical trial information by providing users with more complete and consistent information about expanded access programs for drugs studied in applicable clinical trials than would be available pursuant to section 402(j)(A)(ii)(II)(gg) of the PHS Act alone. We further conclude that we have authority to require that the clinical trial information required under proposed § 11.28(c) be submitted by creating a separate expanded access record in ClinicalTrials.gov under section 402(j)(2)(B)(iv) of the PHS Act, as the expanded access record will ensure that the public may more easily use the data bank to determine whether there is expanded access to a drug and to compare different expanded access programs.

Prior to FDAAA, those submitting information to the ClinicalTrials.gov registry were requested to submit a description of whether and through what procedure, the manufacturer or sponsor will respond to requests for protocol exception, with appropriate safeguards, for single-patient and expanded access use of the investigational drug, particularly in children [Ref. 3]. The data bank also permitted submission of information about expanded access to devices. At that time, the data bank included a ''Has Expanded Access?'' data field, which asked data submitters to ''indicate whether any non-protocol access is to be provided for the investigational drug or device.'' If expanded access were available, data submitters were requested to create an expanded access record via ClinicalTrials.gov. These expanded access records provided information to users of ClinicalTrials.gov about treatment access to investigational drugs or devices for patients for whom there was no satisfactory therapy available for their condition or who were unable to participate in ongoing clinical trials. Expanded access records were used to register all types of non-protocol access to investigational treatments [Ref. 2].

We propose a similar approach in this rule. Proposed § 11.28(a)(2)(ix) would require the responsible party for an applicable clinical trial of a drug that is not approved under section 505 of the FD&C Act to submit the Availability of Expanded Access data element, which is defined in proposed § 11.10(b)(29) to include ''[a]n indication of whether there is expanded access to the drug under section 561 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 360bbb) for those who do not qualify for enrollment in the applicable clinical trial,'' and if expanded access is available, ''the NCT number of the expanded access record.'' The availability of expanded access would be indicated via a yes/no designation in ClinicalTrials.gov. If the NCT number is not available, because an expanded access record has not yet been created, the responsible party would enter ''pending'' for the NCT number.

In addition, if the drug studied in the clinical trial is available through expanded access under section 561 of the FD&C Act and an expanded access record has not been created, the

responsible party would be required to create an expanded access record, consisting of the information specified in proposed § 11.28(c). As was the case prior to FDAAA, the manner in which the responsible party would submit the data elements describing the expanded access program would be to create an expanded access record in ClinicalTrials.gov. Upon completion of the quality control process for the expanded access record, the expanded access record would be assigned its own NCT number and thus would be searchable and retrievable independent of the record(s) for the applicable clinical trial(s) of the investigational product for which expanded access is available. We would expect the sponsor of the expanded access program to be responsible for informing the responsible party(ies) of any applicable clinical trial that studies the drug available under expanded access that an expanded access record has been created and providing them with the NCT number for the expanded access record. The responsible party(ies) would be required to update the related clinical trial record under proposed § 11.64(b) to include the NCT number for the expanded access record within 30 days of receipt. Accordingly, a single expanded access record could be linked, via the expanded access record NCT number, to several applicable clinical trials that study the drug that is available via expanded access.

If an expanded access record has already been completed at the time of registration of an applicable clinical trial (e.g., to fulfill the registration or updating requirements for a previously registered applicable clinical trial), the responsible party would be required to submit the NCT number for that expanded access record as part of the Availability of Expanded Access data element. If an expanded access program is in place but an expanded access record has not been created at the time an applicable clinical trial of a drug is registered, the responsible party would not be required to submit the expanded access data elements under proposed § 11.28(c) prior to the date on which clinical trial registration information under proposed § 11.28(a) is due (i.e., in order to have the expanded access program NCT number available at the time of registration of the applicable clinical trial). Rather, the responsible party would be required at the time of registration to indicate that expanded access is available, to submit the data elements required by § 11.28(c), and to indicate that the NCT number for the expanded access record is ''pending.'' As described previously, within 30 days of receipt of the NCT number for the expanded access record, the responsible party would be required to update the applicable clinical trial record with the NCT number assigned to the Expanded Access record.

We note that expanded access is available via treatment INDs, which provide widespread access, expanded access for intermediate-size patient populations, and expanded access for individual patients. Because requests for individual patient access generally are handled on a case-by-case basis, a responsible party likely would not be able to provide detailed information describing individual patient access at the time of registering an applicable clinical trial. In cases where expanded access is only available for individual patients on a case-by-case basis, we would not require the responsible party to submit the expanded access record, as described below, and we expect that users of ClinicalTrials.gov may direct inquiries regarding individual patient access to the facility contact.

Finally, we note both that expanded access to a drug may not be available at the time an applicable clinical trial is registered and that an expanded access program may be discontinued on a date other than the completion date of an applicable clinical trial. We believe that information about changes in the availability of expanded access should be conveyed to users of ClinicalTrials.gov in a timely manner and thus that the availability of expanded access is a data element that should be updated more frequently than once every 12 months. Accordingly, as explained in further detail in section IV.D.3 of this preamble, we propose that the availability of expanded access data element be updated within 30 calendar days of either the initiation or termination of an expanded access program, consistent with proposed § 11.64(b).

(3) Location and Contact Information

Name of the Sponsor. Section 402(j)(2)(A)(ii)(III)(aa) of the PHS Act expressly requires responsible parties to submit the name of the sponsor as part of clinical trial information at the time of registration. Proposed § 11.28(a)(3)(i) implements this provision. In this part, the term ''sponsor'' is defined as ''either a 'sponsor' or 'sponsor-investigator,' as each is defined in 21 CFR 50.3, or any successor regulation.'' If the sponsor is a sponsor-investigator, we would expect the name of the sponsor to be the name of an individual; otherwise the name of the sponsor may be an organizational name. Hence, in proposed § 11.10(b)(30), Name of the Sponsor is defined as ''the name of the entity or the individual that is the sponsor of the clinical trial, as defined in § 11.10(a).''

Responsible Party, by Official Title. Section 402(j)(2)(A)(ii)(III)(bb) of the PHS Act expressly requires the submission of the ''responsible party, by official title'' as part of clinical trial registration information. We recognize that the responsible party for an applicable clinical trial may be the sponsor of the clinical trial (a term defined by this regulation to include the sponsor or the sponsor-investigator, as each is defined in 21 CFR 50.3) or a designated principal investigator. A responsible party that is the sponsor will typically be an organizational entity (e.g., a drug or device manufacturer that is the sponsor of an applicable clinical trial). A responsible party that is a sponsor-investigator will be an individual. A responsible party that is a designated principal investigator will be an individual. When an organizational entity is the responsible party, we believe that the official name of the entity (e.g., company name, university name, name of government agency) should be included to satisfy the requirement for the Responsible Party, by Official Title. When the responsible party is an individual, we believe that the official job title and the organizational affiliation of the individual are necessary (e.g., ''Director of Clinical Research, Institution X'' or ''Professor of Medicine, Institution Y''). In addition, we believe it is important to ask whether the responsible party is the sponsor, sponsor-investigator, or a principal investigator designated by the sponsor, grantee, contractor, or awardee. Collection of this information will help determine what information must be provided for the official title and will allow a principal investigator to provide an affirmative acknowledgement that he or she has been designated the responsible party. In light of these considerations, proposed § 11.10(b)(31) defines Responsible Party, by Official Title to mean an ''[i]ndication of whether the responsible party is the sponsor of the clinical trial, as that term is defined in 21 CFR 50.3, the sponsor-investigator, as that term is defined in 21 CFR 50.3, or a principal investigator designated pursuant to this part'' (this indication would be provided by selecting among these three options) and either ''the official name of the entity'' if the responsible party is an organizational entity, or ''the official title and primary organizational affiliation of the individual'' if the responsible party is an individual. An

individual who serves as a responsible party and has multiple affiliations (e.g., a research university and a teaching hospital, or a research institution and a private company), would be required to submit only one such affiliation; namely, the affiliation they consider their primary affiliation. We note that proposed § 11.10(b)(38) defines a related data element, Responsible Party Contact Information.

Facility Information. Section 402(j)(2)(A)(ii)(III)(cc) of the PHS Act expressly requires the submission of ''the facility name and facility contact information'' as part of clinical trial information at the time of registration and describes facility contact information as ''including the city, State, and zip code for each clinical trial location, or a toll-free number through which such location information may be accessed.'' In considering how to implement this provision, we took into consideration section 402(j)(2)(B)(i) of the PHS Act, which requires the Director to ensure that the public may search the entries in ClinicalTrials.gov by one or more of several enumerated criterion, one of which is ''location of the clinical trial.'' We interpret ''location of the clinical trial'' in this context as meaning each location of the clinical trial because section 402(j)(2)(A)(ii)(III)(cc) of the PHS Act describes ''facility contact information'' as meaning contact information ''for each clinical trial location.'' In order for users of ClinicalTrials.gov to be able to search the data bank by each location of the clinical trial, the responsible party must submit to the data bank the location of each facility at which the applicable clinical trial is conducted. In our view, a toll-free telephone number is not a substitute for the location information for each facility or site but rather is a source of supplementary information about the clinical trial overall and an alternative to site-specific contact information for each location.

For these reasons, we believe including this information improves and does not reduce the clinical trial registration information. Under our authority in section 402(j)(2)(A)(iii) of the PHS Act, we therefore propose in § 11.28(a)(3)(iii) to modify the requirement in section 402(j)(2)(A)(ii)(III)(cc) of the PHS Act for ''facility name and facility contact information'' to require Facility Information for each participating facility in the clinical trial, which we define in proposed § 11.10(b)(32) as (1) ''Facility Name, meaning the full name of the organization where the clinical trial is being conducted''; (2) ''Facility Location, including city, state, country and zip code for U.S. locations (including territories of the United States) and city and country for locations in other countries,'' and (3) either ''[for each facility location submitted], a Facility Contact, including the name or title, telephone number, and email address of a person to whom questions concerning the trial and enrollment at that site can be addressed,'' or a ''Central Contact person, including the name or title, toll-free telephone number and email address of a person to whom questions concerning enrollment at any location of the trial can be addressed.''

As noted above, the Agency intends to exercise its authority under section 402(j)(2)(B)(i) to enable the public to search the data bank by the location of the clinical trial and, in our view, satisfactory searching by location can only be accomplished if responsible parties submit complete facility location information for each clinical trial location. In addition, our proposal to allow (but not require) responsible parties to submit the name or title of a person knowledgeable about the clinical trial at each site, along with the phone number and email address of that person, would help prospective human subjects obtain additional, specific information about a clinical trial at a particular location. Our proposal to permit responsible parties to submit a Central Contact in lieu of Facility Contact is intended to reduce the burden on responsible parties who must submit clinical trial registration information. However, the central contact person should be fully informed of, and able to respond to, requests for information concerning the clinical trial at all of its sites. This approach is similar to the one used prior to FDAAA, when those submitting information to the ClinicalTrials.gov registry were requested to include each facility name and facility contact information for the registered clinical trial and were permitted to include a ''central contact'' rather than contact information for each facility of the trial [Ref. 4]. At the time, the term ''facility name'' was defined to include the ''full name of the organization where the protocol is being conducted'' and central contact was defined as a ''person providing centralized, coordinated recruitment information for the entire study'' [Ref. 2].

(4) Administrative Data

Section 402(j)(2)(A)(ii)(IV) of the PHS Act provides for certain ''administrative data'' to be submitted by responsible parties as part of clinical trial registration information; however, unlike the other categories of clinical trial registration information, the statute specifies that the Secretary may make administrative data ''publicly available as necessary.'' Accordingly, in the descriptions below of each administrative data element, the Agency indicates whether it proposes to make the information publicly available through ClinicalTrials.gov.

Unique Protocol Identification Number. Section 402(j)(2)(A)(ii)(IV)(aa) of the PHS Act expressly requires the submission of ''the unique protocol identification number'' as part of clinical trial information at the time of registration, but it does not define the term. We propose in § 11.10(b)(33) to define ''unique protocol identification number'' as ''any unique identification number assigned to the protocol by the sponsor.'' Once entered into ClinicalTrials.gov, that unique protocol identification number cannot be assigned to another protocol for another clinical trial in the sponsor's ClinicalTrials.gov account. In cases in which multiple identification numbers may have been assigned to a clinical trial (e.g., a funding organization's grant number, a unique identifier established by another clinical trial registry), we believe that interpreting this term as a number ''assigned by the sponsor'' will remove any ambiguity for responsible parties about which number to submit as the unique protocol identification number for purposes of registration on ClinicalTrials.gov. We also expect that the unique protocol identification number would be readily available to the responsible party, whether the sponsor or a designated PI, who would have access to the protocol itself and/or be able to obtain the unique protocol number from the sponsor. Further, these numbers often are used in other clinical trial documentation, which will enable cross-referencing of information submitted to different data systems. To enable such cross-referencing, we plan to make this data element publicly available in ClinicalTrials.gov.

This approach is consistent with that used in ClinicalTrials.gov prior to FDAAA, when those submitting information to the registry were requested to include the unique protocol ID of the trial [Ref. 4]. This term was defined to mean any ''unique identification assigned to the protocol by the sponsoring organization, usually an accession number or a variation of a grant number. Multiple studies conducted under the same grant must each have a unique number'' [Ref. 2]. The wording of our proposed description modifies the previous one by, among other things, removing the

reference to ''a variation of a grant number'' because all grant-related information is proposed to be collected under the Secondary IDs data element.

Secondary IDs. Section 402(j)(2)(A)(ii)(IV)(bb) of the PHS Act expressly requires the submission of ''other protocol identification numbers, if any,'' at the time of registration, but does not define this term. Prior to FDAAA, those submitting information to ClinicalTrials.gov were requested to include secondary IDs of the clinical trial. This term was defined as ''other identification numbers assigned to the protocol, including ISRCTN . . . and NIH grant numbers, if applicable'' [Ref. 2]. This definition is consistent with ''secondary identification number(s)'' (data item #3) of the WHO Trial Registration standard (version 1.0) and ICMJE registration policies [Ref. 13, 10]. To maintain consistency with these widely used terms and definitions, we propose in proposed § 11.10(b)(34) to define the term, in part, as ''[a]ny identification number(s) other than the organization's unique protocol identification number or NCT number that is assigned to the clinical trial . . .'' We also propose that the Secondary IDs include ''any unique clinical trial identification numbers assigned by other publicly available clinical trial registries,'' such as EudraCT in the European Union. We intend to post publicly the Secondary IDs, as such information will enable users to locate additional information about the clinical trial that may be included in other registries; it also will enable users to determine if registration information listed in another registry refers to the same trial that is registered in ClinicalTrials.gov, thereby avoiding potential confusion.

In addition, we propose that Secondary IDs include the complete grant or contract number for any clinical trial that is funded, in whole or in part, by a U.S. federal government agency. This requirement would enable users of ClinicalTrials.gov to identify government-funded clinical trials. It also would assist agencies of the Department (including NIH, FDA, CDC, and the Agency for Healthcare Research and Quality) to verify that clinical trial information for each applicable clinical trial for which a grantee is the responsible party has been submitted consistent with sections 402(j)(2) and (3) of the PHS Act and this proposed Part before they release any remaining funding for a grant or provide funding for a future grant to such grantee. Such verification procedures are required under section 402(j)(5)(A)(ii) of the PHS Act of any agency of the Department that funds applicable clinical trials. In addition, although the requirement of section 402(j)(5)(A)(ii) of the PHS Act applies only to the agencies of the Department, the inclusion of grant and contract numbers for awards from other federal agencies (e.g., Department of Veterans Affairs, Department of Defense) would facilitate efforts by the Secretary, as required under section 402(j)(5)(A)(iv) of the PHS Act, to consult with such other agencies and to develop comparable procedures for verification of compliance with the requirements of sections 402(j)(2) and (3) of the PHS Act.

Finally, in order that users can interpret the various Secondary IDs that might be provided in response to this requirement, we propose to require responsible parties to submit ''[a] description of the type of Secondary ID'' for each Secondary ID submitted. These descriptions should be brief, but should clearly indicate the source of the identifier, e.g., ''U.S. NIH Grant Number'' or ''[XYZ] Registry Identifier.'' To facilitate data entry and improve comparability across registered clinical trials, we will include a list of several common identifier types in ClinicalTrials.gov, while permitting free-text entries, as well. Currently, ClinicalTrials.gov allows responsible parties to select from the following options: ''US NIH Grant/Contract Award Number,'' ''Other Grant/Funding Number,'' ''Registry Identifier,'' ''EudraCT Number,'' and ''Other Identifier.'' Responsible parties who select ''Other Grant/Funding Number,'' ''Registry Identifier,'' or ''Other Identifier'' are required to enter the name of the granting organization or a brief description of the identifier.

Food and Drug Administration IND or IDE number. Section 402(j)(2)(A)(ii)(IV)(cc) of the PHS Act expressly requires the ''Food and Drug Administration IND/IDE protocol number'' to be submitted to ClinicalTrials.gov at the time of registration in ClinicalTrials.gov, but it does not define this term. FDA does not issue an ''IND/IDE protocol number,'' as referred to in section 402(j)(2)(A)(ii)(IV)(cc) of the PHS Act; rather it issues an IND or IDE number. We therefore propose to use the term ''Food and Drug Administration IND or IDE number'' to identify this data element in ClinicalTrials.gov. We also recognize that not all applicable clinical trials will be conducted under an IND or IDE (e.g., because they are exempt).

Because CDER, CBER, and CDRH each issues IND or IDE numbers using a similar format, we believe that, for purposes of registration with ClinicalTrials.gov, a complete, unambiguous IND or IDE number must include the name of the FDA center that issued it. In addition, if several clinical trials are conducted under a single IND, for example, each such clinical trial may have a different serial number assigned to it. We believe that any such serial number must also be specified to avoid confusion. Moreover, if multiple serial numbers are assigned to a single IND (e.g., to reflect different clinical trials, protocols, or protocol amendments), the responsible party should submit only the first serial number that corresponds to the clinical trial being registered.

Taking the foregoing into consideration, we propose in § 11.10(b)(35) to define the Food and Drug Administration IND or IDE Number data element to include an indication whether or not there is an IND or IDE for the clinical trial (a yes/no response) and, if so, each of the following elements: (1) ''Name or abbreviation of the FDA center with whom the IND or IDE is filed;'' (2) ''IND or IDE number assigned by the FDA center;'' and (3) for an IND, ''the IND serial number (as defined in 21 CFR 312.23(e), or any successor regulation), if any, assigned to the clinical trial.'' In specifying the FDA center with which the IND or IDE is filed, responsible parties would select from the following limited set of options: CDER, CBER, or CDRH. These abbreviations correspond to the FDA Center for Drug Evaluation and Research, Center for Biologics Evaluation and Research, and Center for Devices and Radiological Health, respectively, which are the three FDA centers with which INDs and IDEs are filed.

Our proposed approach for IND or IDE numbers is consistent with that used prior to FDAAA, when those submitting information to the ClinicalTrials.gov registry were requested to include ''the IND number and serial number and designate whether the IND is located in the Center for Drug Evaluation and Research (CDER) or the Center for Biologics Evaluation and Research (CBER)'' [Ref. 4]. Also consistent with previous ClinicalTrials.gov practice, we do not intend to make the Food and Drug Administration IND or IDE number available to the public. Section 402(j)(2)(A)(ii)(IV) of the PHS Act indicates that administrative data submitted as part of clinical trial information may be made publicly available ''as necessary.'' We do not consider public posting of information in this field to be necessary for the effective use of ClinicalTrials.gov or for

understanding of the information submitted.

Human Subjects Protection Review Board Status. We propose to require the submission of information about human subjects protection review board status as part of clinical trial information. Submission of this information is not required by section 402(j) of the PHS Act, but we propose to add this requirement pursuant to the authority given by section 402(j)(2)(A)(iii) of the PHS Act to modify the requirements for clinical trial registration information if such modification ''improves and does not reduce such clinical trial information.'' We believe that submission of the Human Subjects Protection Review Board Status, as specified below, to ClinicalTrials.gov would improve and not reduce clinical trial information by indicating to users of the data bank whether a clinical trial registered in ClinicalTrials.gov is undergoing or has undergone human subjects protection review board review.

We believe that the submission of Human Subjects Protection Review Board Status is consistent with the purpose of the data bank ''to enhance patient enrollment,'' as described in section 402(j)(2)(A)(i) of the PHS Act. While review and approval by a human subjects protection review board, such as an IRB, cannot guarantee the scientific merit of a clinical trial or the safety of human subjects enrolled in it, it may provide some assurance that such factors are considered by a group of individuals who are not directly involved in the conduct of the clinical trial and who are charged to consider the safety of human subjects. Inclusion of such information in ClinicalTrials.gov would demonstrate to potential human subjects whether the clinical trials they find in ClinicalTrials.gov have undergone at least one human subjects protection review board review, have received necessary approvals for human subjects research from at least one human subjects protection review board, or were exempt from such review. For clinical trials conducted in the United States or under an IND or IDE, human subjects review would be conducted by an IRB as described in 45 CFR 46 and 21 CFR 50 and 56, as applicable, or any successor regulations. For clinical trials conducted outside the United States, we would expect the review to be conducted by a human subjects protection review board that is charged with providing independent ethics review that is aimed at ensuring the protection of the rights, safety, and well-being of human subjects involved in a clinical investigation by a group that is adequately constituted to provide assurance of that protection.

Inclusion of this data element is consistent with longstanding Agency practice. Prior to FDAAA, those submitting information to ClinicalTrials.gov were requested to include information regarding human subjects review [Ref. 4]. Human subjects protection review board approval information was not required to be submitted if the data submitter indicated that the trial was conducted under an IND or IDE because IRB approval is a requirement for conducting a clinical trial under an IND or IDE. We therefore interpreted the presence of an IND or IDE number as an acceptable indication that the trial had received necessary human subjects protection review board review. For trials not conducted under an IND or IDE, data providers were requested to submit information for only one human subjects protection review board even if multiple boards had reviewed the trial. Although it did not provide information on the status of review by every human subjects protection review board with authority over a trial, we viewed submission of information about one human subjects protection review board as establishing a minimum floor for studies listed in ClinicalTrials.gov by indicating whether they had been approved by at least one human subjects protection review board, or were seeking approval from such a board, or were exempt from such review.

Our current proposal requires submission of Human Subjects Protection Review Board Status for all applicable clinical trials and other clinical trials registered with ClinicalTrials.gov, but it does not require information about the specific review board. Under proposed § 11.28(a)(4)(v), responsible parties would be required to submit Human Subjects Protection Review Board Status as part of clinical trial information at the time of registration. We define Human Subjects Protection Review Board Status in § 11.10(b)(36) as ''information to indicate whether a clinical trial has been approved by a human subjects protection review board or is exempt from human subjects protection review board approval, . . .'' Human Subjects Protection Review Board Status would be provided by the Responsible Party selecting from a limited set of options described in ClinicalTrials.gov that are intended to cover all of the possible types of status: ''Request not yet submitted'' (review board approval is required but has not yet been requested); ''Submitted, pending'' (review board approval has been requested but not yet granted); ''Submitted, approved'' (review board approval has been requested and obtained); ''Exempt'' (an exemption in accord with applicable law and regulation has been granted); ''Submitted, denied'' (review board has denied the approval request); and ''Submission not required'' (review board approval is not required because the study is not subject to laws, regulations, or applicable institutional policies requiring human subjects review). No ''other'' option is proposed. We request comment on whether the above menu of options adequately captures all possible types of review status for applicable clinical trials and voluntarily registered trials that would be subject to this regulation. The status must be listed as ''approved'' if at least one human subjects protection review board has approved the clinical trial. An applicable clinical trial could be registered prior to human subjects protection review board approval by indicating that the status is, for example, pending, not yet submitted, or exempt. If the status subsequently changes, the responsible party would be required, consistent with proposed § 11.64(b), to update the Human Subjects Protection Review Board Status not later than 30 calendar days after the change.

Consistent with longstanding practice, responsible parties would be required to indicate that the clinical trial is approved when at least one human subjects protection review board has granted approval. To clarify for users that the human subjects protection review board status pertains to only one human subjects protection review board, we would indicate that fact in ClinicalTrials.gov and instruct potential human subjects to communicate with the site-specific point-of-contact or the central contact for the clinical trial (included as part of the Facility Information that is submitted as part of clinical trial information under proposed § 11.28(a)(3)(iii)) in order to determine the status of human subjects protection review board review at other sites of interest. We believe this approach will provide users with important information about human subjects review without burdening responsible parties with updating information on multiple sites.

Our proposal deviates from current practice with regard to the information that would be necessary for clinical trials conducted under an IND or IDE. We considered maintaining the current requirement that human subjects protection review board information (which is currently more extensive than

the single status element) be submitted only for clinical trials that are not conducted under an IND or IDE. We believe, however, that there would be an advantage in applying a consistent requirement across all registered clinical trials. Doing so would reduce confusion among responsible parties who might otherwise face different information submission requirements for different clinical trials and among users who might not be sure why certain clinical trials contain human subjects review information but others do not (as indicated above, we do not propose to make information about IND or IDE numbers publicly available in the data bank). We do not expect the burden of providing the human subjects protection review board status for a particular clinical trial to be significant, especially as it would be limited to a single data element about one human subjects protection review board.

Record Verification Date is a data element required by section 402(j)(2)(A)(ii)(IV)(cc) of the PHS Act to be submitted as part of clinical trial information at the time of registration, but the statute does not define this term. The statutory provision calls for the submission of ''the Food and Drug Administration IND/IDE protocol number and the record verification date.'' We believe record verification date is intended to be submitted as a separate data element that indicates to users of the data bank how recently the information for a particular clinical trial was verified and, hence, whether or not it may be out of date. We therefore intend to collect and post publicly the Record Verification Date data element in ClinicalTrials.gov. Our interpretation of this term is consistent with that used prior to FDAAA when those submitting information to the registry were requested to list the ''record verification date'' of the trial, meaning the ''date the protocol information was last verified'' [Ref. 4].

We propose to require responsible parties to include the Record Verification Date data element as part of an initial submission of clinical trial registration information to ClinicalTrials.gov and to update it any time the responsible party reviews the complete clinical trial record for accuracy, such as when making a periodic review of an entire clinical trial record. For example, if a responsible party examines the entire record as part of a monthly or annual review and determines that no additional or updated information needs to be submitted, the responsible party would be required to update the Record Verification Date data element to indicate the date on which the review occurred. Or, if a responsible party updates a data element and also reviews the rest of the record for accuracy, the responsible party would also be required to update the Record Verification Date data element. However, if the responsible party submits updates to one or more data elements without reviewing the accuracy of the rest of the record, the Record Verification Date would not be updated. This proposal would not require a responsible party to review records more frequently or regularly than would be needed in order to update submitted information as specified in proposed § 11.64 (should the responsible party use this method to help ensure that updates are submitted on time), but it would require that the Record Verification Date be updated if the complete record were reviewed for accuracy during such an update. This proposal is consistent with current practice. Starting prior to FDAAA, those submitting data to ClinicalTrials.gov were requested to update the verification date when reviewing the record for accuracy and completeness, even if no other changes were made'' [Ref. 2]. At the time, we also suggested that records be reviewed at least every six months to help ensure that information available to the public in the data bank was up-to-date. Under proposed § 11.10(b)(37), we define Record Verification Date as ''the date upon which the responsible party last verified the clinical trial information in the entire ClinicalTrials.gov record for the clinical trial, even if no additional or updated information was submitted at that time.''

Responsible Party Contact Information. Section 402(j)(1)(B) of the PHS Act requires the Secretary to develop a mechanism ''by which the responsible party for each applicable clinical trial shall submit the identity and contact information of such responsible party to the Secretary at the time of submission of clinical trial information . . .'' We propose that the mechanism whereby the responsible party communicates the identity and contact information to the Secretary shall be via submission of such information at the time clinical trial information is first submitted to Clinical Trials.gov. Using the authority in section 402(j)(2)(A)(iii) of the PHS Act, we propose to modify the requirements for clinical trial information submitted at the time of registration to require responsible parties to submit Responsible Party Contact Information. In proposed § 11.10(b)(38), we describe Responsible Party Contact Information as ''[a]dministrative information to identify and allow communication with the responsible party by telephone, email, and regular mail or delivery service. Responsible Party Contact Information includes the name, official title, organizational affiliation, physical address, mailing address, phone number, and email address of the individual who is the responsible party or of a designated employee of the organization that is the responsible party.'' We believe that the addition of this information will improve and not reduce clinical trial information by providing a mechanism for the Agency to communicate with the responsible party about submitted information, which can improve its quality, accuracy and completeness. We do not intend to post the physical address, mailing address, phone number or email address of the responsible party. The system will contain other information, such as central or site-specific contact information that interested parties can use to request additional information about a clinical trial or inquire about participation. In general, we do intend to post the name of the responsible party if the responsible party is an individual, e.g., a sponsor-investigator who holds the IND or IDE for a clinical trial or a designated principal investigator. We would post the name of the responsible party, along with the Responsible Party, By Official Title, which section 402(j)(2)(A)(ii)(III)(bb) of the PHS Act requires to be made publicly available. We believe that posting of the individual's name is necessary to avoid ambiguity, e.g., if the responsible party is a university professor, there might be numerous individuals with the same title and affiliation (professor of medicine at ABC University). Posting the name of the individual when the individual is the responsible party would also be consistent with posting of the name of an entity when an entity is the responsible party of an applicable clinical trial. Responsible Party Contact Information would be required to be updated as specified in proposed § 11.64.

(b) Data elements required to register a pediatric postmarket surveillance of a device that is not a clinical trial. Proposed § 11.28(b) specifies the clinical trial information that must be submitted to ClinicalTrials.gov to register a pediatric postmarket surveillance of a device that is not a clinical trial as defined in this part, but is required to be registered under proposed § 11.22. Section 801(c) of

FDAAA recognizes that not all of the clinical trial information specified in section 402(j) of the PHS Act or proposed in this rule will apply to all pediatric postmarket surveillances of a device and directs the Secretary to issue guidance explaining how the registration and results submission provisions of section 402(j) of the PHS Act apply to a pediatric postmarket surveillance of a device that is not a clinical trial. The Agency intends this and the other discussions in this preamble related to pediatric postmarket surveillances of a device to serve as draft guidance that will be finalized when the final rule is issued.

In 21 CFR 822.3, ''postmarket surveillance'' is defined as the ''active, systematic, scientifically valid collection, analysis, and interpretation of data or other information about a marketed device.'' The Agency interprets a pediatric postmarket surveillance of a device as a postmarket surveillance of a device used in a pediatric population (i.e., patients who are 21 years of age or younger at the time of diagnosis or treatment). (*See* 21 U.S.C. 360j(m)(6)(E)). The clinical trial information specified in proposed § 11.28(a) and defined in proposed § 11.10(b), would apply to any pediatric postmarket surveillance of a device that is a clinical trial (i.e., Study Type would be ''interventional''). However, because not all pediatric postmarket surveillances under section 522 of the FD&C Act are clinical trials, as defined in this part, many of the data elements listed in proposed § 11.28(a) or the definitions proposed in § 11.10(b) might not apply to them. Therefore, proposed § 11.28(b) specifies a more limited set of data elements required to register a pediatric postmarket surveillance of a device that is not a clinical trial; moreover, it also modifies the definitions of certain of the data elements that are defined in § 11.10(b).

As set forth in proposed § 11.28(b), to register a pediatric postmarket surveillance of a device that is not a clinical trial, the responsible party must provide the following data elements: (1) Brief Title; (2) Official Title; (3) Brief Summary; (4) Study Type; (5) Whether the Study is a Pediatric Postmarket Surveillance of a Device; (6) Primary Disease or Condition Being Studied, or the Focus of the Study; (7) Intervention Name(s); (8) Other Intervention Name(s); (9) Intervention Description; (10) Intervention Type; (11) Study Start Date; (12) Completion Date; (13) Name of the Sponsor; (14) Responsible Party, by Official Title; (15) Contact Information; (16) Unique Protocol Identification Number, if any; (17) Secondary IDs; (18) Human Subjects Protection Review Board Status; (19) Record Verification Date; and (20) Responsible Party Contact Information. Consistent with the elaboration of these data elements in section IV.B.4 of this preamble, for a pediatric postmarket surveillance of a device that is not a clinical trial the Study Type must be designated as ''observational'' and Whether the Study is a Pediatric Postmarket Surveillance of a Device must indicate ''yes.''

In general, the definitions of these data elements are consistent with the definitions of the named data elements in proposed § 11.10(b); however, we have modified them, where appropriate, to better match the characteristics of pediatric postmarket surveillances of a device that are not clinical trials. For example, Study Start Date, which is defined in proposed § 11.10(b)(16) for a clinical trial as ''the estimated date on which a clinical trial will be open to enrollment of human subjects, or the actual date on which the first human subject was enrolled, is defined in proposed § 11.28(b)(1)(xi) as the ''date on which FDA approves the postmarket surveillance plan, as specified in 21 CFR 822.19(a) (or any successor regulation).'' Similarly, the definition of Completion Date in section 402(j)(1)(A) of the PHS Act and proposed § 11.10(b)(17) generally would not apply to a pediatric postmarket surveillance of a device that is not a clinical trial; hence, in proposed § 11.28(b)(1)(xii), we propose to require submission of the Completion Date data element, which is defined as ''[t]he estimated date on which the final report summarizing the results of the pediatric postmarket surveillance of a device is expected to be submitted to FDA. Once the final report has been submitted, the actual date on which the final report is submitted to FDA.''

The Agency considers the proposed list of required data elements for a pediatric postmarket surveillance of a device that is not a clinical trial to be the most inclusive set of data elements that could be expected to apply to all pediatric postmarket surveillances of a device that are not clinical trials, regardless of the design of the surveillance. The proposed required information would allow users to access records of a pediatric postmarket surveillance of a device that is not a clinical trial by searching using a number of relevant criteria, retrieve basic descriptive information about the surveillance, and find a point-of-contact for additional surveillance information.

We do not propose the submission of those data elements listed under section 402(j)(2)(A)(ii) of the PHS Act that are not expected to apply to all pediatric postmarket surveillances of a device that are not clinical trials. For example, Study Phase is relevant only to clinical trials involving drugs. The specific elements of Study Design (e.g., Interventional Study Model, Allocation, Masking, Single Arm Controlled?) would not apply to most studies that are not interventional clinical studies (i.e., clinical trials). Eligibility Criteria, Age, and Gender might not be defined specifically for the study population in a pediatric postmarket surveillance of a device that is not a clinical trial. Enrollment would not be relevant to a pediatric postmarket surveillance of a device that takes the form of a literature review. We expect that some information about the study design and relevant study population would be included in the brief summary of the pediatric postmarket surveillance of a device.

In addition, for pediatric postmarket surveillances of a device that are not clinical trials, we would recommend that the responsible party submit any other registration information data elements that are consistent with the surveillance design and are capable of being accepted by ClinicalTrials.gov. For example, for a pediatric postmarket surveillance of a device that takes the form of a prospective observational study, information such as the location(s) of the surveillance, its eligibility criteria, recruitment status, and outcome measures would also be relevant and should be submitted. We believe the public would be best served if additional descriptive information about these pediatric postmarket surveillances of devices were included in the data bank, but, given the lack of experience to date, we cannot at this time specify which additional information would be relevant to a particular type of pediatric postmarket surveillance of a device that is not a clinical trial. We invite public comments on alternative approaches to specifying the registration requirements for a pediatric postmarket surveillances of a device that is not a clinical trial, including specific information that should be required to be submitted for such a surveillance and approaches to help ensure that important information is not missing from the record when such information might not be relevant to all pediatric postmarket surveillances of a device that are not clinical trials.

(c) Data elements required to create expanded access records. Proposed § 11.28(c) describes the clinical trial information that must be submitted to ClinicalTrials.gov to register an

applicable drug clinical trial that studies an unapproved drug or unlicensed biological product that is available via an Expanded Access Program under section 561 of the FD&C Act to those who do not qualify for enrollment in a clinical trial. Under our proposal in § 11.28(c), the following set of data elements would be required to be submitted to ClinicalTrials.gov at the time of registration of such clinical trials: (1) Brief Title; (2) Official Title; (3) Brief Summary; (4) Study Type (which would be ''expanded access program'' for this type of record); (5) Primary Disease or Condition; (6) Intervention Name(s); (7) Other Intervention Name(s); (8) Intervention Description; (9) Intervention Type (which would be a drug, including biological products, for applicable clinical trials that are required to submit such information under the proposed part, but could be a device if clinical trial information is submitted voluntarily for an expanded access program for a device); (10) Eligibility Criteria, (11) Gender, (12) Age Limits, (13) Expanded Access Status; (14) Name of the Sponsor; (15) Responsible Party, by Official Title; (16) Contact Information; (17) Unique Protocol Identification Number; (18) Secondary IDs; (19) Food and Drug Administration IND Number; (20) Record Verification Date; and (21) Responsible Party Contact Information.

We consider the proposed set of data elements to be the most inclusive set of data elements that would be relevant to all expanded access programs (other than individual patient access), regardless of design, and would be helpful to users of ClinicalTrials.gov who wish to determine whether they might be eligible to receive treatment through the expanded access program and obtain additional information about such access. The proposed list is, in most part, a subset of the data elements that would be required to register an applicable clinical trial of a drug. The descriptions of the data elements generally parallel the definitions of the data elements in proposed § 11.10(b) that are required to be submitted when registering a clinical trial under proposed § 11.28(a) but have been modified to refer to expanded access programs rather than clinical trials and to be limited to expanded access programs for drugs and biologics. One data element that is not defined in proposed § 11.10(b) and would be required to be submitted only for expanded access records is the Expanded Access Status data element. It is defined in proposed § 11.28(c)(2)(iv) to mean ''[t]he status of availability of the investigational drug through the expanded access program.'' When submitting this data element, responsible parties would be required to select from the following limited set of options for describing the current status of availability of the investigational drug through the expanded access program: ''Available'' (expanded access is currently available), ''No longer available'' (expanded access was available previously but is not currently available and is not expected to be available in the future), ''Temporarily not available'' (expanded access was previously available, is not currently available, but is expected to be available in the future), and ''Approved for marketing'' (expanded access was available previously but is not currently available because the drug or device has been approved, licensed, or cleared by the Food and Drug Administration). No ''other'' option is proposed. These proposed options are consistent with those used in ClinicalTrials.gov prior to enactment of FDAAA [Ref. 2] and would provide patients and other users of ClinicalTrials.gov with what we believe is more valuable information about expanded access status than a simple ''yes'' or ''no'' indication. We invite comment on whether this list of options is sufficient to describe the status of an expanded access program for which information would be submitted to ClinicalTrials.gov under this proposed rule.

We note that, notwithstanding the foregoing, if some form of expanded access were offered to a medical device that is studied in an applicable clinical trial, such information could be submitted voluntarily under section 402(j)(4)(A) of the PHS Act to create an expanded access record for the device. Accordingly, even though the expanded access data elements are intended for expanded access programs for drugs, a responsible party who voluntarily submits information about an expanded access program for a device would be able to submit the IDE number that CDRH assigns to the expanded access program. We would require that a responsible party who voluntarily creates an expanded access record for a device expanded access program submit all of the data elements that are required for a drug expanded access program. In other words, an expanded access record may be created voluntarily, but it must be complete. In addition, we would require that an expanded access record that is submitted voluntarily must be updated following the same requirements that would apply to an expanded access record that is required to be submitted under this part. *See* proposed 11.64(b)(1(iv).

We propose to require the submission of information to create an Expanded Access record using the statutory authority in section 402(j)(2)(A)(iii) of the PHS Act, which allows the Secretary by regulation to modify the requirements for clinical trial registration information if the Secretary provides a rationale why such a modification ''improves and does not reduce such clinical trial information.'' Information about the availability of expanded access is a data element that a responsible party is required to submit under section 402(j)(2)(A)(ii)(II) of the PHS Act and thus meets the definition of ''clinical trial information'' as that term is used in section 402(j)(1)(A)(iv) of the PHS Act. We believe the additional data elements describing expanded access would improve and not reduce clinical trial information by providing users with more complete and consistent information about expanded access programs for drugs studied in applicable clinical trials than would be available pursuant to section 402(j)(A)(ii)(II)(gg) of the PHS Act alone. We further conclude that we have authority to require that the clinical trial information required under proposed § 11.28(c) be submitted by creating a separate expanded access record in ClinicalTrials.gov under section 402(j)(2)(B)(iv) of the PHS Act, as the expanded access record will ensure that the public may more easily use the data bank to determine whether there is expanded access to a drug and to compare different expanded access programs. In addition, this approach is consistent with the practice followed prior to enactment of FDAAA when those registering trials in compliance with FDAMA submitted expanded access information in the form of expanded access records at ClinicalTrials.gov. As discussed above in section IV.A.5 of this preamble, in the rare instance in which an expanded access program for a drug is controlled and meets all of the elements of an applicable drug clinical trial, the expanded access program must be registered as an applicable drug clinical trial.

We considered alternative approaches, such as requiring the responsible party to submit the name, phone number, and email address of a point-of-contact or Web site for information about the expanded access program for each clinical trial of a drug that has such a program. However, we believe that such an approach would not ensure that complete information is

available in a consistent form and would not allow users of ClinicalTrials.gov to as quickly and easily review eligibility criteria and the disease or condition for which expanded access is available. In addition, by including such information as part of clinical trial registration information, we can better ensure that the information is kept up-to-date because it would be subject to the updating requirements described in proposed § 11.64. We also believe that our proposal could reduce the burden a responsible party faces when providing information about expanded access. An alternative we considered was to require responsible parties to enter the additional data elements describing expanded access with every applicable clinical trial of a drug or biological product for which expanded access is available. Under our proposal, in situations in which multiple applicable clinical trials study the same drug that is available via the expanded access program, the expanded access record would be submitted only once, and thereafter, any responsible party could link the expanded access record to his or her clinical trial record(s) using the NCT number assigned to the expanded access record. As explained further in section IV.D.3 in this preamble, only that responsible party who registered the initial clinical trial that included the expanded access record would be responsible for updating the expanded access program information in the expanded access record.

As explained in section IV.B.4, in the discussion of the Availability of Expanded Access data element, the expanded access record generated in ClinicalTrials.gov pursuant to the submission of the data elements at proposed § 11.28(c) would be assigned its own NCT number and would be searchable and retrievable independent of the record(s) for the clinical trial(s) that study(ies) the drug or biological product to which expanded access is offered. To establish the link between the expanded access record and the clinical trial record(s), the responsible party(ies) for any applicable clinical trials of the drug available via expanded access would be required to include the NCT number that is assigned to the expanded access record as part of the registration information submitted for that clinical trial. The expanded access record could be linked in this fashion to several applicable clinical trials that study the drug or biological product that is available via the expanded access program.

We seek comment on the proposed approach.

5. By when will NIH post clinical trial information submitted under § 11.28?—§ 11.35.

Proposed § 11.35 describes the timelines by which NIH will post publicly on ClinicalTrials.gov the clinical trial information that is required to be submitted for registration of applicable drug clinical trials and applicable device clinical trials, respectively. Proposed § 11.35 takes into account the timelines described for posting registration information in section 402(j)(2)(D) of the PHS Act.

The timelines in proposed § 11.35 apply only to clinical trials that are required to register with ClinicalTrials.gov under 402(j)(2)(C) of the PHS Act. If a clinical trial is registered with ClinicalTrials.gov and appears to be a voluntary submission according to the approach specified in proposed § 11.22(b), we will post the registration information as soon as practicable after it has been submitted and reviewed as part of our quality review procedures.

(a) Applicable drug clinical trials. For applicable drug clinical trials, section 402(j)(2)(D)(i) of the PHS Act requires NIH to publicly post registration information not later than 30 days after it is submitted in accordance with section 402(j) of the PHS Act. Proposed § 11.35(a) implements this provision, stating that NIH will post publicly the registration information ''not later than 30 calendar days after the responsible party has submitted such information in accordance with § 11.24 of this part.''

(b) Applicable device clinical trials of devices that previously were approved or cleared. For applicable device clinical trials of devices that previously were approved or cleared by FDA for any indication, section 402(j)(2)(D)(ii)(II) of the PHS Act requires that registration information be posted ''not later than 30 days after'' results information is required to be posted. The Agency interprets section 402(j)(2)(D)(ii)(II) of the PHS Act as providing a deadline by which such registration information must be posted. In other words, the Agency considers the requirement to post registration information ''not later than 30 days after [results information] is required to be posted'' to be the last possible date on which it may post registration information.

The Agency believes that for applicable device clinical trials of devices that previously were approved or cleared it is permissible and appropriate to post registration information prior to the deadline. Posting this information prior to the deadline would be consistent with the objectives of expanding the registry and results data bank by rulemaking, facilitating enrollment in clinical trials and providing a mechanism to track subsequent progress of clinical trials. (See sections 402(j)(2)(A)(i) and (3)(D)(i) of the PHS Act.) Conversely, waiting to post registration information for applicable device clinical trials of devices that previously were approved or cleared until after results information is required to be posted would delay access to information about such clinical trials and would eliminate the possibility for the data bank to be used to facilitate enrollment in such trials and to allow the public to track such trials while they are ongoing.

The Agency proposes in § 11.35(b)(1) to post registration information for an applicable device clinical trial of a device that previously was approved or cleared ''not later than 30 calendar days after clinical trial results information is required to be posted in accordance with § 11.52 of this part.'' However, in light of the objectives of the data bank discussed above we intend, in practice, to post registration information for such applicable device clinical trials as soon as practicable after submission, but not later than 30 calendar days after clinical trial results information is required to be posted.

(c) Applicable device clinical trials of devices that have not been approved or cleared previously. Section 402(j)(2)(D)(ii)(I) of the PHS Act provides that for applicable device clinical trials of devices that have not previously been approved or cleared (i.e., unapproved or uncleared devices), registration information must be posted publicly not earlier than the date of approval or clearance of the device and not later than 30 days after such date. Proposed § 11.35(b)(2) reflects this statutory provision. In order to help us meet the posting deadline and identify the set of applicable device trials for which registration information needs to be posted after approval or clearance of a device, we have included a requirement in proposed § 11.64(b)(2) for the responsible party to update the U.S. FDA Approval, Licensure, or Clearance Status data element not later than 15 calendar days after a change in status has occurred. The responsible party would be required to update that data element for all applicable clinical trials that study the device that was approved or cleared.

(d) Exception to posted information. Section 402(j)(2)(A)(ii)(IV) of the PHS Act specifies that the Secretary ''may make publicly available *as necessary*'' (emphasis added) administrative data that are submitted as part of clinical

trial registration information. We interpret this provision as permitting the Secretary not to post certain administrative data in the data bank if the data are not considered necessary for understanding the clinical trial or for recruitment. As explained more fully in section IV.B.4(a) of this preamble, we do not believe it is necessary to make public the following administrative data and currently do not intend to post them publicly in ClinicalTrials.gov for any applicable clinical trials: (1) Food and Drug Administration IND or IDE Number and (2) Responsible Party Contact Information other than the name of the responsible party if the responsible party is an individual (as opposed to an entity). Note that Responsible Party, by Official Title, which is proposed in § 11.28(a)(3)(ii), is not considered an element of administrative data and will be publicly posted in the data bank as required by section 402(j)(2)(A)(ii)(III)(bb) of the PHS Act.

C. Results Submission—Subpart C

Proposed subpart C establishes requirements and procedures related to the submission of results information. In addressing what constitutes results information, proposed subpart C does not specify what results information must be collected during an applicable clinical trial or other clinical trial, but which elements of the collected data must be submitted and in what required format. Proposed Subpart C also specifies when NIH will post results information in ClinicalTrials.gov. Finally, proposed subpart C specifies the procedures that may be used to request a waiver of any applicable requirements for results submission.

1. Who must submit results information?—§ 11.40

Proposed § 11.40 requires that the responsible party for an applicable clinical trial specified in proposed § 11.42 submit results information for that clinical trial. This approach is consistent with section 401(j)(3)(E)(i) of the PHS Act.

2. For which applicable clinical trials must results information be submitted?—§ 11.42

Proposed § 11.42 identifies the applicable clinical trials for which results information must be submitted to ClinicalTrials.gov, according to this proposed rule unless the requirement is waived under proposed § 11.54. Pursuant to section 402(j)(3)(D)(ii)(I)of the PHS Act, we propose to require the submission of results information for specified: (1) Applicable clinical trials of drugs that are approved under section 505 of the FD&C Act or licensed under section 351 of the PHS Act; and (2) applicable clinical trials for devices that are cleared under section 510(k) of the FD&C Act or approved under section 515 or 520(m) of the FD&C Act. For reasons described in section III.C.5 of this preamble, we also propose to require the submission of results information for specified applicable clinical trials of drugs or devices that are not approved, licensed, or cleared for any indication (regardless of whether the sponsor seeks approval, licensure, or clearance). This proposal is consistent with the requirement in section 402(j)(3)(D)(ii)(II) of the PHS Act that the Secretary establish through regulation whether or not results information must be submitted for applicable clinical trials of drugs and devices that have not been approved, licensed, or cleared by FDA, whether or not approval, licensure, or clearance is sought.

In order to maintain consistency with the registration requirements proposed in this rule, the proposed requirements for results submission would apply to those applicable clinical trials that are required to be registered with ClinicalTrials.gov under the requirements of proposed § 11.22 and that meet the criteria under proposed § 11.42, unless a waiver were granted in accordance with proposed § 11.54. We note as described in section III.D of this preamble, responsible parties would not be required to submit results information under this proposed subpart if the completion date of the applicable clinical trial is prior to the effective date of this rule, except if any of the following situations applies: (1) The completion date is prior to the effective date of the rule, but results information is neither due under proposed § 11.44 nor submitted until on or after the effective date of the rule; or (2) the completion date is prior to the effective date of the rule, but secondary outcome measures are neither due under proposed § 11.44 nor submitted until on or after the effective date of the rule.

3. When must results information be submitted for applicable clinical trials subject to § 11.42–§ 11.44?

Proposed § 11.44 specifies the deadlines for submitting results information for applicable clinical trials. Subsection (a) specifies the standard submission deadlines for applicable clinical trials that are clinical trials. Subsections (b) and (c) specify procedures for delaying the standard submission deadlines when seeking initial approval or approval of a new use of a drug or device studied in an applicable clinical trial. Subsection (d) describes procedures for requesting a good-cause extension of the submission deadline. Subsection (e) establishes the timeline for submitting results of a pediatric postmarket surveillance of a device that is not a clinical trial.

(a) Standard submission deadlines. Proposed § 11.44(a) prescribes the standard deadlines for submitting results information for applicable clinical trials that are clinical trials subject to proposed § 11.42. This proposed deadline would apply to all applicable clinical trials for which the responsible party does not submit a certification to delay results submission, as permitted under proposed § 11.44(b) or (c), or for which the Director has not granted a good-cause extension of the results submission deadline pursuant to proposed § 11.44(e).

(1) In general. Proposed § 11.44(a)(1) specifies that, in general, the deadline for submitting results information for applicable clinical trial would be 1 year after the completion date of the clinical trial. Sections 402(j)(3)(E)(i)(I) and (II) of the PHS Act specify that results information is to be submitted not later than 1 year after the ''earlier of'' the estimated completion date or the actual completion date. Under proposed § 11.64(b)(1), however, we would require responsible parties to update the completion date not later than 30 calendar days after a change has occurred or after the clinical trial has reached its completion date. Therefore, the estimated completion date would be updated to reflect the actual completion date not later than 30 calendar days after the applicable clinical trial has reached its completion date and results would be due not later than 1 year after the actual completion date of the applicable clinical trial.

The 1 year deadline would apply to applicable clinical trials of drugs and devices, whether or not approved, licensed, or cleared, except as described in (2) and (3) below. Section 402(j)(3)(D)(iv)(III) of the PHS Act requires the Secretary to determine by regulation ''the date by which . . . clinical trial [results] information [for applicable clinical trials of unapproved, unlicensed, or uncleared products] shall be required to be submitted . . .'' As discussed further in section III.C.5 of this preamble, our proposal would apply the same general deadline for results submission to both applicable clinical trials of approved, licensed, or cleared products and applicable clinical trials of unapproved, unlicensed, or uncleared products in order to simplify

results submission procedures and provide consistency between the deadlines for applicable clinical trials, regardless of the approval status of the products under study. Applicable clinical trials of unapproved, unlicensed, or uncleared drugs and devices (and of approved, cleared, and licensed drugs and devices that are studied for a new use) may, however, qualify for delayed submission of results, as described in section IV.C.3(b) below.

Section 402(j)(3)(D)(iv)(I) of the PHS Act requires the Secretary to determine whether to increase the general deadline for results submission from 1 year to ''a period not to exceed 18 months'' after the earlier of the estimated or actual completion date. We solicited comment on this topic as part of the public meeting held in April 2009 but received few comments on this issue. Comments that supported a longer deadline cited concerns about applicable clinical trials for which data collection for secondary outcome measures and adverse events would continue beyond the completion date of the clinical trial. During the time that we have been operating the data bank, we have seen only few clinical trials in which this situation occurs. Rather than extending the general results submission deadline to as long as 18 months in order to accommodate what we believe would be a small number of such trials, we propose instead alternative methods for addressing such trials in proposed § 11.44(a)(2).

(2) Submitting results information following initial product approval, licensure, or clearance. Proposed § 11.44(a)(2) specifies the timeline for submitting results information for any applicable clinical trial of an FDA-regulated drug (including biological product) or device that is unapproved, unlicensed, or uncleared as of its completion date. It would require that results information as specified in proposed § 11.48(a) must be submitted for such trials by the earlier of 1 year after the completion date, or 30 calendar days after FDA approves, licenses, or clears the drug or device for any indication studied in the applicable clinical trial. This proposal is consistent with section 402(j)(3)(E)(iv) of the PHS Act.

(b) Delayed results submission with certification. Proposed §§ 11.44(b) and (c) establish procedures whereby responsible parties may delay submission of results information for a particular applicable clinical trial beyond the general deadline specified in proposed § 11.44(a)(1) (i.e., 1 year after the completion date).

(1) Seeking approval, licensure, or clearance of a new use for the drug or device. Consistent with section 402(j)(3)(E) (iii) and (v) of the PHS Act, we propose in § 11.44(b) to allow a delay in the submission of results information if the responsible party certifies that an applicable clinical trial meets the following criteria: (1) The drug (including biological product) or device studied in the applicable clinical trial previously has been approved, licensed, or cleared by FDA; (2) the sponsor of the applicable clinical trial is the manufacturer of the product; and (3) the manufacturer has filed, or will file within 1 year, an application seeking approval, licensure, or clearance of the use being studied in the applicable clinical trial (a use that is not included in the labeling of the approved, licensed, or cleared product). As proposed, this certification would be required to be submitted to ClinicalTrials.gov before the general results submission deadline specified in proposed § 11.44(a)(1), i.e., 1 year or less after the completion date. The record for the clinical trial would indicate that results submission has been delayed, but would not specify the particular reason for the delay. (See section IV.C.3 of this preamble).

In accordance with section 402(j)(3)(E)(v) of the PHS Act, once a certification has been submitted, proposed § 11.44(b)(2) would permit a delay in the submission of results information of up to two years after the date on which the certification is submitted, unless one of the following events occurs: (1) FDA approves, licenses, or clears the drug or device studied in the applicable clinical trial for the use studied in the clinical trial; (2) FDA issues a letter that ends the regulatory review cycle for the application or submission (e.g., a complete response letter, a not substantially equivalent letter, or a not approvable letter) but does not approve, license, or clear the product studied in applicable clinical trial for the use studied in the clinical trial; or (3) the manufacturer, which is also the sponsor of the applicable clinical trial, withdraws the application or premarket notification and does not resubmit it within 210 calendar days. In the event that any one of these ''triggering events'' occurs, the responsible party would be required to submit results information for the applicable clinical trial for which a certification had been submitted under proposed § 11.44(b)(1) not later than 30 calendar days after the earliest of the triggering events occurred, consistent with section 402(j)(3)(E)(v)(I).

If the responsible party for an applicable trial for which a new-use certification has been submitted is not the sponsor/manufacturer of the drug (including biological product) or device studied in the clinical trial, the sponsor/manufacturer may need to notify the responsible party of the occurrence of these triggering events in order to help ensure that the responsible party is aware that results submission is required. As discussed in section IV.A.2 of this preamble, the sponsor may designate a principal investigator as responsible party under proposed § 11.4 only if, among other things, the principal investigator ''has the ability to meet all of the requirements for submitting and updating clinical trial information as specified in this part.'' Accordingly, a responsible party who is not the sponsor will only be able to comply with the results submission requirements subsequent to a certification under sections 402(j)(3)(E)(iii) and (v) of the PHS Act, if notified by the sponsor when one of these triggering events occurs. In a situation in which a sponsor is not willing or able to provide the principal investigator with this information, the conditions for designation under proposed § 11.4 cannot be met.

In addition, consistent with section 402(j)(3)(E)(v)(II) of the PHS Act, if a manufacturer makes a certification to delay submission of results information because the manufacturer is seeking or will seek within 1 year approval of a new use for a drug or device, the responsible party shall make such a certification ''with respect to each applicable clinical trial that is required to be submitted in an application or report for licensure, approval, or clearance'' of the use studied in the clinical trial. Proposed § 11.44(b)(3) implements this provision. For purposes of this requirement, we interpret ''manufacturer'' to mean ''manufacturer/sponsor who is the responsible party'' because section 402(j)(3)(E)(v) of PHS Act applies only when the manufacturer is the sponsor of the applicable clinical trial, and under section 402(j)(3)(E)(iii) of the PHS Act, it is the responsible party who must submit the certification for delayed submission of clinical trial results information.

(2) Seeking initial approval, licensure, or clearance for the drug or device. Proposed requirements for delayed submission of results information with certification when seeking initial approval, licensure, or clearance of a drug or device are described in proposed § 11.44(c). As discussed above in section III.C.5 of this preamble, this proposal reflects our efforts to adhere to

the statutory requirement that, when proposing to require the submission of results information for trials of unapproved, unlicensed, or uncleared products, we take into account the certification process in section 402(j)(3)(E)(iii) of the PHS Act ''when approval, licensure, or clearance is sought,'' and that we determine ''whether there should be a delay of submission when approval, licensure or clearance will not be sought.'' See section 402(j)(3)(D)(iv)(III) of the PHS Act.

We propose in § 11.44(c) that submission of results information may be delayed if the responsible party certifies that the following criteria apply: (1) The drug (including biological product) or device studied in the applicable clinical trial previously was not approved, licensed, or cleared by FDA for any use before the completion date of the clinical trial; and (2) the sponsor of the applicable clinical trial intends to continue with product development and is seeking, or may at a future date seek, FDA approval, licensure, or clearance of the product under study. As proposed, this certification would be required to be submitted to ClinicalTrials.gov before the general results submission deadline specified in proposed § 11.44(a)(1), i.e., 1 year or less after the completion date.

The intent of this certification is to permit delayed results submission only if the sponsor of the applicable clinical trial intends to continue with product development of the drug (including biological product) or device under study, such that there is an expectation that marketing approval or clearance will be sought. We do not believe that results submission should be delayed for applicable clinical trials of products that the sponsor has no intention of marketing or for which product development has been abandoned.

Hence, our proposal would permit delayed submission of results information only if the responsible party certifies that the sponsor of the applicable clinical trial is continuing to study the product with an expectation of seeking future marketing approval, licensure, or clearance. We recognize that it may be difficult for the sponsor of the applicable clinical trial to know early on in the product development process whether it will seek approval, licensure, or clearance for a product studied in an applicable clinical trial, but we would, in general, view further development of a product through subsequent clinical trials as an indication that the product development process is continuing and may lead to seeking initial approval, licensure, or clearance. When the responsible party is not the sponsor of the applicable clinical trial and wishes to delay results submission, we would expect the responsible party to obtain such information from the sponsor before submitting a certification, in order to help ensure the truthfulness of the certification.

Under our proposal, submission of a certification would delay the deadline for submitting results for the applicable clinical trial by up to two years from the date on which the certification is submitted to ClinicalTrials.gov. However, in the event that FDA approves, licenses, or clears the drug or device studied in the applicable clinical trial for any indication that is studied in the clinical trial within this two-year period, the responsible party would be required to submit results information not later than 30 calendar days after such approval, licensure, or clearance. Similarly, if the sponsor withdraws the application or premarket notification without resubmission for 210 calendar days during this two-year period, the responsible party would be required to submit results information not later than 30 calendar days after such date. The agency believes that this latter situation represents a significant enough interruption to product development to trigger the submission of results information.

We note that, unlike delayed results submission with certification that the sponsor of the applicable clinical trial is seeking approval, licensure, or clearance of a new use, we do not propose to require the submission of results 30 days after FDA issues a letter not approving, licensing, or clearing the product under study because we do not think that the issuance of such a letter necessarily indicates abandonment of product development. For the reasons set forth above in ''(1) ''Seeking approval, licensure, or clearance of a new use for the drug or device[,]'' a responsible party who is not the sponsor (i.e., a responsible party who is a principal investigator) will be able to comply with the results submission requirements subsequent to a certification under sections 402(j)(3)(E)(iii) and (iv) of the PHS Act, only if notified by the sponsor when one of the triggering event occurs. In a situation where the sponsor is not willing or able to provide the principal investigator with this information, then the conditions for designation under proposed § 11.4 cannot be met, and/or the responsible party will not be eligible to delay results submission.

(3) Two-Year Limitation of Delay. With regard to the maximum delay pursuant to a certification submitted under section 402(j)(3)(E)(iii) of the PHS Act, the agency expects that in most situations a delay of an additional two years beyond the date the certification is submitted (i.e., up to three years after the completion date of the clinical trial, if the certification is submitted 1 year after the completion date) provides sufficient time for the sponsor of the applicable clinical trial to protect its competitive advantage, a concern expressed in public comments. Within this time frame, a sponsor would likely make a decision about whether to halt product development, initiate another clinical trial (e.g., a phase 3 clinical trial to follow a phase 2 clinical trial), or submit a marketing application or premarket notification to FDA. Subsequent trials would most likely be required to register at ClinicalTrials.gov and, for applicable drug clinical trials, the clinical trial registration information for those subsequent trials would be posted publicly in the data bank, thereby providing some information to competitors about the outcome of previous trials and the objectives of future trials. As discussed further in Section III.C.5 of this preamble, we believe any competitive disadvantage caused by the disclosure of summary results information three years or more after the completion date of the trial would be limited and outweighed by the public health benefits of making such information publicly available. We invite public comment on this approach.

For applicable clinical trials that meet the criteria for delayed results submission with certification—whether seeking initial approval, licensure, or clearance or seeking approval, licensure, or clearance of a new use—measuring the maximum delay of two years from the date on which the certification is submitted may result in responsible parties submitting certifications as close as possible to the general results submission deadline under proposed § 11.44(a)(1) (i.e., 1 year after the completion date). Submitting a certification just before the general results submission deadline would postpone results submission until as late as three years after the completion date of the clinical trial, while submitting a certification on the completion date of the clinical trial would extend the results submission deadline only as long as two years beyond the completion date. We believe that users of ClinicalTrials.gov would benefit from knowing as early as possible that results submission for an applicable clinical trial of interest

would be delayed. Until a certification is submitted, users may expect that results will be submitted not later than 1 year after the completion date. If a certification were submitted soon after the completion date, the clinical trial record could be updated at that time to indicate that results submission would be delayed, and users could adjust their expectations accordingly.

The statute does not appear to permit us to change the timeline for results submission when a responsible party submits a certification when seeking approval of a new use for the drug or device under section 402(j)(3)(E)(v) of the PHS Act and proposed § 11.44(b). For delayed submission of results when seeking initial approval, licensure, or clearance, however, the statute offers greater flexibility in establishing the timeline: Section 402(j)(3)(D)(iv)(III) of the PHS Act expressly authorizes the Secretary to establish the date by which clinical trial information for applicable clinical trials of unapproved products must be submitted to ClinicalTrials.gov. We considered establishing the maximum available delay with certification when seeking initial approval, licensure, or clearance to be three years from the completion date of the applicable clinical trial, regardless of when during the one-year period following the completion date the certification is submitted. Such a provision would accomplish the same objective as the statutory provision for delayed submission when seeking approval, licensure, or clearance of a new use by allowing responsible parties to delay results submission by as long as three years beyond the completion date of a clinical trial, without creating a disincentive to submit the certification early. We did not include this provision in this proposed rule so that we could keep the same maximum delay for results submission whether seeking initial approval, licensure, or clearance or seeking approval, licensure, or clearance of a new use. We invite public comments on the advantages and disadvantages of establishing maximum different timelines for results submission under the two delayed-results-with- certification provisions. We also invite public comment on alternative approaches we could take to encourage early submission of certifications in a way that is consistent with the statutory requirement for seeking approval, licensure, or clearance of a new use, without causing a responsible party to have to submit results information earlier than the latest deadline they could have under the statute.

We note that the maximum delay of two years pursuant to a certification submitted under section 402(j)(3)(E)(iii) of the PHS Act applies to all primary outcomes and any secondary outcomes for which the final subject was examined or received an intervention for the purposes of final data collection by the completion date. In the event that data collection for any secondary outcome measure(s) will not be completed as of the completion date, clinical trial results information for such secondary outcome measure(s) shall be due under proposed § 11.44(b) and (c) by the later of: (1) ''1 year after the date on which the final subject is examined or receives an intervention for the purposes of final collection of data for such secondary outcome measure(s), whether the applicable clinical trial was concluded according to the pre-specified protocol or was terminated;'' or (2) ''the date on which the primary outcomes are due pursuant to . . . [proposed §§ 11.44(b) or (c).''

(c) Explanation of ''initial approval,'' ''initial clearance,'' and approval or clearance of a ''new use.'' For purposes of proposed §§ 11.44(b) and (c), we interpret the term ''drug'' in sections 402(j)(3)(E)(iv) and 402(j)(3)(E)(v) of the PHS Act to mean ''drug product'' or ''biological product,'' referring to a finished product that is approved or licensed for marketing, and not to the active ingredient or active moiety in such a product. We conclude that this is the most appropriate interpretation of the statutory term and that this interpretation is consistent with the statutory intent to draw a distinction between applicable drug clinical trials that are ''completed before the drug is initially approved'' (See section 402(j)(3)(E)(iv) of the PHS Act) and those pertaining to uses that are ''not included in the labeling of the approved drug'' (See section 402(j)(3)(E)(v) of the PHS Act). Accordingly, ''initial approval'' pertains to the approval or licensure of an original NDA, abbreviated new drug application (ANDA) or BLA, and ''new use'' pertains to the approval or licensure of a supplemental NDA, ANDA, or BLA for an additional indication for that particular drug product or biological product. Similarly, we interpret ''initial approval'' of a device under sections 515 or 520(m) of the FD&C Act to pertain to the approval of an original premarket approval application (PMA) or humanitarian device exemption application (HDE) and ''new use'' to pertain to the approval of a supplemental PMA for an additional indication for that particular device.

In addition, for purposes of proposed § 11.44(c), the first 510(k) cleared for a particular device type would be considered ''initial clearance'' of the device. For example, when a device is reclassified from Class III to Class II, then the first 510(k) that is cleared as having demonstrated substantial equivalence to the reclassified device would be considered initial clearance of the device. Consequently, for purposes of proposed § 11.44(b), all other 510(k)s cleared for a device type other than the first one, would be considered clearance of a new use.

We recognize that in some cases a responsible party may not know whether a particular applicable clinical trial will be used to support an original NDA, ANDA, BLA, PMA, or HDE as opposed to a supplemental NDA, ANDA, BLA, PMA, or HDE, or whether a clinical trial will be used to support a 510(k) seeking initial clearance of a device as opposed to a 510(k) seeking clearance of a new use. Responsible parties should use their best judgment based on information available at the time of certification in order to determine which type of certification is appropriate. We solicit comments on whether these are appropriate interpretations and distinctions for purposes of proposed §§ 11.44(b) and (c).

(d) Submitting partial results. Proposed § 11.44(d) specifies procedures for submitting results when required results information, as specified in proposed § 11.48, has not been collected for all secondary outcome measures by the date on which results information is due. Under the definition of completion date in proposed § 11.10(a), whether or not a clinical trial is completed is determined by the status of data collection for solely the primary outcome measure(s). An applicable clinical trial may therefore still be collecting data for the secondary outcome measure(s) after it has reached its completion date.

In this situation, the responsible party would be required to submit results information for the primary outcome measure(s) by the required due date specified in proposed § 11.44(a), (b), or (c), as applicable. Under proposed § 11.44(d)(i). If a certification to delay results submission has not been submitted under proposed § 11.44(b) or (c), results for each remaining secondary outcome measure would be due not later than 1 year after the date on which the final subject is examined or receives an intervention for the purposes of final collection of data for that secondary outcome measure, whether the clinical trial was concluded according to the

pre-specified protocol or was terminated. If the responsible party has submitted a certification to delay results submission under proposed § 11.44(b) or (c), results of the secondary outcome measures could be submitted by the later of the date specified proposed § 11.44(d)(i) or the date on which the primary outcome measures would be required to be submitted. We note that in either situation, if data collection for a secondary outcome measure is completed as of the completion date, results information for that secondary outcome measure would be required to be submitted on the same date as the primary outcome measure(s).

With respect to adverse event information (which is considered to be part of clinical trial results information described under proposed § 11.48), a responsible party would be required to submit information summarizing serious and frequent adverse events recorded to-date each time results information for a secondary outcome is submitted, until all the adverse event information required by this part has been submitted. We believe that this approach provides a better mechanism for handling submission of adverse event information than extending the general results submission deadline for all applicable clinical trials up to 18 months after the completion date. It would ensure that key results information for primary outcome measures is submitted to ClinicalTrials.gov within 1 year of the completion date, while allowing subsequent data collection to continue as planned.

We recognize that this approach may not be suitable for all applicable clinical trials for which data collection for secondary outcome measures extends more than 1 year beyond the completion date. In some circumstances, submitting results information for the primary outcomes not later than 1 year after the completion date might compromise the scientific integrity of the applicable clinical trial, for example, by requiring the applicable clinical trial to be unblinded before all data for the secondary outcome measures are collected. In those circumstances, we would expect a responsible party to seek a good-cause extension of the results submission deadline in proposed § 11.44(a)(1), following the procedures specified in proposed § 11.44(e).

We clarify in proposed § 11.44(d)(2) the way to handle results submission if results related to the primary outcome(s) were submitted prior to the effective date of the rule, but results data for the secondary outcome(s) are required to be submitted after the effective date. In such cases the responsible party would be required to provide results information for all primary and secondary outcome(s) as specified in § 11.48 of this proposed rule. We believe that consistent data must be provided for all outcome measures in a single clinical trial and therefore would apply the requirements of proposed § 11.48 to the clinical trial as a whole.

(e) Requesting a good-cause extension of the results submission deadline. Proposed § 11.44(e) outlines procedures for requesting good-cause extensions of the deadline for submitting results information. Section 402(j)(3)(E)(vi) of the PHS Act authorizes the Director to ''provide an extension of the deadline for submission of clinical trial [results] information . . . if the responsible party for the trial submits to the Director a written request that demonstrates good cause for the extension and provides an estimate of the date on which the information will be submitted.'' We interpret this authority as allowing the Director to grant an extension of any results submission deadline that may be in effect for a given applicable clinical trial, e.g., the general 12-month results submission deadline; a delayed submission deadline established by the submission of an appropriate certification under section 402(j)(3)(E)(iii) of the PHS Act; or an extended deadline established by a previously-granted good-cause extension. As for the latter, section 402(j)(3)(E)(vi) of the PHS Act explicitly allows the Director to ''grant more than one [good-cause] extension for a clinical trial.'' For a pediatric postmarket surveillance of a device that is not a clinical trial, the agency also proposes to allow more than one good-cause extension for such a surveillance. Good-cause extensions apply only in the context of applicable clinical trials subject to the results submission requirements of section 402(j)(3) of the PHS Act because the good-cause extension provision specifically refers to results submission under 402(j)(3)(E)(i) of the PHS Act. Accordingly, good-cause extensions do not apply to clinical trial results that are submitted under section 402(j)(4)(A) of the PHS Act, i.e., voluntarily submitted trials (see proposed rule § 11.60(a)(2)(i)) and triggered trials (see § 11.60(a)(2)(iii) of this proposed rule).

Section 402(j)(3)(E)(vi) of the PHS Act does not define ''good cause.'' Similarly, this proposed rule does not contain specific proposals for determining which situations will and will not be considered good cause for an extension. Instead we intend to develop guidance (which would be subject to public comment) as the agency gains more experience with extension requests and communicate with the regulated community via other channels, including the ClinicalTrials.gov Web site. In order to assist responsible parties who are considering submitting a good-cause extension request, we intend to prepare, update periodically, and post on ClinicalTrials.gov a list of reasons that the agency generally will consider to be ''good cause'' and not ''good cause'' for granting an extension under section 402(j)(3)(E)(vi) of the PHS Act and proposed § 11.44(e). The list would not necessarily be an exhaustive list of reasons for which applicable clinical trials have or have not been granted an extension, but would contain those reasons that we believe would serve as useful examples for responsible parties of other applicable clinical trials. All good-cause extension requests would be considered on a case-by-case basis, and any generalizable conclusions that can be drawn from the granting or denial of a request may be added to the list of good causes and not-good causes for granting extensions.

In general, we believe that there are likely to be only a few situations that would constitute good cause under section 402(j)(3)(E)(vi) of the PHS Act and proposed § 11.44(e). To-date, we have identified only two situations that we believe would constitute good cause, as follows:

(1) The need to preserve the scientific integrity of an applicable clinical trial for which data collection is ongoing. This would include situations in which the submission of results information for the primary outcome(s) of an applicable clinical trial would impair or otherwise bias the ongoing collection, analysis, and/or interpretation of data for secondary outcome(s). We recognize that permitting an extension in such circumstances could provide an incentive for someone wishing to delay results submission to add to their applicable clinical trial a secondary outcome measure with a very long data collection time frame, even if the outcome measure has limited significance or relevance to the clinical trial. Because protocols are typically revised by outside entities (e.g., human subjects protection review boards), one way to protect against such behavior is to ensure that the secondary outcome measures are pre-specified in the protocol or statistical analysis plan. Accordingly, in order to demonstrate good cause, we believe that an extension should be granted only in those situations in which it can be demonstrated that the data collection for the secondary outcome(s) of interest

extends more than 1 year beyond the completion date, that the secondary outcome(s) is pre-specified in the protocol or statistical analysis plan (consistent with the definition of secondary outcomes in this proposed part), and the planned analysis of the outcome measure is also described in the protocol or statistical analysis plan. The responsible party could provide this information either by voluntarily submitting copies of the protocol or statistical analysis plan with the good-cause extension request or describing them in the extension request itself.

(2) Emergencies that prevent timely submission of clinical trial results information. This would include situations in which one or more data collection sites are affected by natural disasters or other catastrophes outside the responsible party's or sponsor's control. In such cases we generally would expect to grant the responsible party an initial extension of up to 6 months, after which time additional extensions could be granted, as necessary. We generally would not consider events that might reasonably have been avoided or anticipated through standard contingency planning, e.g., transition planning for key staff members who leave an organization, to constitute good cause for an extension under section 402(j)(3)(E)(vi) of the PHS Act or proposed § 11.44(e).

The following non-exhaustive list enumerates scenarios that we generally do not believe ordinarily would constitute good cause:

- Pending publication. The ICMJE has asserted that results submission to ClinicalTrials.gov in compliance with section 402(j) of the PHS Act will not be considered ''prior publication'' and would not preclude future publication [Ref. 10].
- Delay in data analysis for unspecified causes. A general statement that provides no specific reason for a delay in data analysis, e.g., ''data could not be analyzed fully within 12 months,'' would not be considered to have demonstrated good cause.

If the estimated completion date displayed in the applicable clinical trial record is earlier than the actual (or current estimated) completion date, a responsible party must update the estimated completion date in the clinical trial record to reflect the actual (or revised estimated) completion date within 30 calendar days, as required by 11.64(b)(1)(viii) and should not request an extension based on the outdated completion date posted in the data bank. The fact that the responsible party has updated the completion date will be reflected in ClinicalTrials.gov, consistent with the handling of all updates under proposed § 11.64.

We invite public comment on these specific situations and on more general criteria that could be used to determine what constitutes good cause for an extension.

Proposed § 11.44(e)(1) outlines procedures for submitting a good-cause extension request. It indicates that extension requests must be submitted to NIH via ClinicalTrials.gov prior to the date on which results information would otherwise be due in accordance with the results submission deadlines established in proposed § 11.44(a), or § 11.44(b), or § 11.44(c), if the relevant certification has been submitted. The proposed process for submission of extension requests calls for direct electronic submission to ClinicalTrials.gov at *http://prsinfo.clinicaltrials.gov/.* Consistent with section 402(j)(3)(E)(vi) of the PHS Act, our proposal would require an extension request to include a description of the reason(s) why results information cannot be provided according to the applicable deadline and an estimated date on which results information will be submitted. Requests missing either piece of information would be considered incomplete and the responsible party would be notified that the request would not be considered by the agency until missing information is provided. The submitted extension request would be reviewed by an NIH official designated by the Director.

Proposed § 11.44(e)(2) specifies that a response to the good-cause extension request would be communicated electronically to the responsible party, providing notice as to whether or not the requested extension has been granted. This communication would take place via ClinicalTrials.gov. As indicated, if a request were granted, a revised deadline for results submission would be communicated in the notice, taking into account the particulars of the request. We note that the agency may grant a deadline that is earlier than that requested by the responsible party in the good-cause extension request. If a request were denied, the deadline for submitting results would be the later of the original submission deadline (e.g., 1 year after the completion date or the delayed submission deadline if a certification has been filed under subparts (b) or (c)) or 15 calendar days after the date the electronic notice of the denial of the request is sent to the responsible party.

Proposed § 11.44(e)(3) establishes an appeals process that would permit a responsible party a single opportunity to appeal the decision of the agency to deny an extension request or the deadline specified in a granted extension request. An appeals process was a feature that was requested at the public meeting in April 2009 (see, Ref. 1). Under proposed § 11.44(e)(3), a responsible party who appeals a denied extension request must submit the appeal in letter form to the Director not later than 15 calendar days after the date on which electronic notification of grant or denial of the request was sent to the responsible party.'' The appeal must explain why, in the view of the responsible party, the initial decision to deny an extension request or to grant an extension request with a shorter deadline than requested by the responsible party should be overturned or revised, e.g., by providing further elaboration of the grounds for the request or by highlighting factors that justify an extension. Generally, new information should not be submitted upon appeal, unless such information was not available at the time of the initial request. The submitted appeal will be considered by the Director.

If an appeal is granted, a revised deadline for results submission would be set by the Director, based on the particulars of the request, and provided to the responsible party in an electronic notification. If the appeal of a denied extension request is denied, the deadline for submitting results would be the later of the original submission deadline or 15 calendar days after the electronic notification of the denial of the appeal is sent to the responsible party. If the appeal of an extension request that was granted with a shorter deadline than was originally requested is denied, the deadline for submitting results would be the later of the deadline specified in the notification granting the extension request or 15 calendar days after the electronic notification of the denial of the appeal is sent to the responsible party.

(f) Posting of information about certifications for delayed submission and about good-cause extensions. We believe that ClinicalTrials.gov should indicate when the results submission deadline for a particular applicable clinical trial has been postponed because an extension request has been granted or the responsible party has submitted a certification for delayed submission. Without such an indication, users who view a clinical trial record that contains no results information more than 1 year after the completion date might be led to believe, incorrectly, that the responsible party has not complied with the results submission requirements of section 402(j)(3)(E) of

the PHS Act or this proposed rule, or that the agency has failed to post such information.

We believe that there would be value in posting information about the specific mechanism that has been used to delay the submission of clinical trial results information, i.e., a certification under proposed § 11.44(c) seeking initial approval, licensure, or clearance; a certification under proposed § 11.44(b) seeking approval, licensure, or clearance of a new use; or a good-cause extension under proposed § 11.44(e). Doing so would provide a mechanism to track the progress of clinical trials by informing users why clinical trial results information is not yet publicly available.

However, we recognize that the public posting of information about the specific mechanism used to delay results submission could result in the posting of information that might in some circumstances be considered confidential. For example, the fact that a responsible party had submitted a certification under proposed § 11.44(b) would indicate that the sponsor or manufacturer had submitted or was planning to submit within 1 year a marketing application or premarket notification to FDA for a new use of a drug or device that was studied in the applicable clinical trial. Such certification could be submitted to ClinicalTrials.gov prior to any public statement by the sponsor or manufacturer about its plans to apply for a new use. Similarly, the reasons underlying a request for a good-cause extension might contain details about the applicable clinical trial that previously have not been made public.

Our proposed approach attempts to balance the desire to indicate that the submission of clinical trial results information has been postponed for reasons that are permitted by statute and the need to avoid disclosure of confidential information. In order to avoid putting responsible parties in a position where they must agree to the release of information that would otherwise be considered confidential in order to delay results submission in accordance with a mechanism specified in section 402(j) of the PHS Act and this proposed part, we would post only minimal information about delayed results submissions in these circumstances. If a responsible party delays results submission via certification or is granted a good-cause extension of the deadline for submitting clinical trial results information, we propose to indicate in the clinical trial record only that results submission has been delayed. We would not indicate which mechanism was used to delay submission or the reason for which an extension may have been granted for a particular applicable clinical trial. In order to provide responsible parties with insight into the general types of reasons that have and have not been considered to constitute good cause for an extension, we propose to post and update periodically on the ClinicalTrials.gov Web site a generalized list of reasons for which extensions have and have not been granted. The listing would not indicate which applicable clinical trials have been granted or denied extensions based on the listed reason(s), and we would attempt to remove from the list any information that might allow a user to identify a specific applicable clinical trial.

We invite public comments on our proposed approach and whether more specific information could be provided about extensions and certifications for an individual applicable clinical trial (e.g., whether submission was delayed via extension or certification, and, if so, which type of certification) without releasing confidential information, what types of certification and extension information responsible parties would consider confidential, and alternative approaches that we could take that would provide more information to the public about the reasons for delayed submissions of clinical trial results information. We specifically invite comments on the advantages and disadvantages of providing more specific information about extension requests, e.g., that a request has been submitted for a clinical trial, the specific reason for the extension request, the responsible party's estimate of the date on which clinical trial results information could be submitted, whether or not the request was subsequently granted or denied, whether a denial has been appealed, and whether the appeal was granted or denied. Making such information available in ClinicalTrials.gov would further increase transparency into agency decisions and would provide an alternative means of informing interested parties about the types of situations that we consider good cause for an extension. We additionally invite public comment on whether extension requests could be submitted without containing any information that would be considered confidential and thus not suitable for release to the public.

(g) Results submission deadline for a pediatric postmarket surveillance of a device that is not a clinical trial. We recognize that the proposed deadlines for submitting clinical trial results information under proposed §§ 11.44(a)–(d) are not well adapted to a pediatric postmarket surveillance of a device that is not a clinical trial. Such surveillances generally do not have a completion date that can be easily measured by the date that the final subject was examined or received an intervention for the purposes of final collection of data for the primary outcome. However, these surveillances will have a date on which a final report must be sent to FDA, as specified in the approved postmarket surveillance plan. Hence for a pediatric postmarket surveillance of a device that is not a clinical trial, we propose in § 11.44(e) that results information be submitted not later than 30 calendar days after the date that the final report is submitted to FDA. We believe that 30 days is sufficient additional time to allow the responsible party to format data as required by this part and submit it to ClinicalTrials.gov.

4. What constitutes results information?—§ 11.48

Proposed § 11.48 specifies procedures for submitting results information for an applicable clinical trial. Proposed § 11.48(a) specifies the general requirements that would apply to an applicable clinical trial other than a pediatric postmarket surveillance of a device that is not a clinical trial. Proposed § 11.48(b) describes the requirements for a pediatric postmarket surveillance of a device that is not a clinical trial.

In specifying the results information that must be submitted for a clinical trial proposed § 11.48(a) separates the data elements into the following general categories of information: (1) Participant flow, (2) demographic and baseline characteristics of the study population; (3) outcomes and statistical analyses; (4) adverse event information; (5) administrative information; and (6) additional results information for applicable device clinical trials of unapproved or uncleared devices. Note that whenever possible ClinicalTrials.gov will use information that was submitted during registration to pre-populate column and row names of the tables of information that required as part of results submission. Doing so would reduce the data entry burden on responsible parties and minimize the possibility of clerical errors. However, in all cases, the responsible party would be required to revise the information, as needed, so that the results information appropriately and accurately reflects the way data were collected and analyzed in the clinical trial. Each of the categories of results information that is required to

be submitted is addressed, in turn, below.

(a) Participant flow: As part of the requirements related to the demographic and baseline characteristics of the patient sample, section 402(j)(3)(C)(i) of the PHS Act specifies that a responsible party must submit ''[a] table of . . . data collected overall and for each arm of the clinical trial to describe the patients who participated in the clinical trial, including the number of patients who dropped out of the clinical trial and the number of patients excluded from the analysis, if any.'' We consider this information to be part of what we call ''participant flow.'' Participant flow refers to information, organized by arm of the clinical trial that documents the progression of human subjects through the clinical trial.

Consistent with section 402(j)(3)(C)(i) of the PHS Act and pursuant to our authority under section 402(j)(3)(D)(iii)(IV) of the PHS Act, we propose in § 11.48(a)(1) to require the submission of the following participant flow information: (1) Participant Flow Arm Information, consisting of ''[a] brief description of each arm used for describing the flow of participants through the clinical trial, including a descriptive title used to identify each arm[;]'' (2) Pre-assignment Information, which consists of ''[a] description of any significant events affecting the number of human subjects enrolled in the clinical trial but not assigned to an arm, if any[,]'' and (3) Participant Data, which is ''[t]he number of human subjects that started, and completed the clinical trial, by arm.'' This information permits the construction of a table that shows the flow of participants through the clinical trial.

In our proposed approach, information about the number of participants excluded from the analysis is not contained within participant flow, but would be submitted as part of the information about outcome measures, described below. We propose this approach because the number of participants excluded from analysis generally depends on the particular outcome measure being analyzed. A participant who drops out midway through a clinical trial, for example, may be included in the analysis of one outcome measure for which data collection was completed early in the study, but excluded from the analysis of another outcome measure for which data collection occurred (or continued) after the drop out. Hence, the aggregate number of participants excluded from the analysis could not generally be calculated by arm and the information by outcome measure would give a more accurate representation of the flow of human subjects through the clinical trial.

We intend to continue to provide responsible parties with a means of providing, on a voluntary basis, additional details about participant flow in a manner consistent with CONSORT guidelines [Ref. 24]. This information would consist of details about the flow of participants through different periods or milestones that might have been defined for a clinical trial and the reason(s) why participants did not complete the clinical trial or reach a particular milestone. Clinical trials often proceed through multiple periods (e.g., wash-out, consecutive cycles of the intervention), and having information about the participant flow in each period and reasons why participants did not complete the clinical trial or reach a particular milestone, if applicable, could improve users' understanding of the clinical trial data. Because clinical trials vary considerably in their design and may or may not include specific periods or milestones, there are no generally accepted approaches for submitting such information; nor is there consensus on how best to classify reasons for non-completion using categories that are comprehensive and not overlapping. Therefore, we do not propose a requirement to submit such information in this proposed rule; instead, we would allow such information to be submitted voluntarily by the responsible party. We have built into ClinicalTrials.gov the capability to accept such information, and we expect that continued experience with the voluntary submission of such information and continued efforts by the clinical trial research community may, over time, lead to the development of more widely accepted approaches to organize such information. We welcome public comment on the value of providing such additional information in ClinicalTrials.gov and on approaches for collecting it.

(b) Demographic and baseline characteristics: Section 402(j)(3)(C)(i) of the PHS Act requires submission of the following results information: ''A table of the demographic and baseline data collected overall and for each arm of the clinical trial to describe the patients who participated in the clinical trial . . .''

ClinicalTrials.gov provides pre-formatted rows that enable responsible parties to submit common demographic characteristics, including age, gender, race, ethnicity, and region of enrollment (with countries and geographic regions, such as Europe, Middle East, South America, listed on a pull-down menu), by arm or comparison group and overall for the clinical trial. Race and ethnicity data are submitted in accordance with the classification system of the Office of Management and Budget (OMB) (See 62 FR 58782, Oct. 30, 1997). We do not propose to require the submission of information describing all of these demographic characteristics because they may not all be collected as part of a particular clinical trial, and we do not wish to impose requirements on the data that must be collected during a clinical trial. Instead, in § 11.48(a)(2)(iii), we propose as a minimum requirement that responsible parties submit information describing the age and gender of the human subjects enrolled in the clinical trial. Age information can be provided as either a continuous variable (e.g., average age is 52 years) along with a measure of dispersion (e.g., standard deviation is 4.5 years) or a categorical variable (e.g., pediatrics, adults, seniors). Such information is generally collected in clinical trials and can be expected to be available for applicable clinical trials.

In addition, ClinicalTrials.gov accommodates the submission of information to describe an unlimited number of customized demographic and baseline characteristics. In general, we cannot specify in advance which other demographic and baseline characteristics must be provided for a particular clinical trial. Only those conducting the clinical trial will know which characteristics are important for their clinical trial and which actually were collected. We do believe it is important, however, that demographic and baseline measures be provided for any characteristic that is used in assessing outcome measures. For example, if an outcome measure compares a subject's blood pressure after 6 weeks of treatment with a particular intervention, we believe the baseline measure of blood pressure must be submitted. Similarly, if a clinical trial includes a statistical analysis that uses baseline data as part of the calculation (e.g., a regression analysis) we believe it is necessary to submit the relevant baseline data. The use of this baseline data in analyzing the outcome measure indicates that it would have been collected during the clinical trial and thus would be important to the interpretation of results.

We specify this requirement in proposed § 11.48(a)(2)(iii) which requires, in addition to age and gender, the submission of information for each baseline or demographic characteristic measured in the clinical trial that is used in the analysis of any of the

outcome measures (See section IV.C.4.c of this preamble for a discussion of outcome measures). In order for submitted demographic and baseline characteristic information to be meaningful to users, we specify that the responsible party must submit the following information for each demographic or baseline measure submitted to ClinicalTrials.gov: the Name of the measure (e.g., gender) and Description of the measure (e.g., ''male'' and ''female''); the type of measure (Measure Type) and an associated Measure of Dispersion; and the unit of measure (e.g., milligrams). When specifying the Measure Type, the responsible party would have to select from the following limited list of options: ''number,'' ''mean,'' ''median,'' ''least squares mean,'' ''geometric mean,'' or ''log mean.'' When specifying the associated Measure of Dispersion, the responsible party would have to select from the following limited list of options: ''standard deviation,'' ''inter-quartile range,'' ''full range,'' or ''not applicable'' (which would be permitted only if the specified measure type is ''number''). No ''other'' option is proposed for either the Measure Type or Measure of Dispersion, but responsible parties would have the option of providing voluntarily additional information about the baseline measures as part of a free-text Baseline Measure Description. We believe that this approach would allow a responsible party to accurately describe the baseline characteristics of an applicable clinical trial or other clinical trial that is subject to this proposed rule. We invite public comment on the sufficiency of the proposed approach for submitting baseline characteristics.

Collecting the information in the structured manner proposed is intended to improve the comparability of information across clinical trials and to ensure complete data collection. For example, if a responsible party indicates that the measure of dispersion for a measure is interquartile range, for example, ClinicalTrials.gov could prompt the submission of the two data elements needed to specify the upper and lower bounds of the interquartile range; if a responsible party indicates that the measure of dispersion is a standard deviation, ClinicalTrials.gov could prompt the submission of that single value. Note that baseline characteristic information may also be submitted as a number instead of a central tendency (e.g. number of participants), in which case the measure of dispersion must be indicated as ''Not Applicable.''

We invite comments on whether or not we should require the submission of additional demographic or baseline characteristics that were collected during the clinical trial, the advantages and disadvantages of requiring the submission of such information, and, if so, how such information can be specified in the rule. We also invite comments on other types of demographic information that could be required for all clinical trials, for example, country-of-origin or country-of-residence, which are collected in many clinical trials. We invite comment on whether the fixed list of proposed choices for measures of central tendency and of dispersion is adequate to provide an accurate description of the measures used in any clinical trial.

Our proposal for demographic and baseline characteristics indicates that responsible parties should submit such information by ''arm or comparison group.'' The reference to comparison group recognizes that when analyzing data collected during clinical trials, data are often aggregated into groupings of human subjects (i.e., comparison groups) other than the arms into which they were assigned for the study. This is often the case in clinical trials that use a cross-over study design in which human subjects in different arms of the clinical trial receive the same interventions in a different order; the results are often analyzed not by arm but by intervention (See the discussion of comparison group in section IV.A.5). We believe it is appropriate when submitting demographic and baseline characteristics, as well as other results information, that the information to be submitted according to the same groupings by which it was analyzed, whether the arm of the clinical trial or a different comparison group. So that users of ClinicalTrials.gov can understand how information about human subjects was aggregated for analysis, proposed § 11.48(a)(2)(i) requires submission of a Baseline Characteristic Arm/Group Information data element, which consists of ''[a] brief description of each arm or comparison group used for describing the demographic and baseline characteristics of the human subjects in the clinical trial, including a descriptive title used to identify each arm or comparison group.''

We also propose in § 11.48(a)(2)(ii) to require submission of Overall Number of Baseline Participants, ''[t]he total number of human subjects for whom baseline characteristics were measured, by arm or comparison group and overall.'' This information is necessary to indicate whether some subjects enrolled in the clinical trial were not measured at baseline (e.g., because they dropped out of the clinical trial before that point in time) and to help ensure that results information is submitted for all subjects who were measured at baseline.

(c) Outcomes and statistical analyses: Section 402(j)(3)(C)(ii) of the PHS Act requires the following as results information: ''The primary and secondary outcome measures as submitted under paragraph (2)(A)(ii)(I)(ll), and a table of values for each of the primary and secondary outcome measures for each arm of the clinical trial, including the results of scientifically appropriate tests of the statistical significance of such outcome measures.'' As discussed in section IV.B.4 of this preamble, primary and secondary outcome measures are submitted as part of the registration process. ClinicalTrials.gov was designed to display the results of each pre-specified outcome measure (primary or secondary) in separate tables organized by arm or comparison group. The responsible party determines the rows and columns of each outcome measure table: The columns represent arms or comparison groups, and the rows represent data categories (e.g., for categorical data types) and data attributes (e.g., mean and standard deviation). The responsible party populates the table cells with data from the clinical trial. In this way, the system can accommodate either continuous or categorical data, as desired by the responsible party based upon the design of the clinical trial as specified in the protocol and statistical analysis plan. For example, time-to-event data could be provided as either a continuous measure (e.g., median time to response) or as categorical data (e.g., number of participants with response at five-years).

In order to enhance the ability of users to understand and interpret the submitted clinical trial results information and to help ensure that submitted information is complete, we propose in §§ 11.48(a)(3)(i)–(v) that the responsible party submit the following information to create and populate the outcome data tables:

(1) Outcome Measure Arm/Group Information, which is described as ''[a] brief description of each arm or comparison group used for submitting an outcome measure for the clinical trial, including a descriptive title to identify each arm or comparison group.'' As discussed in the section IV.C.4(b) on demographic and baseline characteristics, this information would describe the grouping of human subjects for purposes of analysis, whether by arm

of the clinical trial or other comparison group.

(2) Analysis Population Information, which must include the Number of Participants Analyzed, meaning ''[t]he number of human subjects for which an outcome was measured and analyzed, by arm or comparison group.'' If the analysis is based on a unit other than human subjects (e.g., lesions, eyes, implants), the responsible party would also be required to provide the Number of Units Analyzed, which is defined as ''. . . a description of the unit of analysis and the number of units for which an outcome was measured and analyzed, by arm or comparison group.'' In addition, if the Number of Participants Analyzed in an arm or comparison group differs from the number of human subjects assigned to the arm or comparison group, the responsible party would also be required to provide an Analysis Population Description, which would briefly describe the reason(s) for the difference (e.g., if a clinical trial is terminated after participants are assigned to arms but before one of the outcome measures is assessed, the responsible party would include a statement in the Analysis Population Description indicating that the clinical trial was terminated before the outcome measure was collected). This entry would explain why the total Number of Participants Analyzed is zero even though participants had been assigned to the relevant arm or comparison group.

(3) Outcome Measure Information, which includes the following components: (A) Name of the specific outcome measure, including the titles of any categories into which outcome measure data are aggregated; (B) Description of the metric used to characterize the specific outcome measure; (C) Time point(s) at which the measurement was assessed for the specific metric; (D) Outcome Measure Type, which indicates whether the outcome measure is one of the following types of outcome measure: Primary outcome measure, secondary outcome measure, other pre-specified outcome measure, or post-hoc outcome measure; (E) Outcome Measure Reporting Status, which indicates whether the data for the outcome measure are included in the present submission and, if not, the anticipated submission date; (F) Measure Type, which indicates whether the outcome is measured as a number (e.g., number of subjects with a measured value of hemoglobin 5% above the baseline value) or a measure of central tendency, and the associated Measure of Dispersion or precision; and (G) Unit of Measure (e.g., blood pressure in ''millimeters of mercury'' or ''percent change''). In specifying a Measure Type, the responsible party would be required to select from the following limited list options: ''number,'' ''mean,'' ''median,'' ''least squares mean,'' ''geometric mean,'' or ''log mean.'' In specifying the associated Measure of Dispersion, the responsible party would be required to select from the following limited set of options: ''standard deviation,'' ''inter-quartile range,'' ''full range,'' ''standard error,'' ''95% confidence interval,'' ''90% confidence interval,'' ''geometric coefficient of variation'' (which would be permitted only if the specified Measure Type is ''geometric mean''), or ''not applicable'' (which would be permitted only if the specified Measure Type is ''number''). No ''other'' option is proposed for either the Measure Type or Measure of Dispersion entries, but responsible parties would have the option of voluntarily providing additional descriptive information about the outcome measure type and measure of dispersion as part of a free-text Outcome Measure Description. We propose to collect Measure Type and Measure of Dispersion in this manner to improve the ability to compare submitted information across clinical trials and to ensure complete data submission, e.g., if the responsible party indicates that the Measure of Dispersion is interquartile range, ClinicalTrials.gov can prompt the submission of two values corresponding to the upper and lower bounds of the interquartile range, instead of just the single value needed to submit a standard deviation. We invite public comment on this proposal and whether the proposed options for Measure Type and Measure of Dispersion are sufficient for collecting data from the full range of applicable clinical trials or voluntarily submitted trials that would be subject to this proposed rule.

In most cases, items (A), (B), and (C) above would have been submitted at the time of clinical trial registration and updated during the course of the clinical trial, as specified in proposed § 11.64. Proposed § 11.64(c) specifically requires that responsible parties update information submitted during registration at the time they submit results. To ensure consistent data entry and reduce the data entry burden on responsible parties, ClinicalTrials.gov would automatically pre-populate the results data tables with the previously submitted (and updated) values and allow the responsible party to make further updates, as necessary or desired (e.g., to provide further clarification that would enable a user to better interpret the submitted results values). If data were not collected for an outcome measure in a clinical trial, i.e., the Number of Participants Analyzed in all arms or comparison groups is zero for that outcome measure, the responsible party would not be required to submit items (F) and (G) for that outcome measure, as no Outcome Measure Data would be submitted. This situation might occur, for example, if a clinical trial is terminated before data are collected for all pre-specified outcome measures.

(4) Outcome Measure Data, which consists of the measurement values for each outcome measure for which data were collected, by arm or comparison group. The information provided under Outcome Measure Data must use the Unit of Measure and correspond to the Outcome Measure Type submitted under (3) above, i.e., be a number or a central tendency plus a measure of dispersion or precision.

(5) Statistical analyses, which are specified in proposed § 11.48(a)(v) as the ''[r]esults of scientifically appropriate statistical analyses, if any . . .'' performed on the primary or secondary outcome measure(s). In implementing this requirement we clarify the meaning of ''scientifically appropriate'' as it relates to statistical analyses. We believe that the scientific appropriateness of a statistical analysis in a clinical trial is inherently subjective. For purposes of this rule, we propose that a statistical analysis that meets any of the following criteria be considered scientifically appropriate in the context of a particular applicable clinical trial: (1) The statistical analysis is pre-specified in the protocol or statistical analysis plan; (2) the statistical analysis is made public by the sponsor or responsible party in written form (e.g., in a journal publication) prior to the date on which results submission is otherwise completed for all primary and secondary outcome measures studied in the clinical trial; or (3) the statistical analysis is conducted in response to a specific request from the FDA that is made before complete results information is submitted for all of the primary outcome measures studied in the clinical trial. We limit the requirement to submit FDA-requested statistical analyses to those analyses that are requested prior to the submission of results information for primary outcome measures only, so as to avoid causing a responsible party to have to submit analyses that are requested on data that were previously submitted to ClinicalTrials.gov. We propose that statistical analyses that meet any of

these criteria be submitted to ClinicalTrials.gov at the time of results submission. We clarify that a responsible party would not be required to submit a statistical analysis that is not pre-specified in the protocol or statistical analysis plan, is published after complete results information is submitted to ClinicalTrials.gov, or is requested by the FDA after the date on which complete results information is submitted for all of the primary outcome measures studied in the clinical trial. We further clarify that the requirement to submit results of any scientifically appropriate statistical analyses would not cause a responsible party to conduct a statistical analysis that was not otherwise planned or required. We invite public comments on these proposals and on other criteria the agency should consider determining what constitutes a ''scientifically appropriate'' statistical analysis.

We specify in proposed § 11.48(a)(3)(v) the information that a responsible party must submit for any scientifically appropriate analysis:

(A) Statistical Analysis Overview: The responsible party would identify the arms or comparison groups compared in the statistical analysis (by selecting the arms or comparison groups already defined for the outcome measures) and specify the type of analysis conducted. The type of analysis conducted would be selected from the following limited set of options: ''superiority,'' ''non-inferiority,'' ''equivalence,'' or ''not applicable,'' where ''not applicable'' would be appropriate for a single group analysis, for example. No ''other'' option is proposed. If the type of analysis selected is ''non-inferiority'' or ''equivalence,'' the responsible party would be required to also provide a free-text description of key parameters of the statistical analysis to include, at minimum, information about the power calculation and the non-inferiority or equivalence margin. An additional comment field would be offered to allow the responsible party to voluntarily submit additional information about the statistical analysis. We invite comment on whether the list of proposed options is sufficient for all applicable clinical trials or voluntarily submitted clinical trials for which statistical analysis information might be submitted to ClinicalTrials.gov under this proposed rule.

(B) Statistical Test of Hypothesis: The responsible party would submit the p-value and specify the procedure used for statistical analysis of the outcome data. For convenience in specifying the procedure used for the statistical analysis, ClinicalTrials.gov includes a list of commonly used statistical tests for calculating p-values from which responsible parties may select: ANCOVA; ANOVA; Chi-squared; Chi-squared, Corrected; Cochran-Mantel-Haenszel; Fisher Exact; Kruskal-Wallis; Log Rank; Mantel Haenszel; McNemar; Mixed Models Analysis; Regression, Cox; Regression, Linear; Regression, Logistic; Sign Test; t-Test, 1-sided; t-Test, 2-sided; and Wilcoxon (Mann-Whitney). Responsible parties may also select ''other'' and submit the name of another method that was used. Additional comment fields would be available in ClinicalTrials.gov to allow the responsible party to submit voluntarily additional information about the statistical test of hypothesis, such as a description of the null hypothesis, adjustments for multiple comparisons, a priori thresholds for statistical significance, and degrees of freedom.

(C) Method of Estimation: The responsible party would provide a description of the method of estimation that specifies: The estimation parameter, the estimated value, and a confidence interval. For convenience in describing the method of estimation, ClinicalTrials.gov includes a list of more than a dozen commonly used estimation parameters from which responsible parties may select: Cox Proportional Hazard; Hazard Ratio (HR); Hazard Ratio, log; Mean Difference (Final Values); Mean Difference (Net); Median Difference (Final Values); Median Difference (Net); Odds Ratio (OR); Odds Ratio, log; Risk Difference (RD); Risk Ratio (RR); Risk Ratio, log; and Slope. Responsible parties may also specify ''other'' and provide the name of another estimation parameter using free text. In specifying a confidence interval, the responsible party would submit the confidence level, indicate whether the confidence interval is one-sided or two-sided, and provide the upper and/or lower limits of the confidence interval. A responsible party could specify that the confidence interval is one-sided and provide only the upper or lower limit. If one of the limits of a two-sided confidence interval cannot be calculated, the responsible party would be required to specify that limit as ''Not Available'' and provide a brief narrative explanation (e.g., because an insufficient number of clinical trial participants reached the event at the final time point for assessment). A responsible party would also have the option of submitting voluntarily a dispersion value for the confidence interval. If a dispersion value is submitted, the responsible party would be required to specify the parameter of dispersion by selecting one of the following options: ''Standard deviation'' or ''standard error of the mean.'' No ''other'' option is proposed. An additional comment field would be available to allow the responsible party to submit voluntarily additional information about the method of estimation, such as the direction of the comparison (e.g., for a relative risk).

These proposed requirements for submitting statistical analysis information attempt to balance the benefits of structured data with minimal narrative text against the need to describe what was evaluated in the statistical analysis. In addition to the information specified above, responsible parties also would have the option of voluntarily submitting additional free-text information in order to provide a more complete description of the statistical analyses. This free-text information would not include interpretation of results or conclusions, just a description of the statistical test(s) conducted. Submitted statistical analyses would be linked to each submitted outcome measure. Although a responsible party would not be limited in the number of statistical analyses that could be submitted for each outcome measure, only statistical analyses that are related to a submitted outcome measure could be described.

In specifying requirements for outcome measures and statistical analyses under proposed § 11.48(a)(3), two situations merit further clarification. The first is a clinical trial that is terminated before data are collected for one or more of the pre-specified outcome measures. Certain information would still be required to be submitted for outcome measures for which data were not collected. Under proposed § 11.48(a)(3)(ii) the responsible party would be required to submit the Number of Participants Analyzed, which would be zero (''0'') for an outcome measure for which no data were collected. As noted in (3) above and specified in proposed § 11.48(a)(3)(iii)(F) and (G), the responsible party would not be required to submit the Measure Type and Unit of Measure data elements for any outcome measure for which data were not collected but would be required to provide the other elements of Outcome Measure Information specified in proposed § 11.48(a)(3)(iii). As specified in proposed § 11.48(a)(3)(iv), the responsible party would not be required to submit Outcome Measure Data for the outcome measure(s) for which no data were collected, but would be required to submit Outcome Measure Data for any

other outcomes for which data were collected. The responsible party would nevertheless still be required to meet the requirements specified in proposed §§ 11.48(a)(1), (2), and (4) for the submission of information for the Participant Flow, Baseline Characteristics, and Adverse Events modules. Note, that if a clinical trial enrolls no participants, the information to be submitted for the Actual Enrollment data elements under proposed § 11.64(b)(1)(v)(B) would be zero (''0'') and no results information would be required to be submitted for that clinical trial.

The second situation consists of a clinical trial in which outcome measures are collected but the actual enrollment falls well below the target enrollment. This could occur, for example, if a clinical trial is terminated due to poor enrollment after some participants are enrolled and outcomes are measured. We believe that even in such situations collected results information must be submitted to ClinicalTrials.gov as specified in this proposed rule (taking into consideration the privacy considerations discussed in section III.C.16 of this preamble if actual enrollment is very small). Submission and posting of results information for such a clinical trial would be consistent with section 402(j) of the PHS Act and provide a means of tracking the progress of the clinical trial and demonstrating what happened to the human subjects who were enrolled. If the clinical trial was terminated because of safety concerns or efficacy, the results information would be of considerable interest to human health and safety. In order to reduce the chance that users of ClinicalTrials.gov might misinterpret submitted results information, we would encourage the responsible party to voluntarily submit additional information about the clinical trial in the Analysis Population Description data element and/or in the Limitations and Caveats module of ClinicalTrials.gov. The submitted information would highlight that enrollment in the clinical trial was insufficient to produce statistically reliable results. We would also take steps to highlight in the public display the fact that actual enrollment fell far short of expected enrollment. We would expect that in these situations, no statistical analysis information would be submitted for the affected outcome measure(s) because none would have been conducted or would be considered scientifically valid. We invite public comments on other ways in which the limitations of the submitted data could be highlighted.

(d) Adverse event information. Proposed § 11.48(a)(4) requires the submission of summary information on adverse events that occurred during an applicable clinical trial. Such information is considered part of results information. Our proposal derives from the default provisions in sections 402(j)(3)(I)(ii)–(iii) of the PHS Act, which require the submission of information necessary to complete two tables: (1) A table of all anticipated and unanticipated serious adverse events, and (2) a table of all anticipated and unanticipated adverse events other than serious adverse events with a frequency of more than 5 percent in any arm of the clinical trial (i.e., ''other frequent adverse events''). Sections 402(j)(3)(I)(ii)–(iii) of the PHS Act further specify that the information submitted for each table be grouped by organ system and include the number and frequency of events in each arm of the clinical trial. As explained in greater detail in section III.C.15 of this preamble, our proposal for the submission of adverse event information derives from the default provisions in sections 402(j)(3)(I)(ii)–(iii) of the PHS Act, but includes additional requirements intended to assist users in understanding and interpreting the submitted adverse event information.

In implementing the statutory default provisions, we propose in § 11.48(a)(4) that responsible parties submit the following information for all serious adverse events and for other adverse events with a frequency of more than 5 percent in any arm or comparison group of the clinical trial: (1) A description of each arm or comparison group from which adverse event information was collected (see proposed § 11.48(a)(4)(ii)(A)); (2) for each arm or comparison group, a description of each serious adverse event or other adverse event with a frequency of more than 5 percent in any arm of the clinical trial, along with the organ system that is associated with the adverse event (see proposed § 11.48(a)(4)(ii)(F)); (3) the number of participants experiencing the adverse event (see proposed § 11.48(a)(4)(ii)(G)(1)), and (4) the number of participants at risk for the adverse event (see proposed § 11.48(a)(4)(ii)(G)(2)). In most cases, the number of participants at risk will equal the number of participants who started that arm of the clinical trial, but the two numbers could differ if participants were assigned to an arm but did not receive the intervention (e.g., because they dropped out of the clinical trial) or because a comparison group combines participants from multiple arms of the trial. Using the data submitted for number of participants experiencing the adverse event and the number of participants at risk, ClinicalTrials.gov will automatically calculate the percentage of participants who experienced the event. We believe that this approach will help reduce calculation errors and help users interpret the frequency information in those cases in which the full study population may not have been at-risk.

To assist users of ClinicalTrials.gov in better understanding the number of participants affected by adverse events, we also propose in § 11.48(a)(4) that responsible parties be required to submit the following information both for all serious adverse events and for other adverse events with a frequency of more than 5 percent in any arm or comparison group of the clinical trial: (1) The overall number of human subjects affected, by arm or comparison group, by one or more serious adverse events or other adverse events above the specified threshold (see proposed § 11.48(a)(4)(ii)(B)), (2) the overall number of participants at risk for any adverse event, by arm or comparison group (see proposed § 11.48(a)(4)(ii)(C)), (3) for each organ system class that has one or more adverse events listed in either table, the overall number of participants affected, by arm or comparison group, by any adverse event in that organ system class (see proposed § 11.48(a)(4)(ii)(D)), and (4) for each organ system class that has one or more adverse events listed in either table, the number of participants at risk, by arm or comparison group, for any adverse event in that organ system class (see proposed § 11.48(a)(4)(ii)(E)). ClinicalTrials.gov will automatically calculate the percentage of those at risk that experienced any adverse event and the percentage of those at risk that experienced any adverse event in each organ system class. We believe that this approach will help reduce calculation errors and help users interpret the frequency information in those cases in which the full study population may not have been at-risk for any adverse event or for adverse events affecting particular organ systems.

As explained in section III.C.5 of this preamble, we propose to require responsible parties to submit adverse event information classified according to the scheme specified in ClinicalTrials.gov, which includes the following 26 categories adapted from the Medical Dictionary for Regulatory Affairs (MedDRA) system (*http://www.meddramsso.com/*): Blood and lymphatic system disorders; Cardiac

disorders; Congenital, familial and genetic disorders; Ear and labyrinth disorders; Endocrine disorders; Eye disorders; Gastrointestinal disorders; General disorders; Hepatobiliary disorders; Immune system disorders; Infections and infestations; Injury, poisoning and procedural complications; Investigations; Metabolism and nutrition disorders; Musculoskeletal and connective tissue disorders; Neoplasms benign, malignant and unspecified (including cysts and polyps); Nervous system disorders; Pregnancy, puerperium and perinatal conditions; Psychiatric disorders; Renal and urinary disorders; Reproductive system and breast disorders; Respiratory, thoracic and mediastinal disorders; Skin and subcutaneous tissue disorders; Social circumstances; Surgical and medical procedures; and Vascular disorders organ classes. No ''other'' option is proposed. ''Social circumstances'' is a not an organ class (like most of the other categories) but is used in MedDRA to accommodate the classification of some types of adverse events that are not specific to an organ system, such as ''automobile accident,'' ''homicide,'' or ''fall''. Adverse events that affect multiple systems should be reported only once (to avoid over-counting), preferably under the organ system class that is considered primary. If there is no primary organ system class, the event should be listed under ''General disorders,'' and additional explanation may be provided in the optional free-text field, Adverse Event Term Additional Description. Our experience with submission of adverse event information since September 2008 indicates that responsible parties are able to use these classes effectively to classify the adverse event information submitted to ClinicalTrials.gov. We request comment on whether this organ system classification is sufficient for submitting adverse event information for all applicable clinical trials and voluntarily registered trials that are subject to this rule, or whether additional categories or an ''other'' option are necessary.

As specified in the statutory default provisions, the adverse event information submitted under proposed § 11.48(a)(4)(ii)(G)(1) and (2) would be required to include information on anticipated and unanticipated adverse events. We understand that protocols sometimes specify the collection of only a more limited set of adverse events in a clinical trial, e.g. only unanticipated events, or only events associated with a particular organ system. We do not intend this proposed rule to cause investigators or responsible parties to collect information that is not specified in the clinical trial protocol. Therefore, in those situations in which the protocol specifies a more limited collection of adverse events, we would require the responsible party to submit the specified information about serious and other adverse events with a frequency greater than 5 percent in any arm of the trial for those adverse events that were collected during the trial. To help ensure that users of ClinicalTrials.gov know when adverse event collection was limited, the responsible party would be further required, as indicated in proposed § 11.48(a)(4)(ii)(H), to submit an Additional Description that briefly describes how the scope of adverse events for which information was submitted differs from the broader definitions of adverse event and serious adverse event proposed in this rule.

Finally, we note that the agency interprets section 402(j)(3)(I)(v) of the PHS Act to deem the adverse event information required under section 402(j)(3)(I) of the PHS Act as clinical trial information for all clinical trials, including applicable clinical trials and voluntarily-submitted clinical trials.

(e) Administrative information: Proposed § 11.48(a)(5) describes certain administrative information that we propose to require to be submitted as results information data elements. Section 402(j)(3)(C)(iii) of the PHS Act requires that ''a point of contact for scientific information about the clinical trial results'' be submitted as part of clinical trial results information. Proposed § 11.48(a)(5)(i) implements this provision by requiring the following information: (1) Name or official title of the point of contact; (2) name of affiliated organization; and (3) telephone number and email address of the point of contact. We believe that this is the information is needed in order to allow a user to inquire about the results of the clinical trial. This information would be required to be submitted, even if the point of contact is the same as the responsible party because we do not otherwise plan to make public the responsible party contact information.

Section 402(j)(3)(C)(iv) of the PHS Act requires responsible parties to indicate ''whether there exists an agreement . . . between the sponsor or its agent and the principal investigator . . . that restricts in any manner the ability of the principal investigator, after the completion date of the trial, to discuss the results of the trial at a scientific meeting or any other public or private forum, or to publish in a scientific or academic journal information concerning the results of the trial.'' The statutory provision also provides that this requirement does not apply to an agreement between a sponsor or its agent and the principal investigator solely to comply with applicable provisions of law protecting the privacy of participants in the clinical trial. Consistent with the definition of PI proposed in this part, we interpret this provision as applying to a PI who has oversight over the entire applicable clinical trial, not to site-specific investigators or other investigators (such as those on grant-funded studies) who might be referred to as principal investigators in other contexts but who do not meet the definition of ''principal investigator'' under this part.

In implementing the requirement under section 402(j)(3)(C)(iv) of the PHS Act, we propose in § 11.48(a)(5)(ii) to require responsible parties to indicate (yes/no) whether the PI is an employee of the sponsor. If the PI is an employee of the sponsor, then no further information must be provided, although it may be provided voluntarily. If the responsible party indicates that the PI is not an employee of the sponsor, then the responsible party would be required to indicate (yes/no) whether or not an agreement (other than one solely to comply with applicable provisions of law protecting the privacy of human subjects participating in the clinical trial) exists between the sponsor or its agent and the PI that restricts in any manner the ability of the PI, after the completion date of the clinical trial, to discuss the results of the clinical trial at a scientific meeting or any other public or private forum, or to publish in a scientific or academic journal information concerning the results of the clinical trial.

Although we are only requiring, consistent with section 402(j)(3)(C)(iv) of the PHS Act, that the responsible party indicate whether such an agreement exists, we also propose to permit responsible parties to provide voluntary additional information about existing agreements. In our interactions with responsible parties and consultations with stakeholders, we have learned that certain agreements of the nature described in section 402(j)(3)(C)(iv) of the PHS Act exist routinely in the clinical trials community, although they may vary in their terms and the duration of their limitations on the PI. Such agreements typically permit the sponsor or its agent to review results communications prior to public release and to impose a short-term embargo of 60 days or less, from the date the communication is submitted to the sponsor for review, but other agreements can impose

restrictions that have much longer durations or are broader in scope. In order to provide responsible parties with an opportunity to provide additional information about the agreements that are in place between the sponsor or its agent and the PI, we propose to permit the voluntary submission of additional, structured information about the agreement. Currently in ClinicalTrials.gov, a responsible party who wishes to provide this additional information may select among the following choices:

(1) The only disclosure restriction on the PI is that the sponsor can review results communications prior to public release and can embargo communications regarding clinical trial results for a period that is less than or equal to 60 days from the date the communication is submitted to the sponsor for review. The sponsor cannot require changes to the communication and cannot extend the embargo.

(2) The only disclosure restriction on the PI is that the sponsor can review results communications prior to public release and can embargo communications regarding clinical trial results for a period that is more than 60 days but less than or equal to 180 days from the date the communication is submitted to the sponsor for review. The sponsor cannot require changes to the communication and cannot extend the embargo.

(3) Other disclosure agreement that restricts the right of the PI to discuss or publish clinical trial results after the trial is completed. The responsible party may provide additional description of the disclosure agreement.

Based on our experience to-date in operating ClinicalTrials.gov and on feedback we have received from responsible parties, these categories appear to provide an acceptable way to describe these agreements in a consistent form and manner that can help identify those that deviate from standard practice. These categories could be modified over time in order to reflect changes in clinical trials practice or provide other information of interest to users. We invite public comment on the proposed approach, experience to date with the current approach, and other information that might be collected on a voluntary basis.

(f) Additional results information for applicable device clinical trials of unapproved or uncleared devices. For applicable device clinical trials of unapproved or uncleared devices, the results information specified in (a) through (e) above would be submitted to ClinicalTrials.gov and publicly posted prior to the date on which clinical trial information submitted at the time of registration would have been publicly posted. As a result, users of ClinicalTrials.gov would lack access to certain descriptive information that is necessary to enhance access to and understanding of the submitted results information and to determine whether complete results information has been submitted (e.g., for all arms of the study).

Section 402(j)(3)(D)(iii)(IV) of the PHS Act grants the Secretary wide discretion in determining what information can be required through rulemaking to be submitted as part of results information, stating that the regulations ''shall require, in addition to the elements described in [section 402(j)(3)(C)] . . . [s]uch other categories as the Secretary determines appropriate.'' Thus, the Secretary can require, through rulemaking, submission of not only that results information that is required under section 402(j)(3)(C) of the PHS Act, but also ''such other categories'' of information as the Secretary determines appropriate. We interpret ''such other categories'' of results information for applicable device clinical trials of unapproved or uncleared devices to include, among other things, certain descriptive information that is the same type of information that was required to be submitted under section 402(j)(2)(A)(ii) of the PHS Act.

In order ''to enhance patient access to and understanding of the results of clinical trials'' (See section 402(j)(3)(D)(i) of the PHS Act), we propose to exercise the authority under sections 402(j)(3)(D)(ii)(II) and 402(j)(3)(D)(iii) of the PHS Act to require responsible parties of applicable device clinical trials of unapproved or uncleared devices to submit, as part of results information, certain additional, descriptive information that is the same type of information that is submitted at the time of registration. This descriptive information, defined as part of results information, would be posted not later than 30 calendar days after submission, pursuant to section 402(j)(3)(G) of the PHS Act. A more detailed discussion of how the specified data elements would enhance access to and understanding of clinical trial results information is contained in section III.C.5 of this preamble.

Proposed § 11.48(a)(6)(i) lists the descriptive information we propose that responsible parties must submit as part of the clinical trial results information submitted for applicable device clinical trials of unapproved or uncleared devices. We believe that the listed data elements are necessary to enhance access to and understanding of the results of applicable clinical trials of unapproved or uncleared devices for which information submitted at registration would not have been posted publicly in ClinicalTrials.gov. We interpret this necessary standard broadly to enhance access to and understanding of study results by the lay public, as well as users of the data bank who have high levels of expertise in evaluating the results of clinical trials. Moreover, we interpret this necessary standard broadly to enhance access to and the understanding of results of clinical trials that are posted in ClinicalTrials.gov as well as those that are not posted in ClinicalTrials.gov; for example: the comparison of the results of multiple clinical trials of the same or similar devices may be necessary to understand the results of a clinical trial. We further believe that information indicating the status of any necessary human subjects protection review board approval must be submitted so that users can understand whether results information voluntarily submitted to ClinicalTrials.gov and available in the data bank derives from clinical trials that were reviewed and approved for ethical and scientific considerations, or were exempt from such review.

Because responsible parties for applicable device clinical trials of unapproved or uncleared devices will already have provided this descriptive information to the data bank when submitting (and updating, as necessary) registration information, the agency believes that it would be an unnecessary burden on these responsible parties to require them to resubmit descriptive information as part of clinical trial results information. Instead, we propose under § 11.48(a)(6)(ii) to require responsible parties to affirm that they have verified and updated as necessary the descriptive information that is the same type of information that is submitted when the trial is registered and that this descriptive information is ready to be posted along with the results information. Doing so would allow information that previously had been submitted to the data bank to automatically populate the data elements for these clinical trial results. This approach would also reduce inconsistencies between information that previously had been submitted at registration and information that would be submitted with results, and increase administrative efficiency by reducing the need for the agency to conduct a quality review of this information. In this manner, we can help ensure that the results information necessary ''to

enhance patient access to and understanding of the results of clinical trials,'' section 402(j)(3)(D)(i) of the PHS Act, is submitted and made available publicly, but can reduce the burden placed on responsible parties.

(g) Results information for a pediatric postmarket surveillance of a device that is not a clinical trial. Subsection (b) of proposed § 11.48 specifies the results information that must be submitted to ClinicalTrials.gov for a pediatric postmarket surveillance of a device that is not a clinical trial. We recognize that a pediatric postmarket surveillance of a device may take any of several forms, including prospective surveillance studies and historical reviews of the health records of those who have received a device as an intervention, and may not meet the definition of a ''clinical trial'' under this part. For this reason, we do not believe that it is possible to specify particular data elements or tables of data, similar to those for applicable clinical trials that are clinical trials, that could be required as results information for all types of pediatric postmarket surveillances of a device that are not clinical trials. We are aware, however, that for each pediatric postmarket surveillance of a device that is required by FDA, a final report must be submitted to FDA according to 21 CFR 822.38 (or any successor regulation). Thus, for each pediatric postmarket surveillance of a device that is not a clinical trial, we believe that the final report would contain a suitable summary of the surveillance results, and we propose that it be submitted to ClinicalTrials.gov in a form that can be made available to the public, e.g., after redacting: (a) Any personally identifiable information (other than that required to be submitted under this part), and (b) information that is not required to be submitted under this part and that is commercial confidential information. Any information not redacted would be included in the public data bank. The final report would be required to be submitted in a common electronic document format, such as Portable Document Format (PDF) or Microsoft Word, specified in ClinicalTrials.gov at *http://prsinfo.clinicaltrials.gov/*. The set of acceptable formats may be updated periodically to include new formats that become commonly used in the regulated community. This proposed requirement is included in section 11.48(b). We invite public comment on this approach.

5. When will NIH post submitted results information?—§ 11.52

Proposed § 11.52 provides that the Director will post results information not later than 30 days after the date on which the information is submitted to the agency for an applicable clinical trial. This proposal corresponds to the posting deadline established in section 402(j)(3)(G) of the PHS Act. Proposed § 11.52 does not apply to clinical trials that are not required to register under 402(j)(2)(C) of the PHS Act. For such trials that voluntarily register with ClinicalTrials.gov, regardless of whether they are subject to the requirements for voluntary submission under proposed § 11.60 or are subject to the requirements in § 11.60(a)(2)(ii), we intend to post results information as soon as practicable after clinical trial results information has been submitted and reviewed as part of our quality review procedures.

6. Under what circumstances will the Secretary grant a waiver of the requirements of this subpart?—§ 11.54

Section 402(j)(3)(H) of the PHS Act provides that ''[t]he Secretary may waive any applicable requirements of this paragraph for an applicable clinical trial, upon written request from the responsible party, if the Secretary determines that extraordinary circumstances justify the waiver and that providing the waiver is consistent with the protection of public health or in the interest of national security . . .'' Proposed § 11.54, implements this provision by outlining procedures by which a responsible party may submit a written request for a waiver from the requirements of subpart C for an applicable clinical trial in extraordinary circumstances where provision of the waiver is consistent with protecting public health or in the interest of national security.

We expect that waivers would be requested and granted in only a very limited number of situations. As described in section III.C.16 of this preamble, one example of a situation in which a waiver might be granted is if results information could be submitted only in a manner that would be likely to enable the re-identification of clinical trial participants. We invite public comments on other situations in which a waiver might be granted and would be consistent with the protection of public health or in the interest of national security.

The proposal specifies that waiver requests must be submitted in the form of a written letter to the Secretary or a delegated official and indicate the NCT Number, Brief Title, and Sponsor of the trial. This information is necessary to identify positively the specific trial for which the waiver is requested (the combination of NCT Number and Brief Title will assist in identifying mistyped NCT numbers) and the key parties involved (i.e., sponsor and responsible party). Because the statute grants the Secretary the authority to waive ''any applicable requirements'' of this subpart if justified by ''extraordinary circumstances'', we also propose that the responsible party identify the specific provisions(s) for which a waiver is requested and provide a description of the circumstances that are believed to justify the waiver.

The responsible party would not be required to comply with those provisions of subpart C for which the waiver was granted. Such provisions could include all or just some of the provisions for which the waiver was requested. The responsible party would be expected to comply with any remaining provisions of subpart C for which the waiver was not requested or not granted. The deadline for submitting results information to ClinicalTrials.gov would be the later of the original submission deadline or 15 calendar days after the notification denying the waiver is sent to the responsible party.

In subsection (b), we propose an appeals process that would permit a responsible party to appeal a denied waiver request by writing to the Secretary or delegated official. The delegated official for deciding upon waiver appeals would, as a matter of practice, differ from the delegated official for reviewing the initial waiver request. As with the original request, the responsible party would not be required to comply with specific provisions of subpart C for which the waiver is granted upon appeal; for those provisions for which a waiver is not granted upon appeal, the responsible party would be required to submit results information by the later of the original results submission deadline or 15 calendar days after the notification denying the appeal is sent to the responsible party.

As required by section 402(j)(3)(H) of the PHS Act, if such a waiver is granted, the Secretary will notify the appropriate Congressional committees that the waiver has been granted and explain why it has been granted, not later than 30 calendar days after any part of the waiver is granted. A notation would be made in the record for the applicable clinical trial in ClinicalTrials.gov to indicate that certain requirements for results submission have been waived, pursuant to section 402(j)(3)(H) of the

PHS Act. This notation is intended to inform users of ClinicalTrials.gov that the absence of certain results information does not constitute a failure to comply with the statute and implementing regulation. Because the waiver would be based on extraordinary circumstances that could include considerations of public health and/or national security, the agency proposes not to post publicly information describing the reason for the waiver. We invite public comment on this proposal.

D. Additional Submissions of Clinical Trial Information—Subpart D

Proposed subpart D describes requirements for additional submissions of clinical trial information to ClinicalTrials.gov, including: (1) Voluntary submission of clinical trial information for certain clinical trials that are not otherwise subject to the registration and results submission requirements of this proposed rule; (2) submission of clinical trial information when it is determined that posting of such information is necessary to protect public health; and (3) timelines for updating clinical trial information.

1. What requirements apply to the voluntary submission of clinical trial information for clinical trials of FDA-regulated drugs and devices?—§ 11.60

Proposed § 11.60 describes requirements that would apply to certain voluntary submissions of clinical trial information to ClinicalTrials.gov, specifically, submissions of information for clinical trials that are not otherwise subject to the registration and results submission requirements of section 402(j) of the PHS Act. This proposed section implements section 402(j)(4)(A) of the PHS Act which specifies certain requirements that apply to voluntary submissions of clinical trial information for two types of clinical trials for which submission of information is not otherwise required, as follows: (1) Clinical trials that do not meet the definition of an applicable clinical trial; and (2) clinical trials that are applicable clinical trials but are not required to register under section 402(j)(2)(C) of the PHS Act or proposed § 11.22(a) (i.e., clinical trials that are applicable clinical trials that were initiated on or before September 27, 2007, and that reached their completion dates before December 26, 2007).

If a responsible party wishes to submit clinical trial information voluntarily for one of these two types of clinical trials, the responsible party must: (1) Submit complete registration information as specified in proposed § 11.60(a)(2)(i)(A) or complete results information as specified in proposed § 11.60(a)(2)(i)(B) for the voluntarily-submitted clinical trial; and (2) submit clinical trial information for ''each applicable clinical trial that is required to be submitted under section 351 [of the PHS Act] or under section 505, 510(k), 515, or 520(m) of the [FD&C] Act in an application or report for licensure, approval, or clearance of the drug or device for the use studied in the clinical trial.'' (See section 402(j)(4)(A) of the PHS Act.) While the Agency encourages submissions of complete registration information and complete results information for all types of clinical trials, regardless of whether they are subject to section 402(j) of the PHS Act, responsible parties should consider the above conditions before deciding whether to register a clinical trial or submit results information voluntarily.

In considering which clinical trials fall under this provision, we believe that section 402(j)(4)(A) of the PHS Act should be interpreted in a way that is consistent with the scope of FDA's regulatory authorities and the scope of this proposed regulation. Hence, we interpret the phrase ''a clinical trial that is not an applicable clinical trial,'' in section 402(j)(4)(A) of the PHS Act, to be limited to a clinical trial of an FDA-regulated drug (including biological product) or device that is not an applicable clinical trial. We do not interpret this phrase to include clinical trials of other types of interventions, whether regulated by FDA or not, that would not meet the definition of an applicable clinical trial. Thus, proposed § 11.60 would apply, for example, to a phase 1 trial of an FDA-regulated drug, or to a clinical trial that evaluates the feasibility of an FDA-regulated device, but not to a clinical trial that studies only behavioral interventions that are not drugs, biological products, or devices. In addition, we interpret the phrase ''applicable clinical trial that is not subject to [the mandatory registration requirement of] paragraph (2)(C),'' in section 402(j)(4)(A) of the PHS Act, to mean a clinical trial that meets the definition of an applicable clinical trial, as specified in section 402(j)(1)(A) of the PHS Act and this part, but that was initiated on or before September 27, 2007, and that reached its completion date prior to December 26, 2007. This would mean that proposed § 11.60, and not proposed subparts B and/or C, would apply to submissions of clinical trial information for such applicable clinical trials.

In considering the information that must be submitted to ClinicalTrials.gov for a voluntarily-submitted clinical trial under section 402(j)(4)(A) of the PHS Act, we interpret section 402(j)(4)(A) of the PHS Act as permitting a responsible party to submit voluntarily registration information for a clinical trial without having to submit results information. Section 402(j)(4)(A) of the PHS Act uses the term ''or'' when referring to the submission of ''clinical trial registration information described in paragraph (2) [clinical trial registration information] or (3) [clinical trial results information]'' [emphasis added]. While we encourage those who register clinical trials voluntarily to also submit results information voluntarily, we see value in having voluntarily submitted registration information in ClinicalTrials.gov even if associated results information is not submitted. Clinical trial registration information can, for example, assist with recruitment and indicate the existence of a clinical trial. Similarly, we believe section 402(j)(4)(A) of the PHS Act permits a responsible party to submit voluntarily results information without having to have previously submitted registration information. Hence, proposed § 11.60(a)(2)(i) expressly permits the submission of registration information, results information, or both.

In specifying requirements for the voluntary submission of results information, proposed § 11.60(a)(2)(i)(B) requires the submission of the results information set forth at proposed § 11.48(a). However, we believe that certain descriptive information ordinarily submitted at the time of registration would be necessary to enhance access to results information, render it meaningful to the public, and demonstrate that the clinical trial is not an applicable clinical trial subject to proposed §§ 11.22 and 11.42. Thus, we propose that a responsible party who voluntarily submits only results information for a clinical trial under proposed § 11.60(a)(2)(i)(B), must submit the data elements set forth at proposed § 11.60(a)(2)(i)(B), in addition to the data elements set forth at proposed § 11.48(a), as clinical trial results information.

Sections III.C.5(b) and IV.C.4(f) of this preamble describe our rationale for requiring much of the descriptive information set forth at proposed § 11.60(a)(2)(i)(B). Those sections of the preamble, however, address only those data elements that we believe are necessary to enhance access to and understanding the results of a clinical trial of a device for which complete registration information has been previously submitted to ClinicalTrials.gov. We believe that

additional descriptive information is necessary to enhance access to and understanding of the results of a clinical trial of a drug (or a biological product): ''Study Phase'' is necessary to enable a user to understand the relative stage of development of an experimental drug (including biological product) studied in a clinical trial; and ''Availability of Expanded Access'' is necessary to provide patients with access to information about the availability of the drug to those who do not qualify for enrollment in the clinical trial.

In addition, we believe that several other data elements must be submitted with voluntarily submitted results information in order for users of the data bank and/or the Agency to confirm that a clinical trial for which information is submitted voluntarily is not an applicable clinical trial subject to mandatory registration or results submission under this part. Specifically, we believe that the following data elements are necessary: ''Single Arm Control?,'' ''Whether the Study is a Pediatric Postmarket Surveillance of a Device,'' ''Product Manufactured in the U.S.?,'' and ''U.S. Food and Drug Administration IND or IDE Number.''

For situations in which a responsible party submits voluntarily only clinical trial results information under section 402(j)(4)(A) of the PHS Act, we propose to use our authority under section 402(j)(3)(D)(iii)(IV) of the PHS Act to interpret results information to include the data elements under proposed § 11.60(a)(2)(i)(B) in addition to the data elements set forth at proposed § 11.48(a).

As stated, section 402(j)(4)(A) of the PHS Act specifies that voluntary submissions of information must consist of ''complete'' clinical trial registration or results information. We interpret the reference to ''complete'' in section 402(j)(4)(A) to mean that as a condition of voluntary submission under section 402(j)(4)(A) and proposed § 11.60, responsible parties must submit all registration information or results information data elements specified in proposed §§ 11.60(a)(2)(i)(A) or (B), as applicable. We note, however, that we propose in § 11.60(a)(2)(iv)(A) that a responsible party may submit results information for a voluntarily-submitted clinical trial once results information is available for the primary outcome measure(s). If data collection for the secondary outcome measure(s) for such clinical trials is not completed by the completion date of the voluntarily-submitted clinical trial, then results information for the secondary outcome measure(s) must be submitted by the later of the date that the results information is voluntarily submitted for the primary outcome measure(s) or 1 year after the date on which the final subject was examined or received an intervention for the purposes of final collection of data for the secondary outcome measure(s), whether the clinical trial was concluded according to the pre-specified protocol or was terminated.

Section 402(j)(4)(A) of the PHS Act also specifies that a responsible party who voluntarily registers or submits results information for a clinical trial must also submit clinical trial information for ''each applicable clinical trial that is required to be submitted under section 351 [of the PHS Act] or under section 505, 510(k), 515, or 520(m) of the Federal Food, Drug, and Cosmetic Act in an application or report for licensure, approval, or clearance of the drug or device for the use studied in the clinical trial.'' We believe this condition of section 402(j)(4)(A) of the PHS Act may be intended to help prevent selective voluntary submissions, for example, if a responsible party voluntarily submitted clinical trial information only from clinical trials that showed positive results for a particular product, but not from clinical trials that showed negative or uncertain results for the same product. Voluntary submissions under section 402(j)(4)(A) of the PHS Act only trigger the required submission of clinical trial information for clinical trials that are applicable clinical trials (e.g., not phase 1 trials of a drug or small feasibility studies of a device) that were not required to be submitted to ClinicalTrials.gov under sections 402(i) or 402(j) of the PHS Act (e.g., those applicable clinical trials that were initiated on or before September 27, 2007, and reached their completion date prior to December 26, 2007).

One challenge in implementing this provision of section 402(j)(4)(A) of the PHS Act is that a responsible party who voluntarily submits clinical trial information about a clinical trial may not know at the time the voluntary submission is made which applicable clinical trials subsequently will be required to be included in a marketing application or premarket notification to FDA for the product for the use studied in the voluntarily-submitted clinical trial. Such a marketing application could be submitted many years after the completion date of the voluntarily-submitted clinical trial. Another challenge is that the responsible party for the voluntarily-submitted clinical trial might not be the responsible party for some or any of the applicable clinical trial(s) for which the submission of clinical trial information is triggered by the voluntary submission. As such, the responsible party voluntarily submitting clinical trial information for a clinical trial under section 402(j)(4)(A) of the PHS Act may not be aware of the triggered applicable clinical trial(s) and/or may not have access to the clinical trial information required to be submitted for such trials. In addition, a manufacturer who ultimately submits a marketing application or premarket notification may not be the responsible party for all of the applicable clinical trials that are required to be included in the marketing application or premarket notification, and might not have access to clinical trial information for those clinical trials.

To address these concerns, we propose in § 11.60(a)(2)(ii) to require a submission of clinical trial information for any triggered trials (i.e., for applicable clinical trials required to be included in a marketing application or premarket notification to FDA for approval, licensure, or clearance of the drug or device and that study the same use studied in the voluntarily-submitted clinical trial) only when the responsible party for the voluntarily-submitted clinical trial is also the manufacturer submitting the marketing application or premarket notification. This approach would reduce the likelihood of a responsible party making selective voluntarily submissions, consistent with our understanding of the intent of section 402(j)(4)(A) of the PHS Act, while ensuring that a responsible party would not be required to submit clinical trial information for a triggered applicable clinical trial for which he or she is not also the responsible party and does not have access to the relevant data. This approach also would avoid a situation in which one responsible party would be unaware that its clinical trials are subject to the requirements of section 402(j)(4)(A) of the PHS Act by virtue of a previous voluntary submission of clinical trial information made by another responsible party. We request public comment on our proposed approach in § 11.60(a)(2)(ii).

Section 402(j)(4)(A) of the PHS Act does not specify when information from each triggered applicable clinical trial must be submitted to ClinicalTrials.gov. At the time clinical trial information is submitted for a voluntarily-submitted clinical trial, a marketing application or premarket notification that includes such triggered trials may or may not have been submitted to FDA; thus, it may not be apparent at the time the voluntarily-submitted clinical trial is submitted to ClinicalTrials.gov which applicable clinical trials are triggered

under section 402(j)(4)(A) of the PHS Act. Therefore, rather than requiring information on the triggered applicable clinical trials to be submitted at the time the clinical trial information is submitted for the voluntarily-submitted clinical trial, we propose in § 11.60(a)(2)(iv)(B), that the information be submitted not later than the date on which the application or premarket notification is submitted to FDA or the date on which clinical trial information is submitted for the voluntarily-submitted clinical trial to ClinicalTrials.gov, whichever is later. This approach would prevent a responsible party from having to submit information for a clinical trial that is not subsequently included in the marketing application or premarket notification. We note that, in many cases, we expect that a triggered applicable clinical trial will have reached its completion date by the time clinical trial information for the voluntarily-submitted clinical trial is submitted because, given the scope of applicable clinical trials subject to 402(j) or the PHS Act, generally, most or all applicable clinical trials for which submission would be triggered by a voluntary submission would have been initiated on or before September 27, 2007, and reached their completion dates prior to December 26, 2007.

Proposed § 11.60(a)(2)(iii) specifies which clinical trial information must be submitted for a triggered applicable clinical trial. Section 402(j)(4)(A) requires that the responsible party submit ''clinical trial information'' for all triggered applicable clinical trials. Because section 402(j)(1)(A)(iv) of the PHS Act defines ''clinical trial information'' to mean ''. . . those data elements that the responsible party is required to submit under paragraph (2) [clinical trial registration information] or under paragraph (3) [clinical trial results information],'' the information required to be submitted for a triggered applicable clinical trial could include registration information, results information, or both. The construction of this requirement mirrors that in section 402(j)(4)(A) of the PHS Act, which specifies that clinical trial information that is voluntarily submitted to ClinicalTrials.gov may consist of registration information or results information. Hence, we propose that the type(s) of clinical trial information required to be submitted for a triggered applicable clinical trial be, at minimum, the same as that for the voluntarily-submitted clinical trial. In other words, if a responsible party voluntarily submits registration information for a clinical trial pursuant to section 402(j)(4)(A) of the PHS Act and proposed § 11.60(a), the responsible party must submit complete registration information specified under proposed § 11.28(a) for any triggered applicable clinical trial(s). Likewise, if a responsible party voluntarily submits results information for a clinical trial pursuant to section 402(j)(4)(A) of the PHS Act and proposed § 11.60(a), then the responsible party must submit complete results information specified under proposed §§ 11.60(a)(2)(i)(B) for any triggered applicable clinical trial(s). Because the submission of clinical trial information for a triggered applicable clinical trial is a condition of voluntary registration under section 402(j)(4)(A) of the PHS Act, the Agency does not propose to treat the submission of such information as a voluntary submission under section 402(j)(4)(A) or proposed § 11.60(a)(2)(ii) that itself could trigger the submission of clinical trial information for other applicable clinical trials. However, as indicated in proposed § 11.60(a)(2)(v), responsible parties who voluntarily submit clinical trial information to ClinicalTrials.gov would be required to update submitted information, including information submitted for triggered trials, in accordance with proposed § 11.64. As noted in section IV.C.5 of this preamble, clinical trial information submitted under proposed § 11.60 will be posted on ClinicalTrials.gov as soon as practicable after it has been submitted and reviewed as part of our quality review procedures. Corrections would be required, in accordance with proposed § 11.66.

We clarify that because section 402(j)(4)(A) of the PHS Act has been in effect since September 27, 2007, any voluntarily-submitted clinical trial submitted on or after September 27, 2007, is subject to the requirements of section 402(j)(4)(A) of the PHS Act. We interpret the relevant marketing application or premarket notification under section 402(j)(4)(A) of the PHS Act to be any marketing application or premarket notification submitted to FDA on or after September 27, 2007. However, we propose that the requirements of proposed § 11.60 apply only to clinical trial information submitted to ClinicalTrials.gov on or after the effective date of this rule. We do not propose to impose the requirements of proposed § 11.60 with respect to any voluntarily-submitted clinical trial or any triggered applicable clinical trial that was submitted under section 402(j)(4)(A) of the PHS Act, prior to the effective date. The Agency is aware that many clinical trials were registered on a voluntary basis at ClinicalTrials.gov before publication of this proposed rule in an effort to comply with other policies (e.g., the policy of the ICMJE), to enhance recruitment, or to enhance transparency related to such clinical trials. To the extent that a responsible party complied with section 402(j)(4)(A) of the PHS Act prior to the effective date of the final rule, we do not believe it is reasonable to require the responsible party to comply with the requirements of proposed § 11.60.

Proposed § 11.60(b) specifies the text of ''a statement to accompany the entry for an applicable clinical trial when the primary and secondary outcome measures for such clinical trial are submitted under [section 402(j)(4)(A) of the PHS Act] after the date specified for the submission of such information in paragraph (2)(C) [clinical trial registration information submission].'' (See section 402(j)(3)(D)(v)(V) of the PHS Act.) Because primary and secondary outcome measures are data elements under both clinical trial registration and results information (See sections 402(j)(2)(A)(ii)(I)(ll) and (3)(C)(ii).), we interpret section 402(j)(3)(D)(v)(V) of the PHS Act to require submissions of registration information or results information under section 402(j)(4)(A) of the PHS Act and/or proposed § 11.60(a) for applicable clinical trials to be accompanied by a statement to clarify that the submission was not subject to the deadlines imposed by section 402(j) of the PHS Act for registration and results information. The required statement would apply to any applicable clinical trial, including any triggered applicable clinical trial, submitted under section 402(j)(4)(A) of the PHS Act and proposed § 11.60(a). Accordingly, the proposed statement is as follows: ''Clinical trial information for this applicable clinical trial was submitted under section 402(j)(4)(A) of the PHS Act and 42 CFR 11.60 and is not subject to the deadlines established by sections 402(j)(2) or (3) of the Public Health Service Act or 42 CFR 11.24 or 11.44.''

2. What requirements apply to applicable clinical trials for which submission of clinical trial information has been determined by the Director to be necessary to protect the public health—§ 11.62

Proposed § 11.62 implements the requirement in section 402(j)(4)(B) of the PHS Act for submission of clinical trial information if the Director determines that the posting of such information on ClinicalTrials.gov is necessary to protect the public health.

Section 402(j)(4)(B)(i) of the PHS Act specifically authorizes the Secretary to ''require by notification'' the submission of clinical trial information ''in any case in which the Secretary determines for a specific clinical trial [. . .] that posting in the registry and results data bank of clinical trial information for such clinical trial is necessary to protect the public health.'' This authority has been delegated to the Director of NIH (74 FR 19973, Apr. 30, 2009). If the Director so determines, clinical trial information must be submitted for that clinical trial in accordance with sections 402(j)(2) and (3) of the PHS Act, except with regard to timing requirements. With respect to timing, such clinical trial information must be submitted to ClinicalTrials.gov ''not later than 30 days after the date specified by the [Director] in the notification,'' unless the responsible party submits a certification for delayed results submission under section 402(j)(3)(E)(iii) of the PHS Act. (See section 402(j)(4)(B)(i)(II) of the PHS Act.) Proposed § 11.62(a) implements this provision by requiring the responsible party for an applicable clinical trial who receives notification pursuant to section 402(j)(4)(B) of the PHS Act that the Director has determined that posting of clinical trial information is necessary to protect the public health to submit such information to ClinicalTrials.gov in accordance with proposed § 11.62(c). We invite public comment on the types of situations in which the posting of clinical trial information might be necessary to protect the public health and on the criteria that the Director should consider when making such a determination.

Proposed § 11.62(b) implements section 402(j)(4)(B)(ii) of the PHS Act, which specifies that the types of clinical trials subject to this provision are limited to those that are: (1) ''an applicable clinical trial for a drug that is approved under section 505 of the Federal Food, Drug, and Cosmetic Act or licensed under section 351 of this Act or for a device that is cleared under section 510(k) of the Federal Food, Drug, and Cosmetic Act or approved under section 515 or section 520(m) of such Act, whose completion date is on or after the date 10 years before the date of the enactment of the Food and Drug Administration Amendments Act of 2007;'' or (2) ''an applicable clinical trial that is described by both by paragraph (2)(C) and paragraph (3)(D)(ii)(II)) [sic].'' As explained in section III.D of this preamble, we interpret the approval status of a product studied in an applicable clinical trial (i.e., either ''unapproved, unlicensed, or uncleared'' or ''approved, licensed, or cleared'') to be the approval status of the product on any given date. In this context, we interpret the approval status of the product to be the approval status on the date that the Director notifies the responsible party that clinical trial information must be submitted to ClinicalTrials.gov for an applicable clinical trial under proposed § 11.62. The clinical trials specified in (1) would consist of applicable clinical trials of approved, licensed, or cleared drugs (including biological products) or devices that reached their completion dates on or after September 27, 1997. We note that this set of clinical trials would include applicable clinical trials that reach their completion dates on or after the date of enactment of FDAAA, many of which already would be subject to the registration and results submission requirements of section 402(j) of the PHS Act, with the exception of applicable clinical trials that were initiated prior to the date of enactment of FDAAA (i.e., September 27, 2007) and were not ongoing as of December 26, 2007. The clinical trials specified in (2) would consist of applicable clinical trials that are required to register at ClinicalTrials.gov pursuant to section 402(j)(2)(C) of the PHS Act and proposed § 11.22(a) of this part and that study drugs (including biological products) or devices that are unapproved, unlicensed, or uncleared by FDA (regardless of whether or not approval, licensure, or clearance was sought). This set of clinical trials would consist of registered applicable clinical trials that are not required to submit clinical trial results information to ClinicalTrials.gov under section 402(j) of the PHS Act because they are not subject to the results provision in section 402(j)(3)(C) of the PHS Act. However, many of these applicable clinical trials would be required to submit results information under this proposed rule. (See, e.g., proposed § 11.42 and the discussion of effective date implementation in section III.D of this preamble.)

Proposed § 11.62(c) specifies which information must be submitted to ClinicalTrials.gov and the timelines for submitting such information pursuant to a notification from the Director under section 402(j)(4)(B)(i) of the PHS Act. In general, we interpret the references to ''clinical trial information'' in section 402(j)(4)(B)(i) of the PHS Act and submission ''in accordance with paragraphs (2) and (3)'' in section 402(j)(4)(B)(i)(I) of the PHS Act to mean registration information and results information as enumerated in proposed §§ 11.28(a) and 11.48(a). Consistent with section 402(j)(4)(B)(i)(II) of the PHS Act, such information generally must be submitted ''not later than 30 days after the date specified by the [Director] in the notification.'' We are interpreting ''the date specified . . . in the notification'' to mean the date established by the Director for submission of clinical trial information under proposed § 11.62. We note that section 402(j)(4)(B)(i)(II) of the PHS Act permits an exception to the submission deadline if a certification for delayed results submission is submitted not later than 30 days after the submission date specified by the Director in the notification and in accordance with section 402(j)(3)(E)(iii) of the PHS Act. Because a certification under section 402(j)(3)(E)(iii) of the PHS Act would delay only the submission of results information, we propose that if the responsible party has submitted such a certification, only the submission of results information may be delayed. Accordingly, if a responsible party for an applicable clinical trial subject to proposed § 11.62 submits a certification under section 402(j)(3)(E)(iii) of the PHS Act not later than 30 calendar days after the submission date specified in the Director's notification, the responsible party still would be required to submit registration information not later than 30 calendar days after the submission date specified in the notification, although results information would be required to be submitted by the applicable deadline established under proposed §§ 11.44(b) or (c).

To clarify the submission requirement in those situations in which registration information was submitted to ClinicalTrials.gov before a notification under section 402(j)(4)(B)(i)(I) of the PHS Act was sent to the responsible party, we indicate in proposed § 11.62(c)(3) that the registration information must be updated, if necessary, not later than 30 calendar days after the submission date specified in the notification. Notwithstanding this initial update, we propose that the requirements of proposed § 11.64 would apply to clinical trial information submitted pursuant to proposed § 11.62.

All clinical trial information submitted to ClinicalTrials.gov under proposed § 11.62 would be subject to the quality review procedures described in section III.C.12 of this preamble. We would intend to post such information as soon as practicable after it has completed quality review. This timeline for posting would apply to all clinical trial information submitted under

proposed § 11.62, including registration information for an applicable clinical trial of a device that has not previously been approved or cleared by FDA. Section 402(j)(4)(B) of the PHS Act applies equally to applicable clinical trials of drugs and devices that are approved, licensed, or cleared or are unapproved, unlicensed, or uncleared. It applies to ''any case'' in which the Director, as delegated by the Secretary, determines that posting of clinical trial information in ClinicalTrials.gov—not just submission of the information to ClinicalTrials.gov—is necessary to protect public health. Although section 402(j)(4)(B) of the PHS Act specifically allows for a delay in submission of results information if the responsible party submits a certification for delayed results submission under section 402(j)(3)(E)(iii) of the PHS Act, it does not specifically delay or prohibit posting submitted registration information until a device is cleared or approved. We therefore believe that registration information for all applicable clinical trials subject to section 402(j)(4)(B) of the PHS Act may be posted as soon as practicable after it has completed quality review, regardless of the approval, licensure, or clearance status of the devices studied.

We do not interpret the waiver provisions in section 402(j)(3)(H) of the PHS Act or proposed § 11.54 to permit a responsible party to request a waiver of the requirement to submit clinical trial information pursuant to a notification from the Director under section 402(j)(4)(B) of the PHS Act or proposed § 11.62. The waiver provisions in section 402(j)(3)(H) of the PHS Act and proposed § 11.54 apply only to submissions of results information that would be required by section 402(j)(3) of the PHS Act or proposed subpart C. We invite public comment on this proposed interpretation.

3. When must clinical trial information submitted to ClinicalTrials.gov be updated?—§ 11.64

Proposed § 11.64 establishes requirements for updating clinical trial information that has been submitted to ClinicalTrials.gov. Section 402(j)(4)(C)(i) of the PHS Act requires responsible parties for applicable clinical trials to submit updates to ClinicalTrials.gov to reflect changes to previously submitted registration information. Section 402(j)(4)(C)(i)(I) of the PHS Act provides that, in general, updates must be made ''not less than once every 12 months, unless there were no changes to the clinical trial information during the preceding 12-month period.'' Section 402(j)(4)(C)(i)(III) of the PHS Act specifies that the responsible party must update recruitment status not later than 30 days after a change in the recruitment status of a registered applicable clinical trial, and section 402(j)(4)(C)(i)(IV) of the PHS Act specifies that the responsible party must update the completion date not later than 30 days after the completion date of the applicable clinical trial. We believe the shorter update time frames specified for these two elements of registration information in section 402(j)(4)(C) of the PHS Act are intended to help ensure that information in ClinicalTrials.gov of particular importance to prospective human subjects is updated in a timely fashion. Section 402(j)(4)(C)(i)(II) of the PHS Act indicates updates to submitted clinical trial information ''shall include identification of the dates of any such changes.''

In addition, section 402(j)(3)(D)(v)(IV) of the PHS Act requires the Secretary to establish, by regulation, ''the appropriate timing and requirements for updates of clinical trial information.'' Pursuant to this authority, we propose to modify the updating requirements under section 402(j)(4)(C)(i) of the PHS Act. First, we propose to require updates for all clinical trials that are subject to section 402(j) of the PHS Act and/or this proposed rule with a record in ClinicalTrials.gov, not just the applicable clinical trials that are specified in section 402(j)(4)(C)(i) of the PHS Act. This would include those clinical trials for which clinical trial information was voluntarily submitted under section 402(j)(4)(A) of the PHS Act and/or proposed § 11.60 and those for which clinical trial information was required to be submitted to protect the public health under section 402(j)(4)(B) of the PHS Act and/or proposed § 11.62. Second, we propose to require updates for all clinical trial information submitted to ClinicalTrials.gov. This would include the registration information that is referenced in section 402(j)(4)(C)(i) of the PHS Act, the additional registration data elements, and expanded access record information proposed in § 11.28, and results information.

Proposed § 11.64(a)(1) establishes a general requirement for responsible parties to update clinical trial information not less than once every 12 months if there are changes to any of the data elements previously submitted. We emphasize that this requirement to update clinical trial information not less than once every 12 months includes a requirement to update the estimated Completion Date data element, unless there have been no changes in the preceding 12 months. The public should be able to rely upon the accuracy of this date to assist them in determining when results information may be available on ClinicalTrials.gov. In general, we recommend that the complete clinical trial record in ClinicalTrials.gov be reviewed not less than once every 12 months to help ensure that the clinical trial information it contains remains accurate. Proposed § 11.64(a)(2) specifies that updates to clinical trial information must be submitted until the date on which all required clinical trial results information has been submitted to ClinicalTrials.gov, meaning results for all primary and secondary outcome measures and all adverse events collected in accordance with the protocol. After that time, submitted clinical trial information would continue to be subject to the corrections provisions in proposed § 11.66, and responsible parties would be required to submit corrected information when the responsible party becomes aware of any errors or needed corrections in the clinical trial information.

Proposed § 11.64(b) establishes requirements for a responsible party to update certain clinical trial information more rapidly after a change in the status or conduct of a clinical trial or pediatric postmarket surveillance of a device. We recognize that it would be impractical and potentially burdensome to responsible parties to require rapid updates to all clinical trial information data elements each time a change occurs, but section 402(j) of the PHS Act requires more rapid changes of some elements, and we believe that changes to other data elements are sufficiently time-sensitive to require updates more rapidly than once every 12 months.

Proposed § 11.64(b)(1) would require that the following data elements be updated not less than 30 days after a change has occurred:

(1) Study Start Date. We propose that the Study Start Date data element be updated not later than 30 calendar days after the first human subject is enrolled in the clinical trial. This requirement would apply to clinical trials for which an estimated study start date was provided at the time of registration, rather than an actual study start date, i.e., clinical trials that were registered prior to enrollment of the first human subject. The update would ensure that potential human subjects know in a timely fashion that recruitment has begun. It also would ensure that the record reflects the actual start date, as opposed to an estimated start date, and it would provide a mechanism to demonstrate whether a clinical trial had

been registered not later than 21 days after enrollment of the first subject.

(2) Intervention Name(s). We propose that the Intervention Name(s) data element be updated to a non-proprietary name not later than 30 calendar days after a non-proprietary name is established for an intervention studied in a clinical trial. Intervention Name is frequently used as a search term to identify and retrieve clinical trials of interest. If it is not updated for as long as a year, users of ClinicalTrials.gov would not be able to accurately retrieve trials of interest during that time or to easily compare information among multiple trials of the same intervention.

(3) Availability of Expanded Access. We propose that the clinical trial information submitted under the Availability of Expanded Access data element in proposed § 11.10(b)(29) be updated not later than 30 calendar days after an expanded access program is initiated or terminated, or an NCT number is assigned to an expanded access record. This data element informs patients whether access to a drug to treat serious or life-threatening diseases or conditions is available outside of the clinical trial. Expanded access may not be available at the time a clinical trial is registered, and an expanded access program may be terminated on a date other than the completion date of the clinical trial. We therefore propose three specific update requirements:

First, for clinical trials registered on or after the effective date of this regulation, we propose that when an expanded access program for a particular drug is implemented after the clinical trial(s) of that drug is (are) registered, the responsible party must change the indication in proposed § 11.10(b)(29)(i) of whether there is expanded access to the drug not later than 30 calendar days after expanded access becomes available.

Second, we propose that not later than 30 calendar days after the initiation of the expanded access program, the responsible party must create an expanded access record by submitting the data elements required under proposed § 11.28(c), unless an expanded access record for the drug already was already created by another responsible party. The responsible party would be required to enter the NCT number of the expanded access record in the relevant clinical trial record(s) not later than 30 calendar days after the date on which the responsible party receives such NCT number. In the event that there are multiple clinical trials of the same drug that is available through an expanded access program, the responsible party who first changes the Availability of Expanded Access data element from ''yes'' to ''no'' would be required to create the expanded access record under proposed § 11.28(c); once the NCT number is assigned, responsible parties for other clinical trials of that drug would be required to update their clinical trial records by changing the Availability of Expanded Access data element and providing the NCT number. We would expect the sponsor to inform these relevant responsible parties that an expanded access record has been created and provide them with the NCT number.

Third, we propose that if expanded access is terminated, a responsible party must update the Availability of Expanded Access data element not later than 30 calendar days after termination of the program. We note that the expanded access record, including the NCT number, would remain available in ClinicalTrials.gov as archived information. We would expect the sponsor to inform relevant responsible parties that the drug is no longer available through an expanded access program so that the responsible parties may update their clinical trial records accordingly. To help sponsors and responsible parties in this process, we could consider developing procedures to send electronic notification to responsible parties of all applicable clinical trials that list the NCT number of the expanded access record of the discontinued terminated expanded access program.

Consistent with the discussion in the Effective Date/Compliance Date in section III.D of this preamble, the responsible party for an applicable clinical trial that is registered under section 402(j) of the PHS Act and reaches its completion date prior to the effective date of this regulation would be required to update the expanded access program information required under section 402(j)(2)(A)(ii)(II)(gg) of the PHS Act not later than 12 months after a change in the availability of expanded access, as specified in the updating requirement in section 402(j)(4)(C) of the PHS Act. The responsible party of such a clinical trial would not be subject to the requirement to submit the expanded access record data elements listed in proposed § 11.28(c) or to update them as specified in proposed § 11.64. If a responsible party registers an applicable drug clinical trial prior to the effective date of the regulation, however, and such trial is ongoing after the effective date of the regulation, the responsible party would need to submit the necessary expanded access program information by the compliance date for the clinical trial registration information in the databank to comply with proposed § 11.28(c). In addition, the responsible party would be subject to the requirement to provide updates to expanded access program information within 30 calendar days of any change, consistent with proposed § 11.64(b).

(4) Expanded Access Status. We propose that Expanded Access Status, under § 11.28(c)(2)(iv), must be updated not later than 30 calendar days after a change in the status of an expanded access program, whether or not access to the investigational drug or device is currently available. This data element plays a role in expanded access programs that is similar to the role of Overall Recruitment Status in applicable clinical trials, indicating whether a particular expanded access program is still open to participants. We believe that a timely update of any change in status is important to have reflected in the data bank and is consistent with the requirement in section 402(j)(4)(C)(III). Note that we propose to apply this update requirement to expanded access records that are submitted voluntarily (e.g., for an expanded access record submitted for an applicable device clinical trial) as well as to those that are required to be submitted under this part.

(5) Overall Recruitment Status. We propose that the Overall Recruitment Status data element be updated not later than 30 days after a change in the overall recruitment status of the clinical trial. This proposal is consistent with section 402(j)(4)(C)(i)(III) of the PHS Act. We believe that changes in recruitment status should be communicated promptly so that potential human subjects can know whether or not a clinical trial is currently recruiting subjects.

In addition, we propose that if Overall Recruitment Status is updated to ''suspended,'' ''terminated,'' or ''withdrawn,'' the responsible party must at the same time provide information for the Why Study Stopped data element. We believe that suspension, termination, and withdrawal of a clinical trial are significant changes that should be communicated promptly to prospective human subjects, along with the reason for the change. We propose to allow a responsible party to enter this information as free-text so that he or she has flexibility to explain the reason(s) why a clinical trial stopped prematurely. We believe such information is consistent with the statutory objective in section 402(j)(2)(A)(i) of the PHS Act to enable

users ''to track subsequent progress of clinical trials.''

Similarly, we propose that if Overall Recruitment Status is updated to ''terminated'' or ''active, not recruiting,'' the responsible party also must update the Actual Enrollment data element. In either of these situations, recruitment of human subjects is complete. As explained in more detail in section IV.B.4 of this preamble, submission of actual enrollment information will provide users of ClinicalTrials.gov with a mechanism for tracking the progress of registered clinical trials by enabling comparison of the actual enrollment information with the target or estimated enrollment information. More rapid updating is expected to contribute to more accurate reporting of the Actual Enrollment information and to permit users of ClinicalTrials.gov to know more quickly whether the clinical trial achieved its target enrollment.

(6) Individual Site Status. We propose that Individual Site Status be updated not later than 30 calendar days after a change in status of any individual site. We believe this proposal is consistent with the requirement in section 402(j)(4)(C)(III) of the PHS Act. It also supports the purpose of ClinicalTrials.gov to ''enhance patient enrollment'' (See section 402(j)(2)(A)(I) of the PHS Act) by assisting potential human subjects who search for clinical trials by location and wish to retrieve information about only those trials that are open to recruitment in specified locations.

(7) Human Subjects Protection Review Board Status. We propose that Human Subjects Protection Review Board Status be updated not later than 30 calendar days after a change in Human Subjects Protection Review Board Status. Because such information is intended to demonstrate to potential human subjects whether a registered applicable clinical trial or other clinical trial has undergone necessary human subjects protection review board review, has received necessary approvals for human subjects research, or was exempt from such review, we believe it must be updated in a timely fashion.

(8) Completion Date. Pursuant to section 402(j)(4)(C)(i)(IV) of the PHS Act, proposed § 11.64(b) specifies that the Completion Date data element must be updated not later than 30 calendar days after a clinical trial reaches its actual completion date.

(9) Responsible Party, by Official Title. We propose the Responsible Party, by Official Title data element be updated not later than 30 calendar days after a change in either the name of the responsible party of in the responsible party's official title. We believe this update is necessary to enable NIH and other users of the data bank to accurately identify the responsible party for the clinical trial.

(10) Responsible Party Contact Information. Consistent with (9) above, we propose that Responsible Party Contact Information be updated not later than 30 days after a change in the responsible party or the responsible party's contact information. Given that the responsible party must make updates to clinical trial information and, in general, must submit clinical trial results information, we consider it essential to know of changes to the responsible party and to responsible party contact information in a timely manner. Up-to-date information about the responsible party would ensure that the Agency has contact information for the appropriate person responsible for submitting clinical trial information about the applicable clinical trial or clinical trial.

In addition, we propose in § 11.64(b)(2) that responsible parties be required to update the U.S. FDA Approval, Licensure, or Clearance Status data element not later than 15 calendar days after a change in the approval, licensure, or clearance status of the product under study. Products may appear in the market place or manufacturers may announce the pending availability of a product soon after they receive FDA approval, licensure, or clearance. We believe that a prompt update to the information in ClinicalTrials.gov is necessary to help avoid confusing users who seek information about a drug or device in ClinicalTrials.gov after finding the product in the market place (e.g., after being prescribed a new drug) or finding other public information about it (e.g., a news release announcing a new product). In addition, a shorter update period for this data element would enable users to better anticipate when clinical trial results information would be due for an applicable clinical trial. Furthermore, a change in the approval or clearance status of a device can trigger a requirement for the Agency to post previously-submitted clinical trial registration information within 30 days of the change in status. Updating the U.S. FDA Approval, Licensure, or Clearance Status data element not later than 15 calendar days would provide the Agency timely notice that it must post publicly clinical trial registration information.

In § 11.64(b)(3) we propose that relevant clinical trial registration information be updated not later than 30 calendar days after a protocol amendment is approved by a human subjects protection review board, if the protocol is amended in such a manner that changes are communicated to participants in the applicable clinical trial or other clinical trial. We believe that protocol amendments that are communicated to enrolled participants could be important to those considering enrollment and should be communicated quickly through an update to the record in ClinicalTrials.gov. Rapid updating of this information would be consistent with the stated purpose of ClinicalTrials.gov to ''enhance patient enrollment and provide a mechanism to track subsequent progress of clinical trials.'' (See section 402(j)(2)(A) of the PHS Act.) If such key changes were not reflected in the record in ClinicalTrials.gov for as long as 12 months after the change, the value of ClinicalTrials.gov as a source of reliable, accurate information for the public and potential participants in clinical trials would be compromised. We recognize that other thresholds could be used to determine which protocol changes are significant enough to warrant 30-day updating of affected clinical trial information. For example, updating of relevant data elements could also be required any time a protocol amendment is reported to a human subjects protection review board. We invite public comments on our proposed approach and alternatives.

In § 11.64(b)(4), we propose that the Record Verification Date must be updated any time the responsible party reviews the complete set of submitted clinical trial information for accuracy, even if no other updated information is submitted at that time. The record verification date is intended to demonstrate when the information in ClinicalTrials.gov for a particular clinical trial was last checked for accuracy. As noted in section IV.B.4 of this preamble, a responsible party would be required to update the Record Verification Date if he or she examines the complete set of submitted clinical trial information as part of a monthly or annual review, even if he or she determines that no additional or updated information needs to be submitted. Similarly, the responsible party would be required to update the Record Verification Date data element if he or she updates a data element and reviews the rest of the record for accuracy. However, the responsible party would not be required to update the Record Verification date if he or she submits updates to one or more data elements without reviewing the

accuracy of the rest of the record. This proposal would not require a responsible party to review records more frequently or regularly than would be needed in order to update submitted information as otherwise required by proposed § 11.64, but it would require that the Record Verification Date be updated if the complete record were reviewed for accuracy during such an update. Doing so would indicate to users of ClinicalTrials.gov the currency of the information and provide an additional assurance that it is not out-of-date.

In addition, we propose in § 11.64(c) that responsible parties update clinical trial registration information at the time they submit clinical trial results information to ClinicalTrials.gov (unless there are no changes to the clinical trial registration information). This requirement is intended to help ensure the consistency and accuracy of information in the registry and results portions of the data bank. Updated registration information would then be used to pre-populate certain data elements in the clinical trial record so that responsible parties do not have to enter them again. Because the submission and subsequent posting of clinical trial results information is often a reason for users to retrieve the record for a particular clinical trial, the additional update requirement will also ensure that users have access to complete registration and results information that is up-to-date and internally consistent.

We note that the updating requirements under proposed § 11.64 would be prompted by changes in the clinical trial and not by changes in the information submission requirements for ClinicalTrials.gov or the form and manner in which data must be submitted to ClinicalTrials.gov. For example, if clinical trial results information were submitted prior to the effective date of the rule consistent with the requirements of section 402(j)(3)(C) of the PHS Act, the responsible party would not be required as a result of the updating requirements to submit clinical trial results information for the expanded results data elements required under proposed § 11.48. Similarly, if the Agency were to make administrative changes to the manner in which clinical trial information is submitted to ClinicalTrials.gov after the responsible party has submitted clinical trial information in accordance with section 402(j) of this PHS Act and this proposed part, the Agency's revisions to ClinicalTrials.gov would not themselves give rise to a requirement that the responsible party update the applicable clinical trial information. For example, if the Agency added additional options to a drop-down menu for a particular data element, even if one of the additional options would be more appropriate with respect to an applicable clinical trial, the responsible party would not be required to update its previously-submitted clinical trial information, although they could do so voluntarily. However, if a responsible party makes a required update to previously submitted clinical trial information, e.g., to reflect a change in the conduct or progress of a clinical trial, he or she would be required to submit the updated information in the form and manner required by ClinicalTrials.gov at the time the update is submitted. For example, if the set of options in a drop-down menu had changed since the information had previously been submitted, the responsible party would be required to select from the new set of options.

Updates to clinical trial registration information and clinical trial results information will be posted in accordance with proposed §§ 11.35 and 11.52, respectively. Previously submitted clinical trial information will remain publicly available through the ClinicalTrials.gov archive. See proposed § 11.64(d)(1) and (2).

4. What are the requirements for corrections of clinical trial information?—§ 11.66

Proposed § 11.66 sets out requirements for responsible parties to correct clinical trial information submitted to ClinicalTrials.gov. This would include clinical trial information voluntarily submitted under section 402(j)(4)(A) of the PHS Act and/or proposed § 11.60 as well as clinical trial information necessary to protect the public health and submitted under section 402(j)(4)(B) of the PHS Act and/or proposed § 11.62. We consider corrections of information to be different from updates to information, as described in proposed § 11.64. In our view, updates modify clinical trial information to reflect changes in the status or conduct of an ongoing clinical trial or the associated analysis. Corrections revise submitted clinical trial information that is found to be false, invalid, incorrect, inconsistent, or incomplete.

Proposed § 11.66 addresses several types of corrections. First, § 11.66(a) addresses corrections of errors, or misstatement of facts that are found to be incorrect. Errors include, but are not limited to: Inadvertent, typographical errors, such as transpositions of numbers or characters; or inadvertent omissions of data, such as omission of one component of set of participant exclusion criteria. They also include submitted values that are demonstrably wrong, such as an outcome measure indicating more than 24 hours per day of a given value. We expect to detect some such errors during the quality review procedures described in section III.C.12 of this preamble and may identify others in the course of operating the data bank. We intend to inform responsible parties of errors we identify so that they may be corrected. Responsible parties may also detect errors when reviewing submitted information, or they may be alerted to potential errors by other parties. As indicated in proposed § 11.66(a), we would require responsible parties to correct identified errors not later than 15 calendar days after becoming aware of them, whether they identify the errors themselves, or whether we inform them of errors we have detected, such as through our quality assurance procedures, whichever is earlier.

Second, § 11.66(b) addresses corrections to information that is falsified or based on falsified information. Consistent with FDA's proposed use of the term ''falsification of data'', we consider ''information that is falsified or based on falsified information'' to mean information that was created, altered, recorded, or omitted in such a way that the data do not represent what actually occurred in the clinical trial. (See 75 FR 7414, Feb. 19, 2010.) Examples of information that are falsified or based on falsified information include, but are not limited to, the following (based on examples in 75 FR 7414, Feb. 19, 2010):

(1) Created information that was never obtained (e.g., the values submitted for a primary outcome measure were made up or based on participant-level data that were made up; the actual enrollment value submitted includes subjects who did not exist or were not actually enrolled in the clinical trial).

(2) Information that was altered by replacing original information with something different that does not accurately reflect study conduct or results (e.g., the value submitted for a baseline characteristic is changed to a less extreme deviation from normal or is based on individual measures of the baseline characteristic that were changed be less extreme deviations from normal).

(3) Information that was recorded or obtained from a human subject in a way that does not accurately reflect the study protocol (e.g., a submitted outcome measure is based on measurements from subjects who were given a different dose

of an experimental drug than that specified in the protocol and the ClinicalTrials.gov record).

(4) Omitted information that was obtained and would be appropriate for submission based on study design and conduct (e.g., values are not submitted for a secondary outcome measure for which data were collected during the clinical trial or the values submitted for the secondary outcome measure do not include outcomes that were measured on some subjects so the analysis yields a result that would not have been obtained had all data been analyzed).

As specified in proposed § 11.66(b), we would require a responsible party to inform the Director when a sponsor determines that information submitted to ClinicalTrials.gov was falsified or based on falsified information. The responsible party would be required to inform the Director about falsification at the same time as he or she submits corrected information or informs the Director that either correct information cannot be generated or previously submitted information is correct (i.e., the falsification did not result in incorrect information being submitted to ClinicalTrials.gov). If corrected information can be generated, we would require the responsible party to submit corrected information not later than 15 calendar days after it becomes available. If it is determined that submitted information cannot be corrected or is correct as previously submitted we would require the responsible party to notify the Director not later than 15 days after such a determination is made. For a clinical trial for which corrected data cannot be generated, we would indicate in ClinicalTrials.gov that data for such clinical trial were determined to be falsified or based on falsified information and that corrected information is not available. Such an indication would inform users of ClinicalTrials.gov of the status of the information in the record for that clinical trial. For a clinical trial for which the falsification of data does not affect the information submitted to ClinicalTrials.gov (e.g., because underlying falsified data did not contribute to the analysis of outcomes), we would not include an indication of falsification on the ClinicalTrials.gov record. Information about findings of falsification might be included in published journal articles for which Medline citations are linked from the record, in FDA information that is linked from the record, or in other publicly available information.

We recognize that, in some cases, after determining that submitted information was falsified or based on falsified information, it may take time for a responsible party to assess whether or not the information submitted to ClinicalTrials.gov was affected, determine whether any affected information can be corrected, and generate corrected information, as needed. For example, the results of the clinical trial may need to be reanalyzed after excluding data that have been falsified and the results of such reanalysis compared with previously submitted data. Under our proposal, a responsible party would be required to notify the Director of falsification only after he or she had assessed whether or not the falsification resulted in incorrect data being submitted to ClinicalTrials.gov, determined whether corrected information could be generated, and generated any needed corrections to the data. We considered, but do not include in this proposed rule, a requirement for a responsible party to provide earlier notification to the Director of a determination that information submitted to ClinicalTrials.gov had been falsified or was based on falsified information (e.g., such notification could be provided not later than 15 days after the determination is made). Following such a proposal, the responsible party would then have been required either to make a second notification stating whether the submitted information was correct as submitted or unable to be corrected or to submit corrected information. We invite public comment on the advantages and disadvantages of this alternative approach, including on the amount of time that might typically pass between determining that data have been falsified and determining whether submitted clinical trial information can be corrected or does not need correction. We specifically invite comment on the implications of the proposed approach in cases when that time period may be lengthy. We also invite comment on what, if any, information might be made make publicly available in ClinicalTrials.gov in these situations. We invite comments on all other aspects of our proposal, as well.

Third, § 11.66(c) addresses corrections necessary to address various other deficiencies in submitted information. Such deficiencies include but are not limited to inconsistencies in submitted data, for example, a mismatch between the reported number of subjects enrolled in a clinical trial and the sum of reported number of subjects assigned to different arms, and incomplete entries that are insufficient to convey their intended meaning, such as a description of an outcome measure that does not describe the measurement scale being used. We believe that requiring corrections of such information is necessary step in ensuring that the information contained in ClinicalTrials.gov is not false or misleading. We expect to identify some needed corrections during the quality review procedures described in section III.C.12 of this preamble and in the course of operating the data bank. As with errors, we plan to inform responsible parties of these needed corrections. We expect that responsible parties may also become aware of needed corrections through their own reviews of submitted data or from other parties. Proposed § 11.66(c) provides that responsible parties who become aware of needed corrections or are informed by NIH of needed corrections to clinical trial information submitted under §§ 11.28, 11.48, or 11.60 must submit corrected information as soon as possible, but not later than 15 calendar days after the date that they become aware of the need for correction or that NIH informs them of the needed correction, whichever is earlier.

Compliance with our quality control process, including the requirements set forth in § 11.66, does not necessarily constitute a legal defense to enforcement pursuant to section 301(jj) of the FD&C Act (21 U.S.C. 331) and 303(f) of the FD&C Act (21 U.S.C. 333(f)).

V. Response to Comments

Because of the large number of public comments we normally receive on **Federal Register** documents, we are not able to acknowledge or respond to them individually. We will consider all comments we receive by the date and time specified in the Dates section of this preamble, and will respond generally to the comments in the preamble to any subsequent rulemaking document.

VI. Regulatory Impact Statement

The Agency has examined the impacts of this proposed rule under Executive Order 12866, Regulatory Planning and Review, Executive Order 13563, Improving Regulation and Regulatory Review, the Regulatory Flexibility Act (5 U.S.C. 601–612) (RFA), the Unfunded Mandates Reform Act of 1995 (Public Law 104–4), and Executive Order 13132, Federalism. Executive Order 12866, as amended by Executive Order 13563, directs agencies to assess all costs and benefits of available regulatory alternatives and, when regulation is necessary, to select regulatory approaches that maximize

net benefits (including potential economic, environmental, public health and safety, and other advantages; distributive impacts; and equity). A regulatory impact analysis (RIA) must be prepared for major rules with economically significant effects ($100 million or more in any single year). The Agency estimates that the total cost of the proposed requirements to regulated entities is approximately $49.7 million annually. We believe there are intangible benefits, in the form of increased public trust in clinical research and improvements in human subjects protection, clinical care, clinical research, and product development that may result from enhanced access to clinical trial results. We believe that this proposed rule is not an economically significant regulatory action as defined by Executive Order 12866. Because of the interest in this proposed rule among regulated entities and others involved in conducting or using the results of clinical trials, we have nevertheless prepared an analysis that, to the best of our ability, estimates the costs and benefits of this proposed rule. We request comments on the economic analyses provided in this proposed rule.

The RFA requires agencies to analyze regulatory options that would minimize any significant impact of a rule on a substantial number of small entities. Because the rule is likely to impose estimated costs of approximately $6,700 per applicable clinical trial on organizations that conduct applicable clinical trials, the Agency proposes to certify that the final rule will not have a significant economic impact on a substantial number of small entities.

Section 202 of the Unfunded Mandates Reform Act of 1995 requires, among other things, that agencies prepare a written statement, which includes an assessment of anticipated costs and benefits, before proposing ''any rule that includes any Federal mandate that may result in the expenditure by State, local, and tribal governments, in the aggregate, or by the private sector, of $100,000,000 or more (adjusted annually for inflation) in any one year.'' (See 2 U.S.C. 1352(a)) The current threshold after adjustment for inflation is $141 million, based on the Gross Domestic Price deflator for 2012. The Agency does not expect this proposed rule to result in any 1-year expenditure that would meet or exceed this amount. As explained above, however, the Agency has conducted an analysis of the costs that could result from this proposed rule.

Executive Order 13132 (Federalism) establishes certain requirements that an Agency must meet when it promulgates a proposed rule (and subsequent final rule) that imposes substantial direct requirement costs on State and local governments, preempts State law, or otherwise has Federalism implications.

A. The Proposed Rule

This proposed rule would implement the provisions for the mandatory registration and submission of results information for applicable clinical trials at ClinicalTrials.gov, as required by section 402(j) of the PHS Act (42 U.S.C. 282(j)), added by section 801 of FDAAA. This proposed rule would both clarify the statutory requirements for submission of registration and results information, including adverse events information, and implement the expansion of the registry and results data bank by rulemaking as required by section 402(j)(3)(D) of the PHS Act.

B. Need for the Proposed Rule

The Agency is promulgating this proposed rule to fulfill the requirements of section 402(j) of PHS Act in a manner that will provide broad public access to pertinent clinical trial registration and results information. Section 402(j)(2)(A)(i) of the PHS Act requires the Secretary to expand the clinical trials registry data bank with respect to clinical trial information to ''enhance patient enrollment and provide a mechanism to track subsequent progress'' of the clinical trials. Sections 402(j)(3)(B) and 402(j)(3)(C) of the PHS Act instruct the Secretary to expand the clinical registry data bank not later than 1 year after enactment of FDAAA to include the results information specified in section 402(j)(3)(C) for certain applicable clinical trials. Section 402(j) of the PHS Act also requires responsible parties to submit to the expanded data bank specified registration information (i.e., descriptive information, recruitment information, location information, and administrative information) summarizing key aspects of applicable clinical trials that are subject to the law and specified results information describing the outcomes of applicable clinical trials for which the drugs or devices under study have been approved, cleared, or licensed by FDA. Section 402(j) of the PHS Act further establishes deadlines by which such information must be submitted and establishes penalties for non-compliance. This proposed rule is intended, in part, to implement the statutory requirements and clarify the Agency's interpretation of them. It clarifies the meaning of terms defined in the PHS Act (e.g., responsible party and applicable clinical trial) and of several data elements that are required to be submitted to the data bank (e.g., study design, eligibility criteria). It also exercises the authority given to the Secretary in section 402(j)(2)(iii) of the PHS Act to modify by regulation the requirements for clinical trial registration information. This proposed rule specifies several modifications to the clinical trial registration information that the Agency believes meet the statutory criteria of improving and not reducing the statutorily specified clinical trial registration information.

In addition, this proposed rule is necessary to implement provisions of section 402(j) of the PHS Act that are specifically required to be addressed by regulation. Section 402(j)(3)(I) of the PHS Act, requires the Secretary to determine by regulation the ''best method'' for including in the registry and results data bank appropriate results information on serious adverse and other adverse events collected for certain applicable clinical trials. Section 402(j)(3)(D) of the PHS Act requires, among other things, the Secretary to further expand the registry and results data bank through rulemaking to ''provide more complete results information and to enhance patient access to and understanding of the results of clinical trials.'' That section of the PHS Act specifies several topics that the rule is to address, including: Whether to require the submission of results information for applicable clinical trials of drugs and devices that previously have not been approved, licensed, or cleared by FDA; whether technical or lay summaries of a clinical trial can be included in the data bank without being misleading or promotional; and whether to require responsible parties to submit the full protocol or ''such information on the protocol . . . as may be necessary to help evaluate the results of the trial.'' This proposed rule addresses each of these topics and others specified in section 402(j) of the PHS Act.

C. Benefits of the Proposed Rule

As discussed in this preamble, the overarching aim of this proposed rule is to provide public access to a standardized set of non-technical and technical information describing the conduct and results of certain clinical trials of FDA-regulated drugs (including biological products) and devices. Access to this information will benefit not only the general public, but also other groups of people involved in improving public health. These groups of people include potential and enrolled clinical trial participants, clinical researchers, systematic reviewers, disease and

patient advocacy groups, regulators, drug and device manufacturers, health care providers, patients and their family members. Access to information contained in the data bank is intended to enhance patient enrollment in clinical trials and improve the evidence-base that informs clinical care, enhance public health and safety, increase the efficiency of drug and device development processes, and improve clinical research practice, among other uses. It is also intended to build public trust in clinical research by providing public access to the results of such research. These benefits are intangible.

D. Costs Associated With the Proposed Rule

The costs associated with this proposed rule consist of the time and effort necessary for responsible parties to comply with the proposed requirements to register applicable clinical trials; submit specified results information (including adverse event information); update and correct submitted registration and results information, as needed; submit certifications and/or extension requests to delay the deadline for submitting results information; submit information describing expanded access programs for drugs studied in an applicable clinical trial, and request waivers to any of the requirements for results submission. We do not intend this proposed rule to cause responsible parties to collect any information that was not already intended to be collected during the clinical trial (as described by the study protocol), nor do we intend this proposed rule to cause responsible parties to analyze such information in ways that were not intended, as described in the protocol or the associated statistical analysis plan. Rather, the rule specifies those elements of the collected results information and statistical analyses that must be submitted to the data bank and the format in which they must be submitted.

The calculations below present our estimates of the time and cost associated with meeting the information submission requirements of this proposed rule, including the burden associated with assembling the required information, formatting the information for submission, submitting it to the data bank, and correcting or updating it over time. The calculations break out the estimated annual costs associated with: (1) registering a trial, (2) submitting results information (including adverse event information), (3) submitting certifications, extension requests and appeals to delay the results submission deadline, (4) submitting clinical trial information that is triggered by a voluntary submission; and (5) creating expanded access records for drugs studied in an applicable clinical trial. The estimates include the costs associated with updating submitted information and with correcting errors detected by NIH. We estimate the total annual cost to be $49,713,753. As explained below, we expect that during the first year after the effective date of this proposed rule, responsible parties will incur some additional time and cost to update clinical trial information that previously was submitted to the data bank for trials that were initiated prior to the effective date and ongoing as of that date. We estimate this additional, non-recurring cost to be $2,457,080.

We expect that over time the cost of complying with this proposed rule will decline notably once a final rule is published and responsible parties become more familiar with the registration and results submission requirements as well as the data submission and review processes. Many data providers have developed standard operating procedures for data entry personnel and refined their data management systems to facilitate data submission. A number of clinical trial data management software tools currently allow users to output registration information for automatic uploading of files in bulk to ClinicalTrials.gov. We expect that once the requirements for submission of clinical trial information are clarified, responsible parties will automate portions of the data extraction and formatting processes for required results information, significantly reducing the burden of compliance with this proposed rule.

TABLE 2—ESTIMATED ANNUAL COST OF PROPOSED RULE

Provision	Proposed section(s)	Estimated annual cost prior to rulemaking	Estimated annual cost under the proposed rule	Incremental cost above pre-rule data collection
Registration of applicable clinical trials, including updates	11.28(a),(b), 11.64	$11,005,132	$11,483,616	$478,484
Results submission for applicable clinical trials, including updates.	11.48, 11.64	6,444,954	37,828,800	31,383,846
Submission of certifications, extension requests, and appeals to delay results submission.	11.44(b), (c), (e)	189,783	261,990	72,207
Triggered registration and results submission following voluntary submissions.	11.60	0	129,260	129,260
Submission of expanded access records	11.28(c).	0	10,087	10,087
Total		17,639,869	49,713,753	32,073,884

1. Registration of Applicable Clinical Trials

To estimate the costs of trial registration, we first estimated the number of applicable clinical trials that would be initiated in a given year and be subject to the provisions of this proposed rule. Using the approach described below, we estimate that a total of 7,400 applicable clinical trials of drugs (including biological products) and devices per year would be subject to the registration requirement of this proposed rule. This estimate is based on information from FDA indicating that it receives approximately 5,150 clinical trial protocol submissions annually for applicable clinical trials (76 FR 256, Jan. 4, 2011). This figure includes protocol submissions to CDER, CBER, and CDRH; it does not include clinical trials that were not conducted under an IND or IDE. To estimate the number of such clinical trials, we examined the number of clinical trials registered with ClinicalTrials.gov that appear to meet the criteria of an applicable clinical trial but do not appear to have been conducted under an IND or IDE, e.g., because they are exempt. We found approximately 1,700 and 2,000 such clinical trials in 2012 and 2013, respectively. We increased this figure to 2,250 to accommodate further growth in the number of such clinical trials that would be registered following

publication of the final rule. The sum of these figures (i.e., 5,150 plus 2,250 equals 7,400) provides an estimate of the number of applicable clinical trials that would be subject to the registration requirement of this proposed rule each year.

To calculate the burden associated with registering these clinical trials, we estimated the time required to submit complete clinical trial registration information for an applicable clinical trial. We estimate this time to be 8 hours, including time to extract information from the study protocol, reformat it, and submit it to ClinicalTrials.gov. This figure is one hour more than the estimate used in the existing OMB Paperwork Reduction Act clearance for the ClinicalTrials.gov data collection (77 FR 22579, Apr. 16, 2012) to account for the additional data elements that would be required by this proposed rule. Applying this time estimate to the estimated number of applicable clinical trials yields a burden of 59,200 hours per year for registering applicable clinical trials. Based on our previous experience, we estimate that each registration record would be updated an average of 8 times during the course of the study (e.g., to reflect changes in the conduct of the clinical trial, additions of investigational sites, recruitment status updates). Although clinical trials of long duration and with multiple sites would likely submit more updates during the course of the trial, we have found that many applicable clinical trials have a relatively short duration and a limited number of study sites, which lowers the average per clinical trial. The time required for subsequent updates of clinical trial registration information is expected to be significantly less than for the original registration (as less information must be provided) and is estimated to be 2 hours per update. Using these figures, we calculated the annual hour burden for updates to clinical trial registration information to be 118,400 hours. Combining this figure with the estimated time for initial registrations (59,200 hours) yields an estimate of the total hour burden associated with the submission and updating of clinical trial registration information of 177,600 hours per year.

To calculate the cost of registration, we examined May 2011 data from the U.S. Bureau of Labor Statistics on the average wages of workers in the pharmaceuticals and medical equipment industries who are involved typically in submitting registration information. During the time we have operated ClinicalTrials.gov, we have found that this task is generally performed by junior-level researchers or administrative staff. For purposes of this estimate we used an average hourly wage rate of $32.33, which is equivalent to the weighted 25th percentile wage of a medical scientist in the pharmaceutical and medical equipment industries and is significantly higher than the median wage of other administrative staff in those sectors who sometimes submitting registration information to ClinicalTrials.gov. We doubled these wage figures (to $64.66 per hour) to account for benefits and overhead. Using this adjusted wage figure, we calculated an estimated total annual cost of registration under the proposed rule, including updates over the course of a clinical trial, of $11,483,616 (Table 2). This figure represents an incremental increase of $478,484 per year above the estimated cost of registration under the existing OMB Paperwork Reduction Act clearance for the ClinicalTrials.gov data collection.

2. Results Submission

To estimate the burden associated with submission of clinical trial results information, we start from the premise that every clinical trial required to register in a given year would be required subsequently to submit results information. The statute requires results submission for all applicable clinical trials that study drugs (including biological products) or devices that are approved, cleared, or licensed by FDA; the proposed regulation would require, in addition, the submission of clinical results information for applicable clinical trials of drugs (including biological products) and devices that are not approved, cleared, or licensed by FDA. We therefore estimate the burden associated with results submission for a total of 7,400 applicable clinical trials of drugs (including biological products) and devices per year, recognizing that in most cases, such clinical trial results information would not be submitted in the same year as the associated clinical trial registration information but in accordance with the deadlines specified in proposed § 11.44. We expect, however, that on average the number of clinical trials for which clinical trial results information is submitted in any given year would approximate the number of new trials for which clinical trial registration information is submitted.

To estimate an average amount of time required to submit clinical trial results information, we reviewed a variety of data sources, including publicly available information from various organizations about results submission times [Ref. 45], comments made at the April 2009 public meeting (Ref. 1), responses to the burden estimates included in the current and previous OMB clearance documents (77 FR 22579, Apr. 16, 2012; 73 FR 58972, Oct. 8, 2008), feedback from respondents who tested preliminary versions of the data entry system during the summer of 2008, and feedback from those submitting data to the existing ClinicalTrials.gov system. These sources contain a wide-range of estimates, from as little as 6 hours to as long as 60 hours. We believe the differences in these estimates reflect a number of factors, including the significant variation in the complexity of applicable clinical trials, in terms of their study design, number of outcome measures (primary and secondary), statistical analyses, and adverse event information. They also reflect differences in the responsible party's familiarity with the clinical trial results information and the ClinicalTrials.gov submission process and the time they attribute to assembling the information for submission. Shorter estimates may be indicative of situations in which the responsible party already has assembled (and analyzed) the clinical trial results information for purposes of preparing a journal article or other summary report, while longer estimates may assume the clinical trial results information needs to be compiled. We expect that in most situations, the responsible party would have ready access to the necessary information because it is information that the clinical trial is conducted to collect and analyze (i.e., the information we propose for submission would have been collected during the trial, as specified in the protocol). Nevertheless, for purposes of this analysis, we selected an average time of 40 hours for initial submission of clinical trial results information, which corresponds to the higher range of estimates contained in several industry surveys and in other comments the Agency received. This figure represents an increase of 15 hours over the 25-hour estimate that was included in the most recent OMB Paperwork Reduction Act clearance for the ClinicalTrials.gov data collection and reflects the additional information that would be required to be submitted under this proposed rule. We expect the hour burden would decline as responsible parties become more familiar with ClinicalTrials.gov and implement procedures for streamlining data collection, analysis, and formatting. In the most recent OMB Paperwork Reduction Act clearance for the current ClinicalTrials.gov data collection, we

estimated that results information would be submitted for 1,845 applicable clinical trials per year, which is the estimated number of clinical trials that would have been included in marketing applications for drugs, biological products, and devices that were initially approved, licensed, or cleared by the FDA and subject to the basic results reporting provisions of FDAAA. Under this proposed rule, results information would be required for all applicable clinical trials that were subject to the registration requirement (i.e., an estimated 7,400 clinical trials per year). Applying the 40-hour figure to 7,400 applicable clinical trials per year produces a total estimated burden of 296,000 hours per year for submitting clinical trial results information. This figure compares to an estimated 46,125 hours under the current information collection.

We also estimate that, on average, each results record would be updated twice after the initial submission to reflect changes in data analysis or the submission of additional results from other pre-specified outcome measures. We estimate that each such update would take 10 hours, on average. This figure is 2 hours higher than the 8-hour estimate used in the OMB Paperwork Reduction Act clearance for the current ClinicalTrials.gov data collection and reflects ongoing experience with data submission to ClinicalTrials.gov. Applying these estimates to 7,400 applicable clinical trials per year produces an estimate of 148,000 hours per year for updates to clinical trial results information (two updates per trial), compared to 29,520 hours for the 1,845 applicable clinical trials estimated under the existing information collection. Combining the figure for updates with the estimate of the initial burden of submitting clinical trial results information, produces a total estimated annual hour burden for results submission under the proposed rule of 444,000 hours, compared with 75,645 hours under the existing information collection.

To calculate the economic cost of clinical trial results submission, we examined the average wages of workers in the pharmaceuticals and medical equipment industries who typically are involved in submitting clinical trial results information. Based on our experience in operating the results database and our consultations with data submitters, we believe that this task is performed generally by clinical researchers who are more experienced than those involved in registration. Based on May 2011 data from the U.S. Bureau of Labor Statistics, we use an average hourly wage rate of $42.60, which corresponds to the weighted median hourly wage of a medical scientist in the pharmaceutical and medical equipment manufacturing industries. We doubled this wage rate (to $85.20 per hour) to account for benefits and overhead. Using this adjusted wage rate, we estimate a total annual cost of results submission under this proposed rule, including updates, of $37,828,800 (Table 2). This represents an increase of $31,383,846 per year above the estimated $6,444,954 cost of results submission under the current information collection.

3. Delayed Submission of Results via Certification or Extension Request

We also have estimated the average time and cost associated with the submission of certifications and extension requests to delay results submission, consistent with proposed §§ 11.44(b), (c), and (e). Responsible parties for applicable clinical trials may submit a certification to delay results submission provided that initial approval or approval of a new use is sought. We estimate that the number of clinical trials that would qualify for delayed submission of results in a given year would not exceed the estimated number of newly initiated applicable clinical trials per year that are conducted under an IND or IDE. Such clinical trials would study drugs and devices that are unapproved, unlicensed, or uncleared or that are approved, licensed, or cleared but are studied for possible new uses. While some responsible parties might elect to submit clinical trial results information 1 year after the completion date instead of delaying submission via a certification, for purposes of this estimate, we assume that they all will elect to submit a certification to delay results submission. (Note that the subsequent burden of submitting clinical trial results information is captured by the calculations in section 2 above). Using the same FDA data as was used to estimate the number of applicable clinical trials subject to the registration requirements of this proposed rule, we estimate that certifications would be submitted for 5,150 trials per year. We estimate that it would take no more than 30 minutes for a responsible party to determine that a clinical trial is eligible for a certification (and to verify the eligibility with a sponsor or manufacturer, if necessary) and to submit the necessary information through ClinicalTrials.gov. Using this figure produces an estimated annual hour burden of 2,575 hours for certifications. We estimate that the hourly wage of personnel who would submit the certification is the same as that for submitting clinical trial results information, or $42.60. Doubling this wage rate to account for benefits and overhead produces an annual estimated cost of $219,390 per year.

For good-cause extension requests, we estimate that approximately 200 requests will be submitted each year. This estimate is based on several considerations, including the rate of submission of requests between September 2008 and September 2010, when some 70 extension requests were submitted to ClinicalTrials.gov. In many cases, responsible parties did not need to submit an extension request in order to delay results submission; many of the submitted extension requests indicated that the estimated completion date of the applicable clinical trial had changed or that the clinical trial was not an applicable clinical trial subject to section 402(j) of the PHS Act. We would not expect an extension request to be submitted in these situations; rather, we would expect responsible parties to update their estimated completion date to reflect changes in the progress of the trial or to use the approach described in proposed § 11.22(b) and section IV.B.2(b) of this preamble to determine that the clinical trial is not an applicable clinical trial that is subject to this proposed rule. Excluding such unnecessary requests and considering only those submitted for applicable clinical trials for which the actual completion date had passed, we received approximately 20 requests per year. We expect that the number of extension requests will increase once a final rule is published and responsible parties have more clarity about the deadlines for submitting clinical trial results information. The estimated 200 extension requests per year represent a 10-fold increase over the annual rate of submissions to date and would be equivalent to four percent of all applicable clinical trials for which clinical trial results information is to be submitted in a given year (i.e., 200 out of 5,500). It would also represent more than 10 percent of the applicable clinical trials that do not delay results submission via certification. While responsible parties may request an extension request even after they have filed a certification, we expect this would happen infrequently. Moreover, as explained in section IV.C.3(d) of this preamble, we expect that extensions will be granted in only a limited set of circumstances where ''good cause'' has been demonstrated. In those cases in which an extension request is denied,

the responsible party would have the opportunity to appeal the denial. If we estimate that 50 percent of extension requests are denied and that 50 percent of denials result in an appeal, the number of appeals per year would total 50.

We estimate that the time required gathering the information required for a good-cause extension request or appeal and submitting it to ClinicalTrials.gov would be no more than 2 hours. Using this figure, we estimate that the annualized hourly burden for extension requests and appeals would be 500 hours. We expect that requests will be submitted by those familiar with the results submission requirements and therefore use an hourly wage of $42.60. Doubling this wage rate (to $85.20) to account for benefits and overhead brings the annualized cost of extension requests to $42,600. Combining the estimated costs for certification and extension requests produces a total cost of $261,990 per year (Table 2). The most recent OMB Paperwork Reduction Act clearance for the ClinicalTrials.gov data collection estimated that 3,655 certifications would be submitted by responsible parties seeking initial approval or approval of a new-use of a drug, biological product, or device studied in an applicable clinical trial and that 200 extension requests would be submitted per year. These figures would yield an estimated annual cost of $189,783, meaning that the incremental cost attributable to this rule would be $72,207 per year.

4. Triggered Submission of Clinical Trial Information Following a Voluntary Submission

Proposed § 11.60 implements section (402(j)(4)(A) of the PHS Act and indicates that if a responsible party voluntarily registers or submits results information for a clinical trial of an FDA-regulated drug or device that is not an applicable clinical trial subject to the mandatory clinical trial information submission requirements under the proposed part, that responsible party must, under specified circumstances, also submit information for other applicable clinical trials that are included in a marketing application or premarket notification that is submitted to FDA and for which clinical trial information has not already been submitted to ClinicalTrials.gov. The types of trials for which the voluntary submission of clinical trial information would invoke this requirement would include, e.g., phase 1 trials of drugs, small feasibility studies of devices (neither of which are considered to be applicable clinical trials), or applicable clinical trials that are not otherwise subject to section 402(j) of the PHS Act because they were initiated prior to the date of enactment of FDAAA and were no longer ongoing as of December 26, 2007. The voluntary submission of clinical trial information for such trials would trigger a requirement to submit clinical trial information for other applicable clinical trials that are included in the marketing application for a drug or device, as long as the entity submitting the marketing application or premarket notification is the same as the responsible party for those other trial and still has access to and control over the necessary data.

In practice, we expect that the requirement under section 402(j)(4)(A) of the PHS Act to submit clinical trial information for applicable clinical trials not otherwise registered in ClinicalTrials.gov would be triggered infrequently. In most cases, when clinical trial information is submitted voluntarily, we expect that the applicable clinical trials required to be submitted in a marketing application that includes the voluntarily-submitted clinical trial would have been required to be registered in ClinicalTrials.gov under section 402(j)(2)(C) of the PHS Act and this proposed part. For example, the voluntary submission of information for a phase 1 trial of an unapproved drug would trigger the submission of information for an applicable clinical trial only if that phase 1 trial were included in a marketing application that also included an applicable clinical trial (e.g., a phase 2 clinical trial) that was not otherwise required to submit clinical trial information to ClinicalTrials.gov (e.g., because it completed before September 27, 2007), and if the responsible party of the voluntarily-submitted trial were the same as the entity submitting the marketing application. For these reasons, we do not anticipate many clinical trials that are submitted voluntarily after the date of enactment of FDAAA to be associated—through an FDA marketing application—with applicable clinical trials that pre-date FDAAA. For purposes of this analysis, we estimate that 1 percent of the clinical trials registered voluntarily with ClinicalTrials.gov each year could trigger the submission of clinical trial information for an applicable clinical trial for which clinical trial information was not otherwise required to be submitted to ClinicalTrials.gov. Of the 17,000 clinical trials that are registered every year, on average, with ClinicalTrials.gov, we estimate that 9,600 are voluntary submissions (all but the 7,400 that are applicable clinical trials). Using this figure, voluntary registrations would trigger the required submission of clinical trials information for an estimated 96 clinical trials per year. Based on our experience to-date with voluntary submissions, we expect that for at least three-quarters of those triggered trials (72), registration information only would need to be submitted; for the other quarter, results information would need to be submitted. For those clinical trials for which only registration information is required, we estimate that it would take 8 hours to register the clinical trial by a data submitter with an average hourly wage rate of $32.33 (consistent with the figures used for registration of applicable clinical trials). Doubling the wage rate to account for benefits and overhead produces an estimated cost of $37,244 per year. Submitted information would not generally need to be updated because the clinical trial would, in general, have reached its completion date by the time the requirement to submit clinical trial information is triggered and there would be few, if any, updates to report. For the remaining quarter of the triggered clinical trials (24) we estimate that the hourly burden would equal the 40 hours estimated for results submission for other applicable clinical trials plus 5 hours to account for the additional data elements that are specified in proposed § 11.60(a)(2)(i)(B). Using these figures and doubling the estimated average hourly rate of $42.60, we estimate the annual cost of submission as $92,016. Combining this figure with the $37,244 figure for triggered clinical trials that submit only registration information, produces a total annual estimated cost for the submission of clinical trial information triggered by the voluntary submission of information under proposed § 11.60 of $129,260 (Table 2). Because the submission of clinical trial information triggered by the voluntary submission of information was not included in the most recent OMB Paperwork Reduction Act clearance for the ClinicalTrials.gov data collection, the incremental cost attributable to this rule would be the full estimated cost of $129,260 per year.

We note that a number of voluntary submissions of clinical trial information would likely be made to ClinicalTrials.gov each year. Responsible parties often register clinical trials voluntarily in order to assist in the recruitment of subjects or so that they may publish any resulting scientific papers in leading peer-reviewed scientific journals. Because such clinical trials are not required to be

registered or to submit results information under section 402(j) of the PHS Act, we do not include them in this cost estimate. Because such information is submitted voluntarily to ClinicalTrials.gov, we do account for voluntary submissions in the estimates for Paperwork Reduction Act clearance. See section VII below.

5. Expanded Access Records

As specified in proposed § 11.28(a), if expanded access is available under section 561 of the Federal Food, Drug, and Cosmetic Act to a drug that is studied in an applicable drug clinical trial, the responsible party must include the NCT number of an expanded access record with the clinical trial information submitted at the time of registration. If an expanded access record for the drug has not yet been submitted to ClinicalTrials.gov, the responsible party must create an expanded access record by submitting the data elements listed § 11.28(c). To determine the cost and burden associated with the creation of this record, we relied on information from the FDA that estimates that 10 treatment INDs or treatment protocols and 68 expanded access programs for treatment of an intermediate size patient population are initiated annually. These are the two types of expanded access programs for which the information listed in § 11.28(c) must be submitted to ClinicalTrials.gov under this proposed rule (i.e., as explained in section IV.an expanded access record is not required if expanded access is available for treatment of an individual). We estimate the time required to submit the required information for an expanded access record to be 2 hours, which is one-quarter of the estimated time to register an applicable clinical trial. An expanded access record requires only about one-half of the data elements required for an applicable clinical trial (22 versus 39) and does not require some of the more detailed data elements, such as Primary Outcome Measure, Secondary Outcome Measure, Individual Site Status, and Facility Location information. We therefore estimate the total hour burden associated with expanded access records to be 156 hours per year. We expect that expanded access records are submitted by staff with the same qualifications as those registering applicable clinical trials and, hence use an estimated hourly wage of $32.33. Doubling this wage rate (to $64.66) to account for benefits and overhead results in a total estimated annual cost of $10,087 (Table 1). Because the submission of expanded access records was not included in the most recent OMB Paperwork Reduction Act clearance for the ClinicalTrials.gov data collection, the incremental cost attributable to this rule is the full estimated cost of $10,087 per year.

6. Non-Recurring Cost of Bringing Previously Submitted Registration Information Into Compliance With This Proposed Rule

As discussed in section III.D of this preamble (''Effective Date''), we expect that a responsible party for any applicable clinical trial for which results information would be required to be submitted to ClinicalTrials.gov after the effective date of this rule would have to update any previously submitted clinical trial registration information by the compliance date to meet the requirements of proposed § 11.28. The responsible party would need to submit any data elements specified in proposed § 11.28(a)) that were not submitted at the time the trial was registered and make sure the entries for all required data elements include the complete set of information defined in proposed § 11.10(b) (e.g., include all the specified elements of Study Design).

To estimate the number of clinical trials that might require such updates, we searched ClinicalTrials.gov for clinical trials that were registered after the enactment of FDAAA (i.e., September 27, 2007) and appeared to meet the definition of an applicable clinical trial. We found nearly 3,700 such clinical trials registered each year. Of those clinical trials, approximately 1,800 per year had results information submitted to ClinicalTrials.gov and would therefore not require further submissions of results or updating of previously submitted registration information. Subtracting these 1,800 clinical trials from the 3,700 trials that were registered each year results in an estimated 1,900 clinical trials per year that would be subject to this one-time updating. We estimate that if the final rule were to go into effect 5 years after enactment of FDAAA (e.g., December 2013), there could be as many as 9,500 registered applicable clinical trials for which results have not been submitted (i.e., 1,900 clinical trials per year multiplied by 5 years), although the actual number would probably be smaller because clinical trials that had been initiated earlier would be more likely to have reached their completion date prior to the effective date of the rule and to have submitted complete clinical trial results information. We estimate that the time required to update the registration information would be, on average, 4 hours, which is half the estimated time required to submit the full set of clinical trial registration information and reflects that fact that many registration data elements would already have been submitted and would not need updating. Applying this figure to the estimated 9,500 clinical trials produces an annual hour burden of 38,000 hours. Using an average wage of $32.33 (as for the registration calculation in 1 above) and doubling it to account for benefits and overhead yields an additional cost of $2,457,080. Note that this would be a one-time cost associated with updating registration information previously submitted to ClinicalTrials.gov, not a recurring annual cost.

E. Alternatives to the Proposed Rule

Section 402(j)(3)(D)(v)(VI) of the PHS Act requires the Secretary to promulgate regulations to expand the registry and results data bank and to address specific issues that are enumerated in the statute. Section 402(j)(2)(A)(iii) of the PHS Act also authorizes the Secretary to make additions or modifications to the statutory enumerated clinical trial information required for registration. This proposed rule implements and expands the basic provisions mandated by section 402(j) of the PHS Act that became effective prior to rulemaking on the schedule established by the statute. The preamble describes various alternatives considered by the Agency in exercising its authority to add or modify the statutory provisions and in addressing the topics it was required to address via regulation. It also describes alternatives it considered in implementing statutory provisions of the law that were not required specifically to be addressed by regulation. It also invites comments on alternative approaches.

F. Regulatory Flexibility Act

The RFA (5 U.S.C. 601–612) requires agencies to analyze regulatory options that would minimize any significant impact of a rule on small entities. This proposed rule would affect a number of small entities that conduct clinical trials of drugs and devices, but the Agency estimates that the costs incurred by small entities would be limited, especially in relation to the other costs associated with conducting a clinical trial. As explained below, the Agency believes that the final rule is not likely to have a significant economic impact on a substantial number of small entities.

The companies that would be affected by this proposed rule are classified in seven separate North American Industrial Classification System (NAICS) categories by the Census

Bureau. The affected industries are NAICS 325412—Pharmaceutical Preparation; NAICS 325414—Biological Products (except diagnostic); NAICS 334510—Electromedical and Electrotherapeutic Apparatus; NAICS 339112—Surgical and Medical Instrument; NAICS 339113—Surgical Appliance and Supplies; NAICS 339114—Dental Equipment and Supplies; NAICS 339115—Ophthalmic Goods. The Small Business Administration (SBA) size standards for all these industries define small entities as those companies with less than 500 employees, except for pharmaceutical preparation, for which it defines a small entity as one with less than 750 employees. The most recent data from the U.S. Census of Manufacturers that offers the level of detail for establishments at or near the employee size limits as defined by SBA is from 2007. In each of these establishment size categories, large majorities of the establishments meet the criteria as small entities. Even taking into account that many of these establishments are parts of multi-establishment corporations, significant numbers of companies would still qualify as small entities and have fewer than 100 employees across all of these categories. Although the Agency expects that most companies sponsoring applicable clinical trials would be larger than the average-sized company in their industry, the Agency concludes that a substantial number of companies would still qualify as small entities.

The cost analysis presented above indicates an estimated cost of compliance with this proposed rule of $6,718 per applicable clinical trial ($49,713,753 for 7,400 clinical trials per year). While some larger firms could be the responsible party for multiple applicable clinical trials in the same year, we expect most small firms would be responsible for no more than one applicable clinical trial per year. Using data from the 2007 Census of Manufacturers, the average value of shipments for establishments in these industries with one to four employees ranged from $353,000 to $844,000. Assuming that such small operations had one applicable clinical trial that was required to submit registration or results information each year, the costs of this proposed rule would represent, at most, 1.9 percent of the annual value of shipments. For establishments with 50 to 99 employees, the costs of this proposed rule would represent at most 0.6 percent of the value of shipments, even if they were responsible for 10 applicable clinical trials administered annually. For establishments with 100 or more employees, the costs of this proposed rule would represent at most 0.24 percent of the value of shipments even with 10 applicable clinical trials administered annually. These figures are well below the threshold of 3 to 5 percent of the total revenue for small entities needed to consider that this proposed rule would have a significant economic impact on a substantial number of small entities. The Agency concludes that this proposed rule would not have a significant economic impact on a substantial number of small entities.

In practice, we expect the burden on small firms would be significantly lower than this estimate. In general the applicable clinical trials initiated by small firms would be less complex than the applicable clinical trials initiated by large firms, including, for example, fewer trial locations (sites), shorter duration, and fewer outcome measures. As a result, the amount of results information to be submitted—and the time and cost associated with such submissions—would be less than for larger entities and represent a smaller share of shipments. In addition, these costs would affect only a fraction of small firms in any given year. For example, by our estimates registration information would be required to be submitted (and results information subsequently submitted) for approximately 500 applicable device clinical trials in any given year. Information from the 2007 Census of Manufacturers indicates that there are approximately 5,600 companies in the United States that are involved in the manufacture of medical devices and that almost 4,900 of them have fewer than 100 employees. Even if no company engaged in more than one applicable clinical trial at the same time, then on average, less than 10 percent of all medical device manufacturers would initiate a trial subject to the registration and results submission requirements of this proposed rule in any given year (500 applicable device clinical trials per year divided by 5,600 firms equals 0.089 or 8.9 percent).

G. Unfunded Mandates Reform Act of 1995

Section 1352(a) of the Unfunded Mandates Reform Act of 1995 requires that the agency prepare, among other things, a written statement which includes an assessment of anticipated costs and benefits before proposing ''any rule that includes any Federal mandate that may result in the expenditure by State, local, and Tribal governments, in the aggregate, or by the private sector, of $100,000,000 or more (adjusted annually for inflation) in any 1 year.'' 2 U.S.C. 1532(a). The current threshold, adjusted for inflation using the 2012 Implicit Price Deflator for the Gross Domestic Product, is $141 million. As indicated above, we do not expect the direct burden of this proposed rule, including the cost of compiling, submitting, and updating clinical trial registration and results information for applicable clinical trials, to result in any 1-year expenditure that would meet or exceed this amount. Nor do we expect that State or local governments would bear a significant fraction of this cost, as most of the entities affected by the proposed regulation would be private entities. As a result, we conclude that this rule will have no consequential effect on State, local, or tribal governments or on the private sector. We have determined that this proposed rule would not constitute a significant rule under the Unfunded Mandates Reform Act of 1995, because it would impose no mandates with costs exceeding the current threshold.

H. Federalism

Executive Order 13132, Federalism, establishes certain requirements that an Agency must meet when it promulgates a proposed rule (and subsequent final rule) ''that imposes substantial direct compliance costs on State and local governments,'' preempts State law, or otherwise has federalism implications. The Agency has analyzed this proposed rule in accordance with the principles set forth in Executive Order 13132 and has determined that this proposed rule does not contain policies that would impose any ''substantial direct compliance costs on State or local governments[.]'' This proposed rule, does, however, have federalism implications.

Section 801(d)(1) of FDAAA expressly provides a preemption provision as follows: ''Upon the expansion of the registry and results data bank under section 402(j)(3)(D) of the Public Health Service Act . . . no State or political subdivision of a State may establish or continue in effect any requirement for the registration of clinical trials or for the inclusion of information relating to the results of Clinical trials in a database.'' We interpret this language to prohibit a State or political subdivision of a State from establishing any requirement for the inclusion of information in a database that is: (1) Clinical trial registration information, as that term is defined in § 11.10, i.e., the actual registration data elements; (2) clinical trial results information required to be submitted under section

402(j)(3) of the PHS Act and this part; or (3) information that is otherwise collected through any data element in ClinicalTrials.gov, such as information relating to voluntary submissions and other information whether or not required to be submitted under section 402(j) of the PHS Act and this part. We do not interpret section 801(d)(1) of FDAAA to preempt other types of reporting and/or data collection that States may require related to public health, disease surveillance, clinical care, or the practice of medicine such as patient and disease registries or public health surveillance registries.

Following publication of this proposed rule, the Agency will further consult with appropriate State officials and organizations to review the scope of this proposed rule and to seek input on federalism issues. We specifically solicit comments on this proposed rule from representatives of State and local governments.

VII. Paperwork Reduction Act of 1995

This proposed rule contains requirements that are subject to review by OMB under the Paperwork Reduction Act of 1995 (44 U.S.C. 3501–3520) (PRA). Sections 11.28, 11.48, 11.60, 11.62, and 11.64 of this proposed rule contain information collection requirements that are subject to OMB approval. A revision of the existing PRA clearance for clinical trial registration and results submission (OMB 0925–0586) to meet the requirements of this proposed Part will be submitted to OMB for review.

A description of the information collection requirements included in this proposed rule is provided in the Regulatory Impact Statement (section V) and is summarized in this section of the preamble with an estimate of the annualized burden hours. Included in this estimate is the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing, reviewing, updating, and correcting each collection of information. The Agency invites comments on: (1) Whether the proposed collection of information is necessary for the proper performance of the functions of NIH, including whether the information will have practical utility; (2) the accuracy of the estimate of the burden of the proposed collection of information by NIH, including the validity of the methodology and assumptions used; (3) ways to enhance the quality, utility, and clarity of the information to be collected; and (4) ways to minimize the burden of the collection of information on respondents, including through the use of automated collection techniques, when appropriate, and other forms of information technology .

The information collection provisions of this proposed rule will be submitted to OMB for review. Other organizations and individuals desiring to submit comments on the information collection and submission requirements should send their comments by February 19, 2015 to (1) Ms. Seleda Perryman, Project Clearance Officer, National Institutes of Health, Rockledge Centre 1, 6705 Rockledge Drive, Room 3509, Bethesda, Maryland 20817, telephone 301–594–7949 (not a toll-free number); and (2) the Office of Information and Regulatory Affairs, OMB, *OIRA_submission@omb.eop.gov*, or by fax to 202–395–6974, and mark ''Attention: Desk Officer for the National Institutes of Health, Department of Health and Human Services.'' After we obtain OMB approval, we will publish the OMB control number in the **Federal Register**.

The estimate includes the annual hourly burden for submission, updating, and correction of information both for applicable clinical trials that are subject to this proposed rule and for the larger number of clinical trials for which information is submitted to ClinicalTrials.gov on a voluntarily basis in order to recruit subjects, remain eligible to publish summary articles in scientific journals that follow the guidelines of the ICMJE, to comply with company or other organizational policies regarding public disclosure of clinical trial information, or for other purposes.

The burden for trials that are subject to this regulation follows the estimates presented in section V of this preamble. They differ from the burden estimates contained in the current OMB Paperwork Reduction Act clearance in several ways. For registration, we have increased from 5,500 to 7,400 the estimate of the number of clinical trials that would be subject to mandatory registration under the rule. This increase reflects the revised estimate of the number of protocols for applicable clinical trials that are submitted to the FDA for under and IND or IDE. We also increased the estimated hour burden of registration from 7 hours to 8 hours to reflect the additional data elements that would be required under this proposed rule. For results submission we have increased from 1,845 to 7,400 our estimate of the number of clinical trials that would be subject to mandatory results submission under this proposed rule. This proposed rule would require the submission of results information for all registered applicable clinical trials, regardless of whether or not the drug (including biological product) or device under study in the trial is approved, licensed, or cleared. We have made commensurate increases in the estimated number of clinical trials for which a certification to delay results submission would be submitted. We have also increased the estimated hour burden for submitting results information from 25 hours to 40 hours to account for the additional results information that would be required to be submitted under this proposed rule. In addition, we have added estimates of the burden associated with the submission of registration and results information that could be triggered by some voluntary submissions of clinical trial information under proposed § 11.60. Finally, we have included a separate estimate of the burden associated with the creation of an expanded access record if a drug that is studied in an applicable clinical trial is available via an expanded access program.

TABLE 3—ESTIMATED BURDEN FOR REGISTRATION AND RESULTS SUBMISSION AT CLINICALTRIALS.GOV

Type of respondents	Number of respondents	Frequency of response	Average time per response (hours)	Annual hour burden
Regulated submissions [Subject to this proposed rule]:				
Registration	7,400	1 Initial	8	59,200
		8 Subsequent Updates	2	118,400
Results Information	7,400	1 Initial	40	296,000
		2 Subsequent Updates	10	148,000
Certifications to delay results	5,150	1	0.5	2,575

TABLE 3—ESTIMATED BURDEN FOR REGISTRATION AND RESULTS SUBMISSION AT CLINICALTRIALS.GOV—Continued

Type of respondents	Number of respondents	Frequency of response	Average time per response (hours)	Annual hour burden
Extension requests and appeals	250	1	2	500
Registration triggered by voluntary submission.	72	1	8	576
Results triggered by voluntary submission.	24	1	45	1,080
Expanded access records	78	1	2	156
SUBTOTAL				626,487
Non-regulated submissions [Not subject to this Proposed Rule]:				
Registration	9,600	1 Initial	8	76,800
		8 Subsequent Updates	2	153,600
Results Information	350	1 Initial	40	14,000
		2 Subsequent Updates	10	7,000
SUBTOTAL				251,400
TOTAL				877,887

In order to estimate the burden for clinical trials that are not subject to this proposed rule, we examined ClinicalTrials.gov to determine how many clinical trials were registered during calendar years 2008 through 2011. We found that there were, on average, some 17,000 studies registered per year, and that the number was consistent across the 3-year period. We therefore believe it is a reasonable estimate of total registrations in future years. We subtracted from this total 7,400 clinical trials to account for those applicable clinical trials that would be subject to mandatory submissions under this proposed rule. The remaining 9,600 clinical trials registered would not be subject to section 402(j) of the PHS Act, e.g., because they are studies of interventions not regulated by FDA, are phase 1 studies of drugs or feasibility studies of devices, are observational studies, or otherwise fail to meet the definition of an applicable clinical trial. This figure represents a reduction (from 11,500) in the number of non-regulated submissions to ClinicalTrials.gov that was contained in our previous OMB Paperwork Reduction Act clearance. These clinical trials would be expected to have the same clinical trial registration information submitted for them as is submitted for applicable clinical trials that are subject to this proposed rule. We expect that information submitted for such clinical trials will be updated as frequently as for clinical trials that are subject to the rule. Therefore, for calculating the registration burden associated with voluntarily submitted clinical trials, we use the same assumptions as for applicable clinical trials required to register under section 402(j)(2)(C) of the PHS Act: initial submission of registration information will take an average of 8 hours, updates of 2 hours apiece will take place 8 times during the course of the study. Applying these figures yields an estimated annual burden of 230,400 hours, of which 76,800 derives from the initial registration and 153,600 derives from updates (Table 3).

As for results submission, we do not expect that clinical trial results information will be submitted for most of the clinical trials for which registration information is submitted voluntarily (non-regulated). To estimate of the number of clinical trials for which results information would be submitted voluntarily, we reviewed the more than 7,000 results records that have been posted publicly at ClinicalTrials.gov since late 2008. Of these, about 1,050, or 350 per year, appear to be for studies that are unambiguously not applicable clinical trials, e.g., observational studies, clinical trials of interventions other than drugs (including biological products) and devices, and phase 1 clinical trials of drugs. We expect that this number of results submissions would continue to be made in future years. We estimate that the time required to submit clinical trial results information for such clinical trials would be equivalent to that for applicable clinical trials required to register under section 402(j)(2)(C) of the PHS Act. Using those figures, we estimate that the total annual hour burden for submitting clinical trial results information for voluntarily submitted clinical trials would be 14,000 hours, plus 7,000 hours for updates (Table 3). Thus the total burden associated with the voluntary submission of clinical trial information is 251,400 hours, and the total annual burden for regulated and unregulated submissions of information would be 877,887 hours.

VIII. Congressional Review Act

The U.S. Department of Health and Human Services has determined that this proposed rule is not a major rule as defined in 5 U.S.C. 804, and, thus, does not require review by Congress. The Congressional Review Act (5 U.S.C. 801–808) defines a major rule as one that the Administrator of the Office of Information and Regulatory Affairs of the Office of Management and Budget finds has resulted in or is likely to result in (A) an annual effect on the economy of $100,000,000 or more; (B) a major increase in costs or prices for consumers, individual industries, Federal, State, or local government agencies, or geographic regions; or '(C) significant adverse effects on competition, employment, investment, productivity, innovation, or on the ability of United States-based enterprises to compete with foreign-based enterprises in domestic and export markets. (5 U.S.C. 804).

As described in section V of this preamble (Regulatory Impact Statement), we estimate that the rule will impose annual costs on responsible parties (i.e., sponsors of clinical trials or designated principal investigators) of less than $50 million. We do not believe such costs are significant enough to affect prices of the drugs (including biological products) or medical devices that eventually may be approved, cleared, or licensed for marketing by

FDA. Nor do we believe that the submission and public availability of clinical trial information, as required by this proposed rule, will have significant adverse effects on competition, employment, investment, productivity, or innovation in organizations that are subject to this proposed rule. This proposed rule contains provisions to delay the public posting of information that might be considered commercially relevant, including registration information for trials of previously unapproved or uncleared devices and results information for trials of unapproved products. In addition, this proposed rule would apply to all organizations, domestic and international, that are subject to FDA regulation (i.e., because they are conducting a trial under an IND or IDE or are seeking marketing approval from FDA). Thousands of organizations have submitted information similar to the clinical trial registration information proposed in this rule to publicly available registries, including ClinicalTrials.gov, for more than a decade on a voluntary basis. Many have also made results information publicly available, though not in a consistent manner.

In accordance with the provisions of Executive Order 12866, this proposed rule was reviewed by the Office of Management and Budget.

IX. Legal Authority

These proposed regulations are issued under the authorities contained in 42 U.S.C. 282(i); 42 U.S.C. 282(j); 5 U.S.C. 301; 42 U.S.C. 286(a); 42 U.S.C. 241(a); 42 U.S.C. 216(b); and sections 801(c)–(d), Pub. L. 110–85, 121 Stat. 921–922 (42 U.S.C. 282(note)).

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List of Subjects in 42 CFR Part 11

Biologics, Clinical trial, Data bank, Drugs, Human subjects research, Medical devices, Medical research, Registry, Reporting and recordkeeping requirements, Results information.

For the reasons stated in this preamble, the Department of Health and Human Services proposes to amend Title 42, Chapter I of the Code of Federal Regulations by adding a Part 11 to read as follows.

PART 11—CLINICAL TRIAL REGISTRATION AND RESULTS SUBMISSION

Subpart A—General Provisions

Subpart B—Registration

Subpart C—Results Submission

Subpart D—Additional Submissions of Clinical Trial Information

Authority: 42 U.S.C. 282(i); 42 U.S.C. 282(j); 5 U.S.C. 301; 42 U.S.C. 286(a); 42 U.S.C. 241(a); 42 U.S.C. 216(b)

Subpart A—General Provisions

§ 11.2 What is the purpose of this part?

This part implements section 402(j) of the Public Health Service Act [42 U.S.C. 282(j)] by providing requirements and procedures for the submission of clinical trial information for certain applicable clinical trials and other clinical trials to the Director of the National Institutes of Health (NIH) to be made publicly available via ClinicalTrials.gov, the Internet-accessible clinical trial registry and results data bank established by the National Library of Medicine (NLM) at *http://www.clinicaltrials.gov.*

§ 11.4 To whom does this part apply?

(a) This part applies to the responsible party for an applicable clinical trial that is required to be registered under § 11.22 or a clinical trial for which clinical trial registration information or clinical trial results information is

submitted voluntarily in accordance with § 11.60.

(b) The responsible party must communicate the identity and contact information of the responsible party to the Director by submitting the Responsible Party Contact Information data element under § 11.28(a)(4)(vii) as part of the clinical trial information submitted at the time of registration. Changes to Responsible Party Contact Information must be communicated to the Director by updating this information not later than 30 calendar days after the change has occurred, as specified in § 11.64(b)(1)(ix) and § 11.64(b)(1)(x).

(c) *Determination of responsible party.* For purposes of this part, each applicable clinical trial or other clinical trial must have one responsible party. With respect to a clinical trial, the sponsor of the clinical trial will be considered the responsible party unless and until a principal investigator has been designated the responsible party, in accordance with paragraph (c)(2) of this section. With respect to a pediatric postmarket surveillance of a device that is not a clinical trial, the responsible party is the entity whom FDA orders to conduct the pediatric postmarket surveillance of a device.

(1) *Determination of sponsor.* For purposes of this part, each applicable clinical trial or other clinical trial must have one sponsor.

(i) When an applicable clinical trial or other clinical trial is conducted under an investigational new drug application (IND) or investigational device exemption (IDE), the IND or IDE holder will be considered the sponsor.

(ii) When an applicable clinical trial or other clinical trial is not conducted under an IND or IDE, the single person or entity who initiates the trial, by preparing and/or planning the trial, and who has authority and control over the trial, will be considered the sponsor.

(2) *Designation of a principal investigator as the responsible party.* (i) The sponsor may designate a principal investigator as the responsible party if such principal investigator meets all of the following:

(A) Is responsible for conducting the trial;

(B) Has access to and control over the data from the trial;

(C) Has the right to publish the results of the trial; and

(D) Has the ability to meet all of the requirements for submitting and updating clinical trial information as specified in this part.

(ii) With regard to an applicable clinical trial or other clinical trial, a designation by the sponsor under paragraph (c)(2)(i) of this section shall consist of the sponsor providing notice of the designation to the principal investigator and obtaining from the principal investigator an acknowledgement of the principal investigator's responsibilities under this part as responsible party, and the principal investigator acknowledging the designation as responsible party to the Director in the form and manner specified at *http://prsinfo.clinicaltrials.gov.*

(3) *Withdrawal of the designation of a principal investigator as the responsible party.* (i) In the event a principal investigator who has been designated the responsible party becomes unable to meet all the requirements for being so designated under paragraph (c)(2)(i) of this section, the principal investigator must withdraw the designation in the form and manner specified at *http://prsinfo.clinicaltrials.gov,* at which time the sponsor will be considered the responsible party unless and until the sponsor makes a new designation in accordance with paragraph (c)(2) of this section.

(ii) In the event a principal investigator who has been designated the responsible party is unable because of death or incapacity to withdraw his or her designation, the sponsor will be considered the responsible party unless and until the sponsor makes a new designation in accordance with paragraph (c)(2) of this section.

§ 11.6 What are the requirements for the submission of truthful information?

(a) *General.* The clinical trial information submitted by a responsible party under this part shall not be false or misleading in any particular. Submission of false and/or misleading information would subject the responsible party to civil, criminal, and/or administrative liability under U.S. law.

(b) *Certification.* The responsible party must certify that, to the best of his or her knowledge, the information submitted is truthful and not misleading and that he or she is aware that the submission of false and/or misleading information would subject the responsible party to civil, criminal, and/or administrative liability under U.S. law.

§ 11.8 In what form and manner must clinical trial information be submitted?

Information submitted under this part must be submitted electronically to ClinicalTrials.gov, the Internet-accessible clinical trial registry and results data bank established by the National Library of Medicine, in the form and manner specified at *http://prsinfo.clinicaltrials.gov.*

§ 11.10 What definitions apply to this part?

(a) The following definitions apply to terms used in this part: *Adverse event* means any untoward or unfavorable medical occurrence in a human subject, including any abnormal sign (for example, abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the subject's participation in the research, whether or not considered related to the subject's participation in the research. See also serious adverse event.

Applicable clinical trial means an applicable device clinical trial or an applicable drug clinical trial.

Applicable device clinical trial means: (1) A prospective clinical study of health outcomes comparing an intervention with a device subject to section 510(k), 515, or 520(m) of the Federal Food, Drug, and Cosmetic Act against a control in human subjects (other than a small clinical trial to determine the feasibility of a device, or a clinical trial to test prototype devices where the primary outcome measure relates to feasibility and not to health outcomes); and (2) a pediatric postmarket surveillance as required under section 522 of the Federal Food, Drug, and Cosmetic Act.

Applicable drug clinical trial means a controlled clinical investigation, other than a phase 1 clinical investigation, of a drug subject to section 505 of the Federal Food, Drug, and Cosmetic Act or to section 351 of the Public Health Service Act, where ''clinical investigation'' has the meaning given in 21 CFR 312.3 (or any successor regulation) and ''phase 1'' has the meaning given in 21 CFR 312.21 (or any successor regulation). In addition, a clinical trial of a combination product, where such combination product meets the definition in 21 CFR 3.2(e), shall be considered an applicable drug clinical trial, so long as the clinical trial of the combination product is a controlled clinical investigation, other than a phase 1 clinical investigation, and the combination product is subject to section 505 of the Federal Food, Drug, and Cosmetic Act and/or section 351 of the Public Health Service Act and/or sections 510(k), 515, or 520(m) of the Federal Food, Drug, and Cosmetic Act.

Approved drug means a drug that is approved for any indication under section 505 of the Federal Food, Drug, and Cosmetic Act or a biological product licensed for any indication under section 351 of the Public Health Service Act.

Approved or cleared device means a device that is cleared for any indication under section 510(k) of the Federal Food, Drug, and Cosmetic Act or approved for any indication under sections 515 or 520(m) of that Act.

Arm means a pre-specified group or subgroup of human subjects in a clinical trial assigned to receive specific intervention(s) (or no intervention) according to a protocol.

Clinical trial means a clinical investigation or a clinical study in which human subjects are prospectively assigned, according to a protocol, to one or more interventions (or no intervention) to evaluate the effect(s) of the intervention(s) on biomedical or health related outcomes.

Clinical trial information means the data elements, including clinical trial registration information and clinical trial results information, the responsible party is required to submit to ClinicalTrials.gov under this part.

Clinical trial registration information means the data elements that the responsible party is required to submit to ClinicalTrials.gov, as listed under § 11.28.

Clinical trial results information means the data elements that the responsible party is required to submit to ClinicalTrials.gov under § 11.48 or, if applicable, § 11.60(a)(2)(i)(B).

Comparison group means a grouping of human subjects in a clinical trial that is used in analyzing the results data collected during the clinical trial.

Completion date means, for a clinical trial, 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 pre-specified protocol or was terminated. In the case of clinical trials with more than one primary outcome measure with different completion dates, this term refers to the date upon which data collection is completed for all of the primary outcomes. For a pediatric postmarket surveillance of a device that is not a clinical trial, completion date means the date on which the final report summarizing the results of the pediatric postmarket surveillance is submitted to FDA.

Control or *controlled* means, with respect to a clinical trial, that data collected on human subjects in the clinical trial will be compared to concurrently collected data or to non-concurrently collected data (e.g., historical controls, including a human subject's baseline data), as reflected in the pre-specified primary or secondary outcome measures.

Device means a device as defined in section 201(h) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321(h)).

Director means the NIH Director or any official of the NIH to whom the NIH Director delegates authorities granted in 42 U.S.C. 282(j).

Drug means a drug as defined in section 201(g) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321(g)) or a biological product as defined in section 351 of the Public Health Service Act (42 U.S.C. 262).

Enroll or *enrolled* means a human subject's agreement to participate in a clinical trial, as indicated by the signing of the informed consent document(s).

FDA-regulated device means, for purposes of this part, a device subject to section 510(k), 515, 520(m), or 522 of the Federal Food, Drug, and Cosmetic Act.

FDA-regulated drug means, for purposes of this part, a drug subject to section 505 of the Federal Food, Drug, and Cosmetic Act or a biological product subject to section 351 of the Public Health Service Act.

Human subjects protection review board means an institutional review board (IRB) as defined in 21 CFR 50.3 or 45 CFR 46.102 (or any successor regulation), as applicable, or equivalent independent ethics committee that is responsible for ensuring the protection of the rights, safety, and well-being of human subjects involved in a clinical investigation and is adequately constituted to provide assurance of that protection.

Interventional means, with respect to a clinical study or a clinical investigation, that 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.

Investigational Device Exemption (IDE) has the meaning given in 21 CFR 812, or any successor regulation.

Investigational New Drug Application (IND) has the meaning given in 21 CFR 312.3, or any successor regulation.

NCT number means the unique identification code assigned to each record in ClinicalTrials.gov, including a record for an applicable clinical trial, a clinical trial, or an expanded access program.

Ongoing means, with respect to a clinical trial of a drug or a device and to a date, that one or more human subjects is enrolled in the clinical trial, and the date is before the completion date of the clinical trial. With respect to a pediatric postmarket surveillance of a device, ongoing means a date between the date on which FDA approves the plan for conducting the surveillance and the date on which the final report is submitted to FDA.

Outcome measure means a pre-specified measurement that will be used to determine the effect of experimental variables on the human subjects in a clinical trial. See also primary outcome measure and secondary outcome measure.

Pediatric postmarket surveillance of a device means the active, systematic, scientifically valid collection, analysis, and interpretation of data or other information conducted under section 522 of the Federal Food, Drug, and Cosmetic Act about a marketed device that is expected to have significant use in patients who are 21 years of age or younger at the time of diagnosis or treatment. A pediatric postmarket surveillance of a device may be, but is not always, a clinical trial.

Primary outcome measure means the outcome measure(s) of greatest importance specified in the protocol, usually the one(s) used in the power calculation. Most clinical trials have one primary outcome measure, but a clinical trial may have more than one. ''Primary outcome'' has the same meaning as primary outcome measure.

Principal Investigator (PI) means the individual who is responsible for the scientific and technical direction of the study.

Protocol means the written description of the clinical trial, including objective(s), design, and methods. It may also include relevant scientific background and statistical considerations.

Responsible party means, with respect to a clinical trial, (i) the sponsor of the clinical trial, as defined in 21 CFR 50.3 (or any successor regulation); or (ii) the principal investigator of such clinical trial if so designated by a sponsor, grantee, contractor, or awardee, so long as the principal investigator is responsible for conducting the trial, has access to and control over the data from the clinical trial, has the right to publish the results of the trial, and has the ability to meet all of the requirements under this part for the submission of clinical trial information. For a pediatric postmarket surveillance of a device that is not a clinical trial, the responsible party is the entity whom FDA orders to conduct the pediatric postmarket surveillance of the device.

Secondary outcome measure means an outcome measure that is of lesser importance than a primary outcome measure, but is part of a pre-specified plan for evaluating the effects of the intervention or interventions under

investigation in a clinical trial. A clinical trial may have more than one secondary outcome measure. ''Secondary outcome'' has the same meaning as secondary outcome measure.

Secretary means the Secretary of Health and Human Services or any other official(s) to whom the Secretary delegates the authority contained in 42 U.S.C. 282(j).

Serious adverse event means an adverse event that results in any of the following outcomes: Death, a life-threatening adverse event as defined in 21 CFR 312.32 (or any successor regulation), inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the human subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of a substance use disorder.

Sponsor means either a ''sponsor'' or ''sponsor-investigator'', as each is defined in 21 CFR 50.3, or any successor regulation.

(b) The following definitions apply to data elements of clinical trial information referenced in this part, unless otherwise specified.

(1) *Brief Title* means a short title of the clinical trial written in language intended for the lay public, including any acronym or abbreviation used publicly to identify the clinical trial.

(2) *Official Title* means the title of the clinical trial, corresponding to the title of the protocol.

(3) *Brief Summary* means a short description of the clinical trial, including a brief statement of the clinical trial's hypothesis, written in language intended for the lay public.

(4) *Primary Purpose* means the main objective of the intervention(s) being evaluated by the clinical trial.

(5) *Study Design* means a description of the manner in which the clinical trial will be conducted, including the following information:

(i) *Interventional Study Model.* The strategy for assigning interventions to human subjects.

(ii) *Number of Arms.* The number of arms in the clinical trial. For a trial with multiple periods or phases that have different numbers of arms, the maximum number of arms during any period or phase.

(iii) *Arm Information.* A description of each arm of the clinical trial that indicates its role in the clinical trial, provides an informative title, and, if necessary, additional descriptive information to differentiate each arm from other arms in the clinical trial.

(iv) *Allocation.* The method by which human subjects are assigned to arms in a clinical trial.

(v) *Masking.* The party or parties, if any, involved in the clinical trial who are prevented from having knowledge of the interventions assigned to individual human subjects.

(vi) *Single Arm Controlled.* For a single-armed clinical trial only, whether or not the clinical trial is controlled, as specified by the protocol or statistical analysis plan.

(6) *Study Phase* means, for a clinical trial of a drug, the numerical phase of such clinical trial, consistent with terminology in 21 CFR 312.21, or any successor regulation, such as phase 2 or phase 3, and in 21 CFR 312.85, or any successor regulation, for phase 4 studies.

(7) *Study Type* means the type of study for which clinical trial information is being submitted.

(8) *Whether the Study is a Pediatric Postmarket Surveillance of a Device* means, for a study that includes a device as an intervention and is a pediatric postmarket surveillance of a device, an affirmation that the study is a pediatric postmarket surveillance of a device.

(9) *Primary Disease or Condition Being Studied in the Trial, or the Focus of the Study* means the name(s) of the disease(s) or condition(s) studied in the clinical trial, or the focus of the clinical trial, using, if available, appropriate descriptors from the National Library of Medicine's Medical Subject Headings (MeSH) controlled vocabulary thesaurus *http://www.nlm.nih.gov/mesh/,* or terms from another vocabulary, such as the Systematized Nomenclature of Medicine—Clinical Terms (SNOMED CT), that has been mapped to MeSH within the Unified Medical Language System (UMLS) Metathesaurus, *https://uts.nlm.nih.gov.*

(10) *Intervention Name* means a brief descriptive name used to refer to the intervention(s) studied in each arm of the clinical trial. A non-proprietary name of the intervention must be used, if available. If a non-proprietary name is not available, a brief descriptive name or identifier must be used.

(11) *Other Intervention Name(s)* means other current and former name(s) or alias(es), if any, different from the Intervention Name(s), that the sponsor has used publicly to identify the intervention(s), including, but not limited to, past or present names such as brand name(s), serial numbers, or chemical descriptions.

(12) *Intervention Description* means, details that can be made public about the intervention, other than the Intervention Name and Other Intervention Name(s), sufficient to distinguish it from other, similar interventions studied in the same or another clinical trial.

(13) *Intervention Type* means, for each intervention studied in the clinical trial, the general type of intervention.

(14) *U.S. FDA Approval, Licensure, or Clearance Status* means, for each drug or device studied in the clinical trial, whether that drug or device is approved, licensed, or cleared by the U.S. Food and Drug Administration for any use.

(15) *Product Manufactured in the U.S.* means, for a drug or device studied in a clinical trial, whether or not the drug or device is manufactured in the U.S. or one of its territories.

(16) *Study Start Date* means the estimated date on which the clinical trial will be open to enrollment of human subjects. If the clinical trial has enrolled the first human subject, the actual date on which the first human subject was enrolled.

(17) *Completion Date* means the estimated completion date. Once the clinical trial has reached the completion date, the responsible party must update the Completion Date data element to reflect the actual completion date.

(18) *Enrollment* means the estimated total number of human subjects to be enrolled or target number of human subjects in the clinical trial.

(19) *Primary Outcome Measure Information* means a description of each primary outcome measure, to include the following information:

(i) Name of the specific primary outcome measure;

(ii) Description of the metric used to characterize the specific primary outcome measure; and

(iii) Time point(s) at which the measurement is assessed for the specific metric used.

(20) *Secondary Outcome Measure Information* means a description of each secondary outcome measure, to include the following information:

(i) Name of the specific secondary outcome measure;

(ii) Description of the metric used to characterize the specific secondary outcome measure; and

(iii) Time point(s) at which the measurement is assessed for the specific metric used.

(21) *Eligibility Criteria* means a limited list of criteria for selection of human subjects to participate in the clinical trial, provided in terms of inclusion and exclusion criteria and suitable for assisting potential human subjects in identifying clinical trials of interest.

(22) *Gender* means the biological sex of the human subjects who may participate in the clinical trial.

(23) *Age Limits* means the minimum and maximum age of human subjects who may participate in the clinical trial, provided in relevant units of time.

(24) *Accepts Healthy Volunteers* means whether human subjects who do not have a disease or condition, or related conditions or symptoms, under study in the clinical trial are permitted to participate in the clinical trial.

(25) *Overall Recruitment Status* means the recruitment status for the clinical trial as a whole, based upon the status of the individual sites. If at least one facility in a multi-site clinical trial has an individual site status of ''recruiting,'' then the overall recruitment status for the trial must be ''recruiting.''

(26) *Why Study Stopped* means, for a clinical trial that is suspended or terminated or withdrawn prior to its completion as anticipated by the protocol, a brief explanation of the reason(s) why such clinical trial was stopped.

(27) *Actual Enrollment* means, for a clinical trial for which recruitment of human subjects has terminated or completed, the actual number of human subjects enrolled in the clinical trial.

(28) *Individual Site Status* means the recruitment status of each participating facility in a clinical trial.

(29) *Availability of Expanded Access* means, for an applicable drug clinical trial of a drug that is not an approved drug:

(i) An indication of whether there is expanded access to the drug under section 561 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 360bbb) for those who do not qualify for enrollment in the applicable clinical trial.

(ii) If expanded access is available under section 561 of the Federal Food, Drug, and Cosmetic Act, the NCT number of the expanded access record.

(30) *Name of the Sponsor* means the name of the entity or the individual that is the sponsor of the clinical trial, as defined in § 11.10(a).

(31) *Responsible Party, by Official Title* means:

(i) Indication of whether the responsible party is the sponsor of the clinical trial, as that term is defined in 21 CFR 50.3, the sponsor-investigator, as that term is defined in 21 CFR 50.3, or a principal investigator designated pursuant to this part; and

(ii) Either:

(A) The official name of the entity, if the responsible party is an entity; or

(B) The official title and primary organizational affiliation of the individual, if the responsible party is an individual.

(32) *Facility Information* means, for each participating facility in a clinical trial, the following information:

(i) Facility Name, meaning the full name of the organization where the clinical trial is being conducted;

(ii) Facility Location, including city, state, country and zip code for U.S. locations (including territories of the United States) and city and country for locations in other countries; and

(iii) Either:

(A) For each facility participating in a clinical trial, Facility Contact, including the name or title, telephone number, and email address of a person to whom questions concerning the trial and enrollment at that site can be addressed; or

(B) Central Contact Person, including the name or title, toll-free telephone number and email address of a person to whom questions concerning enrollment at any location of the trial can be addressed.

(33) *Unique Protocol Identification Number* means any unique identification number assigned to the protocol by the sponsor.

(34) *Secondary ID* means:

(i) Any identification number(s) other than the organization's unique protocol identification number or NCT number that is assigned to the clinical trial, including any unique clinical trial identification numbers assigned by other publicly available clinical trial registries. If the clinical trial is funded in whole or part by a U.S. federal government agency, the complete grant or contract number must be submitted as a Secondary ID.

(ii) A description of the type of Secondary ID.

(35) *Food and Drug Administration IND or IDE Number* means whether or not there is an IND or IDE for the clinical trial and, if so, each of the following elements:

(i) Name or abbreviation of the FDA center with whom the IND or IDE is filed;

(ii) IND or IDE number assigned by the FDA center; and

(iii) For an IND, the IND serial number (as defined in 21 CFR 312.23(e), or any successor regulation), if any, assigned to the clinical trial.

(36) *Human Subjects Protection Review Board Status* means information to indicate whether a clinical trial has been approved by a human subjects protection review board or is exempt from human subjects protection review board approval. Human Subjects Protection Review Board Status must be listed as ''approved'' if at least one human subjects protection review board has approved the clinical trial;

(37) *Record Verification Date* means the date upon which the responsible party last verified the clinical trial information in the entire ClinicalTrials.gov record for the clinical trial, even if no additional or updated information was submitted at that time.

(38) *Responsible Party Contact Information* means administrative information to identify and allow communication with the responsible party by telephone, email, and regular mail or delivery service. Responsible Party Contact Information includes the name, official title, organizational affiliation, physical address, mailing address, phone number, and email address of the individual who is the responsible party or of a designated employee of the organization that is the responsible party.

(39) *Studies an FDA-regulated Device* means a clinical trial studies a device subject to section 510(k), 515, or 520(m) of the Federal Food, Drug, and Cosmetic Act.

(40) *Studies an FDA-regulated Drug* means a clinical trial studies a drug subject to section 505 of the Federal Food, Drug, and Cosmetic Act or to section 351 of the Public Health Services Act

Subpart B—Registration

§ 11.20 Who must submit clinical trial registration information?

The responsible party for an applicable clinical trial specified in § 11.22 must register the applicable clinical trial by submitting clinical trial registration information specified in § 11.28 for that clinical trial.

§ 11.22 Which applicable clinical trials must be registered?

(a) *General specification.* (1) Any applicable clinical trial that is initiated after September 27, 2007, must be registered.

(2) Any applicable clinical trial that is initiated on or before September 27, 2007, and is ongoing on December 26, 2007, must be registered.

(3) Determining the date of initiation for an applicable clinical trial. An applicable clinical trial, other than a pediatric postmarket surveillance of a device that is not a clinical trial, is considered to be initiated on the date on which the first human subject is enrolled. A pediatric postmarket surveillance of a device that is not a clinical trial is considered to be initiated on the date on which U.S. Food and Drug Administration (FDA) approves the plan for conducting the surveillance.

(b) *Determination of applicable clinical trial.* For purposes of this part, any clinical trial or study that, at any point in time, is described accurately by the data elements listed in paragraph (b)(1) or (2) of this section will be considered to meet the definition of an applicable clinical trial.

(1) *Applicable device clinical trial.* A clinical trial or study that is described accurately by the data elements listed in either paragraph (b)(1)(i) or (ii) of this section meets the definition of an applicable device clinical trial:

(i) The study is a pediatric postmarket surveillance of a device as required by FDA under section 522 of the Federal Food, Drug, and Cosmetic Act.

(ii) The study is a clinical trial that meets all of the following criteria:

(A) Study Type is interventional;

(B) Primary Purpose of the clinical trial is other than a feasibility study;

(C) Either:

(*1*) Number of Arms is two or more; or

(*2*) Number of Arms is one, and the clinical trial is Single Arm Controlled;

(D) The Intervention Type is other than a combination product;

(E) The clinical trial Studies an FDA-regulated Device; and

(F) One or more of the following applies:

(*1*) At least one Facility Location is within the U.S. or one of its *territories,*

(*2*) A device under investigation is a Product Manufactured in the U.S. or one of its territories and exported for study in another country, or

(*3*) The clinical trial has a U.S. Food and Drug Administration IDE Number.

(2) *Applicable drug clinical trial.* A clinical trial that is described accurately by the following data elements meets the definition of an applicable drug clinical trial:

(i) Study Type is interventional;

(ii) Study Phase is other than phase 1;

(iii) Either:

(A) Number of Arms is two or more, or

(B) Number of Arms is one, and the clinical trial is Single Arm Controlled;

(iv) The clinical trial Studies an FDA-regulated Drug; and

(v) One or more of the following applies:

(A) At least one Facility Location for the clinical trial is within the U.S. or one of its territories,

(B) A drug under investigation is a Product Manufactured in the U.S. or one of its territories and exported for study in another country, or

(C) The clinical trial has a U.S. Food and Drug Administration IND Number.

§ 11.24 When must clinical trial registration information be submitted?

(a) *General.* Except as provided in paragraph (b) of this section, the responsible party for an applicable clinical trial subject to § 11.22 must submit clinical trial registration information, as specified in § 11.28(a), not later than December 26, 2007, or 21 calendar days after the first human subject is enrolled, whichever date is later.

(b) *Exceptions.* (1) The responsible party for an applicable clinical trial subject to § 11.22 that is not for a serious or life-threatening disease or condition must submit clinical trial registration information not later than September 27, 2008, or 21 calendar days after the first human subject is enrolled, whichever date is later.

(2) The responsible party for an applicable device clinical trial that is a pediatric postmarket surveillance of a device and is not a clinical trial must submit clinical trial registration information, as specified in § 11.28(b), not later than December 26, 2007, or 21 calendar days after the U.S. Food and Drug Administration approves the postmarket surveillance plan, whichever date is later.

§ 11.28 What constitutes clinical trial registration information?

(a) For each applicable clinical trial that must be registered with ClinicalTrials.gov as required by § 11.22, other than a pediatric postmarket surveillance of a device that is not a clinical trial, the responsible party must provide the data elements listed below in (1) through (4), as they are defined in § 11.10(b):

(1) Descriptive information:

(i) Brief Title;

(ii) Official Title;

(iii) Brief Summary;

(iv) Primary Purpose;

(v) Study Design;

(vi) Study Phase, for an applicable drug clinical trial;

(vii) Study Type;

(viii) Whether the Study is a Pediatric Postmarket Surveillance of a Device; for an applicable device clinical trial that is a Pediatric Postmarket Surveillance of a Device;

(ix) Primary Disease or Condition Being Studied in the Trial, or the Focus of the Study;

(x) Intervention Name, for each intervention studied;

(xi) Other Intervention Name(s), for each intervention studied;

(xii) Intervention Description, for each intervention studied;

(xiii) Intervention Type, for each intervention studied;

(xiv) Studies an FDA-Regulated Device;

(xv) Studies an FDA-Regulated Drug;

(xvi) U.S. FDA Approval, Licensure, or Clearance Status, for each intervention studied;

(xvii) Product Manufactured in the U.S., for each intervention studied, if the entry for U.S. Food and Drug Administration IND or IDE number in § 11.28(a)(4)(iii) indicates that there is no IND or IDE for the clinical trial, and the entry(ies) for Facility Information in § 11.28(a)(3)(iii) include no facility locations in the United States or its territories.

(xviii) Study Start Date;

(xiv) Completion Date.

(xx) Enrollment;

(xxi) Primary Outcome Measure Information, for each primary outcome measure.

(xxii) Secondary Outcome Measure Information, for each secondary outcome measure.

(2) Recruitment information:

(i) Eligibility Criteria;

(ii) Gender;

(iii) Age Limits;

(iv) Accepts Healthy Volunteers;

(v) Overall Recruitment Status.

(vi) Why Study Stopped?

(vii) Actual Enrollment.

(viii) Individual Site Status;

(ix) Availability of Expanded Access, for an applicable drug clinical trial of a drug that is not an approved drug. If expanded access is available under section 561 of the Federal Food, Drug, and Cosmetic Act, and the expanded access record for the drug has not been submitted in accordance with § 11.28(c), the data elements listed § 11.28(c) must also be submitted.

(3) Location and contact information:

(i) Name of the Sponsor;

(ii) Responsible Party, by Official Title;

(iii) Facility information.

(4) Administrative data:

(i) Unique Protocol Identification Number.

(ii) Secondary IDs.

(iii) Food and Drug Administration IND or IDE number.

(iv) Human Subjects Protection Review Board Status.

(v) Record Verification Date.

(vii) Responsible Party Contact Information.

(b) Pediatric postmarket surveillance of a device that is not a clinical trial. For each pediatric postmarket surveillance of a device that is not a clinical trial, that must be registered with ClinicalTrials.gov as required by § 11.22, the responsible party must provide the information listed below in paragraphs (b)(1) through (3) of this section.

(1) Descriptive information:

(i) *Brief Title.* A short title of the pediatric postmarket surveillance of a device in language intended for the lay public. If an acronym or abbreviation is used to publicly identify the surveillance, it must be provided.

(ii) *Official Title.* The title of the pediatric postmarket surveillance of a device, corresponding to the title of the protocol or the FDA-approved plan for conducting the surveillance.

(iii) *Brief Summary.* A short description of the pediatric postmarket surveillance of a device, including a brief statement of the hypothesis or objective, written in language intended for the lay public, and a general description of the surveillance design including relevant population information.

(iv) *Study Type.* The type of study being registered. In the case of a pediatric postmarket surveillance of a device that is not a clinical trial, a study type of ''observational'' is required.

(v) *Whether the Study is a Pediatric Postmarket Surveillance of a Device.* For a study that includes a device as an intervention and is a pediatric postmarket surveillance of a device, an affirmation that the study is a pediatric postmarket surveillance of a device.

(vi) *Primary Disease or Condition Being Studied, or the Focus of the Study.* The name(s) of the disease(s) or condition(s) being studied in the pediatric postmarket surveillance of a device, or the focus of the study, using, if available, appropriate descriptors from the National Library of Medicine's Medical Subject Headings (MeSH) controlled vocabulary thesaurus, *http://www.nlm.nih.gov/mesh/,* or terms from another vocabulary, such as the Systematized Nomenclature of Medicine—Clinical Terms (SNOMED CT), that has been mapped to MeSH within the Unified Medical Language System (UMLS) Metathesaurus, *https://uts.nlm.nih.gov.*

(vii) *Intervention Name(s).* A brief descriptive name used to refer to each intervention studied in the pediatric postmarket surveillance of a device. A non-proprietary name of the intervention must be used, if available. If a non-proprietary name is not available, a brief descriptive name or identifier must be used.

(viii) *Other Intervention Name(s).* Any other current and former name(s) or alias(es), different from the Intervention Name(s), that the sponsor has used publicly to identify the intervention(s), including, but not limited to, past or present names such as brand name(s), serial numbers, or chemical descriptions.

(ix) *Intervention Description.* Details that can be made public about each intervention, other than the Intervention Name and Other Intervention Name, sufficient to distinguish it from other, similar interventions studied in the same or another clinical trial or pediatric postmarket surveillance of a device that is not a clinical trial.

(x) *Intervention Type.* For each intervention studied in the pediatric postmarket surveillance of a device, the general type of intervention.

(xi) *Study Start Date.* The date on which FDA approves the pediatric postmarket surveillance plan, as specified in 21 CFR 822.19(a) (or any successor regulation).

(xii) *Completion Date.* The estimated date on which the final report summarizing the results of the pediatric postmarket surveillance of a device is expected to be submitted to FDA. Once the final report has been submitted, the actual date on which the final report is submitted to FDA.

(2) Location and contact information:

(i) Name of the Sponsor.

(ii) Responsible Party, by Official Title.

(A) If the responsible party is an entity, the official name of the entity; or

(B) If the responsible party is an individual, the official title and primary organizational affiliation of the individual.

(iii) *Contact Information.* The name or official title, toll-free telephone number and email address of a person to whom questions concerning the pediatric postmarket surveillance of a device can be addressed.

(3) Administrative data:

(i) *Unique Protocol Identification Number.* The unique identification number assigned to the pediatric postmarket surveillance of a device by the sponsor, if any.

(ii) *Secondary IDs.* (A) Identification number(s) other than the organization's unique protocol identification number or NCT number that is assigned to the pediatric postmarket surveillance of a device, if any, including any unique identification numbers assigned by other publicly available registries. If the pediatric postmarket surveillance of a device is funded in whole or part by a U.S. Federal Government agency, the complete grant or contract number must be submitted as a Secondary ID.

(B) For each secondary ID listed, a description of the type of secondary ID.

(iii) *Human Subjects Protection Review Board Status.* Information to indicate whether a pediatric postmarket surveillance of a device has been approved by a human subjects protection review board or is exempt from (or otherwise not required to receive) human subjects protection review board approval. Human Subjects Protection Review Board Status must be listed as ''approved'' if at least one human subjects protection review board has approved the pediatric postmarket surveillance.

(iv) *Record Verification Date.* The date upon which the responsible party last verified the clinical trial information in the entire ClinicalTrials.gov record for the pediatric postmarket surveillance of a device, even if no additional or updated information was submitted at that time.

(v) *Responsible Party Contact Information.* Administrative information sufficient to identify and allow communication with the responsible party by telephone, email, and regular mail or delivery service. Responsible Party Contact Information includes the name, official title, organizational affiliation, physical address, mailing address, phone number, and email address of the individual who is the responsible party or of a designated employee of the organization that is the responsible party.

(c) *Expanded access record.* If expanded access is available under section 561 of the Federal Food, Drug, and Cosmetic Act to a drug studied in an applicable drug clinical trial and the data elements set forth in paragraphs (b)(1) through (4) of this section have not been submitted via an expanded access record for a previously-registered applicable clinical trial of that drug, the responsible party must submit the clinical trial information specified in paragraphs (b)(1) through (4) of this section to ClinicalTrials.gov in the form of an expanded access record. If a responsible party voluntarily submits an expanded access record for a device, then the responsible party must submit the clinical trial information specified in paragraphs (b)(1) through (4) of this section.

(1) Descriptive information:

(i) *Brief Title.* A short title of the expanded access program written in language intended for the lay public. If an acronym or abbreviation is used

publicly to identify the program, it must be provided.

(ii) *Official Title.* The title of the expanded access program, corresponding to the title of the program permitted by FDA.

(iii) *Brief Summary.* A short description of the expanded access program, including the procedure for requesting the treatment.

(iv) *Study Type.* The type of study that is being registered, in this case an ''expanded access program.''

(v) *Primary Disease or Condition.* The name(s) of the disease(s) or condition(s) for which expanded access to the drug is offered, using, if available, appropriate descriptors from the National Library of Medicine's Medical Subject Headings (MeSH) controlled vocabulary thesaurus *http://www.nlm.nih.gov/mesh/,* or terms from another vocabulary, such as the Systematized Nomenclature of Medicine—Clinical Terms (SNOMED CT), that has been mapped to MeSH within the Unified Medical Language System (UMLS) Metathesaurus, *https://uts.nlm.nih.gov.*

(vi) *Intervention Name(s).* A brief descriptive name used to refer to the drug that is available through the expanded access program. A non-proprietary name of the intervention must be used, if available. If a non-proprietary name is not available, a brief descriptive name or identifier must be used.

(vii) *Other Intervention Name(s).* Any other current and former name(s) or alias(es), different from the Intervention Name(s), that the sponsor has used publicly to identify the intervention, including, but not limited to, past or present names such as brand name(s), serial numbers, or chemical descriptions.

(viii) *Intervention Description.* Details that can be made public about each intervention, other than the Intervention Name or Other Intervention Name, sufficient to distinguish it from other, similar interventions available through other expanded access programs or clinical trials.

(ix) *Intervention Type.* For each intervention available through the expanded access program, the general type of intervention.

(2) Recruitment information:

(i) *Eligibility Criteria.* A limited list of criteria for determining who is eligible to receive treatment in the expanded access program, provided in terms of inclusion and exclusion criteria and suitable for assisting potential patients in identifying expanded access programs of interest.

(ii) *Gender.* The biological sex of the patients who may receive treatment in the expanded access program.

(iii) *Age Limits.* The minimum and maximum age of patients who may receive treatment in the expanded access program, provided in relevant units of time.

(iv) *Expanded Access Status.* The status of availability of the investigational drug through the expanded access program.

(3) Location and Contact Information:

(i) Name of the Sponsor.

(ii) Responsible Party, by Official Title.

(A) If the responsible party entering the clinical trial information into the expanded access record is an entity, the official name of the entity; or

(B) If the responsible party entering the clinical trial information into the expanded access record is an individual, the official title and primary organizational affiliation of the individual.

(iii) *Contact Information.* The name or official title, toll-free telephone number, and email address of a person to whom questions concerning the expanded access program can be addressed.

(4) *Administrative data.* (i) Unique Protocol Identification Number. Any unique identification number assigned to the expanded access program by the sponsor.

(ii) *Secondary IDs.*(A) Any identification number(s) other than the organization's unique protocol identification number or the NCT number that is assigned to the expanded access program, including any unique identification numbers assigned by other publicly available clinical trial or expanded access registries.

(B) For each Secondary ID listed, a description of the type of Secondary ID.

(iii) *Food and Drug Administration IND Number.* The IND number for the expanded access program, which must include each of the following elements:

(A) Name or abbreviation of the FDA center with whom the IND is filed (i.e., CDER, CBER);

(B) IND number assigned by the FDA center; and

(C) IND serial number (as defined in 21 CFR 312.23(e), or any successor regulation), if any, assigned to the expanded access program.

(iv) *Record Verification Date.* The date upon which the responsible party last verified the clinical trial information in the entire ClinicalTrials.gov record for the expanded access program, even if no additional or updated information was submitted at that time.

(v) *Responsible Party Contact Information.* Administrative information sufficient to identify and allow communication with the responsible party entering the clinical trial information into the expanded access record by telephone, email, and regular mail or delivery service. Responsible Party Contact Information includes the name, official title, organizational affiliation, physical address, mailing address, phone number, and -email address of the individual who is the responsible party or of a designated employee of the organization that is the responsible party.

§ 11.35 By when will NIH post clinical trial registration information submitted under § 11.28?

(a) *Applicable drug clinical trial.* NIH will post publicly at ClinicalTrials.gov the clinical trial registration information, except for certain administrative data, for an applicable drug clinical trial not later than 30 calendar days after the responsible party has submitted such information in accordance with § 11.24 of this part.

(b) *Applicable device clinical trial.* (1) For an applicable device clinical trial of a device that previously was approved or cleared, NIH will post publicly at ClinicalTrials.gov the clinical trial registration information, except for certain administrative data, not later than 30 calendar days after clinical trial results information is required to be posted in accordance with § 11.52 of this part.

(2) For an applicable device clinical trial of a device that has not been previously approved or cleared, NIH will post publicly at ClinicalTrials.gov the clinical trial registration information, except for certain administrative data, not earlier than the date of FDA approval or clearance of the device, and not later than 30 calendar days after the date of such approval or clearance.

Subpart C—Results Submission

§ 11.40 Who must submit clinical trial results information?

The responsible party for an applicable clinical trial specified in § 11.42 must submit clinical trial results information for that clinical trial.

§ 11.42 For which applicable clinical trials must clinical trial results information be submitted in accordance with subpart C of this regulation?

Unless a waiver of the requirement to submit clinical trial results information is granted in accordance with § 11.54, clinical trial results information must be submitted for any applicable clinical trial for which submission of clinical

trial registration information is required under § 11.22 and that meets one of the following criteria:

(a) The completion date of the clinical trial is on or after the effective date of this rule; or

(b) The completion date of the clinical trial is prior to the effective date of this rule, the applicable deadline established by § 11.44 is on or after the effective date of the rule, and clinical trial results information is submitted on or after the effective date of the rule, consistent with the applicable deadline established by § 11.44.

§ 11.44 When must clinical trial results information be submitted for applicable clinical trials subject to § 11.42?

(a) *Standard submission deadlines* (1) In general, clinical trial results information specified in § 11.48 must be submitted no later than 1 year after the completion date, except as otherwise provided in this section.

(2) Submitting clinical trial results information following initial approval, licensure, or clearance. Except as otherwise provided in §§ 11.44(b), (c), (d) or (e), for any applicable clinical trial of an FDA-regulated drug or device that is not approved, licensed, or cleared as of the completion date and that receives initial FDA approval, licensure, or clearance thereafter, clinical trial results information specified in § 11.48(a) must be submitted by the earlier of the following:

(i) The submission deadline specified in § 11.44(a)(1); or

(ii) The date that is 30 calendar days after FDA approves, licenses, or clears the drug or device for any indication studied in the applicable clinical trial.

(b) *Delayed submission of results with certification if seeking approval, licensure, or clearance of a new use.* (1) If, prior to the results submission deadline specified under paragraph (a)(1) of this section, the responsible party submits to ClinicalTrials.gov a certification that an applicable clinical trial involves an FDA-regulated drug or device that previously has been approved, licensed, or cleared, for which the manufacturer is the sponsor of the applicable clinical trial, and for which an application or premarket notification seeking approval, licensure, or clearance of the use being studied (which is not included in the labeling of the approved, licensed, or cleared drug or device) has been filed or will be filed within 1 year with FDA, the deadline for submitting complete clinical trial results information will be 30 calendar days after the earliest of the following events:

(i) FDA approves, licenses, or clears the drug or device for the use studied in the applicable clinical trial;

(ii) FDA issues a letter that ends the regulatory review cycle for the application or submission but does not approve, license, or clear the drug or device for the use studied in the applicable clinical trial; or

(iii) The application or premarket notification seeking approval, licensure, or clearance of the new use is withdrawn without resubmission for not less than 210 calendar days.

(2) *Two-year limitation.* Notwithstanding the deadlines specified in paragraph (b)(1) of this section, the responsible party must submit complete clinical trial results information not later than the date that is 2 years after the date that the certification was submitted, except to the extent that paragraph (d) of this section applies.

(3) *Additional Requirements.* If a responsible party who is both the manufacturer of the drug or device studied in an applicable clinical trial and the sponsor of the applicable clinical trial submits a certification in accordance with paragraph (b)(1) of this section, that responsible party must submit such a certification for each applicable clinical trial that meets the following criteria:

(i) The applicable clinical trial is required to be submitted in an application or premarket notification for seeking approval, licensure, or clearance of a new use; and

(ii) The applicable clinical trial studies the same drug or device for the same use as studied in the applicable clinical trial for which the initial certification was submitted.

(c) *Delayed submission of results with certification if seeking initial approval, licensure or clearance of a drug or device.* (1) If, prior to the submission deadline specified under paragraph (a)(1) of this section, a responsible party submits to ClinicalTrials.gov a certification that an applicable clinical trial studies an FDA-regulated drug or device that was not approved, licensed, or cleared by FDA for any use before the completion date of the trial, and that the sponsor intends to continue with product development and is either seeking, or may at a future date seek FDA approval, licensure, or clearance of the drug or device under study, the deadline for submitting complete clinical trial results information will be 30 calendar days after the earlier of the date on which:

(i) FDA approves, licenses, or clears the drug or device for any indication that is studied in the applicable clinical trial;

(ii) The marketing application or premarket notification is withdrawn without resubmission for not less than 210 calendar days.

(2) *Two-year limitation.* Notwithstanding the deadlines established in paragraph (c)(1) of this section, the responsible party must submit complete clinical trial results information not later than 2 years after the date on which the certification was submitted, except to the extent that paragraph (d) of this section applies.

(d) *Submitting partial results.* (1) If required clinical trial results information specified in § 11.48 has not been collected for a secondary outcome measure by the completion date, the responsible party must submit clinical trial results information for that secondary outcome measure by the later of:

(i) 1 year after the date on which the final subject is examined or receives an intervention for the purposes of final collection of data for that secondary outcome measure, whether the clinical trial was concluded according to the pre-specified protocol or was terminated, or

(ii) If a certification to delay results submission has been submitted under paragraph (b) or (c) of this section, the date on which results information for the primary outcome measures are due pursuant to paragraph (b) or (c) of this section.

(2) If clinical trial results information was submitted for the primary outcome measure(s) prior to the effective date of the rule but data collection for all of the secondary outcome measure(s) is not completed until on or after the effective date of the rule, clinical trial results information for all primary and secondary outcome measures must be submitted in accordance with § 11.48 not later than 1 year after the date on which the final subject is examined or receives an intervention for the purposes of final collection of data for such secondary outcome measure(s), whether the clinical trial was concluded according to the pre-specified protocol or was terminated.

(e) *Extensions.* (1) Requesting a good-cause extension of the results submission deadline. A responsible party may request a good-cause extension of the deadline for submitting clinical trial results information to ClinicalTrials.gov subject to paragraphs (e)(1)(i) and (ii) of this section. A responsible party may request more than one good-cause extension for the same applicable clinical trial and may request a good-cause extension of a delayed results submission deadline established by the submission of a

certification as described in paragraph (b) or (c) of this section.

(i) The responsible party must submit a request for a good-cause extension to ClinicalTrials.gov prior to the date on which clinical trial results information would otherwise be due in accordance with paragraph (a), (b), (c), (d), or (f) of this section.

(ii) A request for a good-cause extension must contain the following elements:

(A) Description of the reason(s) why clinical trial results information cannot be provided according to the deadline, with sufficient detail to allow evaluation of the request; and

(B) Estimate of the date on which the clinical trial results information will be submitted.

(2) *Decision and submission deadline.* The NIH will provide a written response electronically to the responsible party indicating whether or not the requested extension has been granted, and the responsible party must either submit clinical trial results information not later than the deadline established by paragraphs (e)(2)(i) or (ii) of this section, as applicable, or appeal the denial in accordance with paragraph (e)(3) of this section.

(i) If the good-cause extension request is granted, the responsible party must submit clinical trial results information not later than the date of the deadline specified in the electronic response.

(ii) If the good-cause extension request is denied, the responsible party must either appeal in accordance with paragraph (e)(3) of this section or submit complete clinical trial results information by the later of the original submission deadline specified in paragraph (a), (b), (c), (d), or (f) of this section, as applicable, or 15 calendar days after the date on which the electronic notice of the denial is sent to the responsible party.

(3) *Appealing a denied extension request.* (i) A responsible party who seeks to appeal a denied extension request or the deadline specified in a granted extension must submit an appeal in the form of a written letter to the Director not later than 15 calendar days after the date on which the electronic notification of grant or denial of the request is sent to the responsible party.

(ii) An appeal letter must contain an explanation of the reason(s) why the initial decision to deny an extension request or to grant an extension request with a shorter deadline than requested should be overturned or revised.

(iii) The Director will provide an electronic notification to the responsible party indicating whether or not the requested extension has been granted upon appeal.

(iv) If the Director grants the extension request upon appeal, the responsible party must submit clinical trial results information not later than the deadline specified in the electronic notification specified in paragraph (e)(3)(iii) of this section.

(v) If the Director denies an appeal of a denied extension request, the responsible party must submit clinical trial results information by the later of the original submission deadline specified in paragraph (a), (b), (c), (d) or (f) of this section, or 15 calendar days after the electronic notification of the denial upon appeal specified in paragraph (e)(3)(iii) of this section, is sent to the responsible party.

(vi) If the Director denies an appeal of a deadline specified in a granted extension request, the responsible party must submit clinical trial results information by the later of the deadline specified in the notification granting the extension request, specified in paragraph (e)(2)(i) of this section or 15 calendar days after the electronic notification denying the appeal, specified in paragraph (e)(3)(iii) of this section, is sent to the responsible party.

(f) Pediatric postmarket surveillance of a device that is not a clinical trial. For each pediatric postmarket surveillance of a device that is not a clinical trial as defined in this part, the responsible party must submit clinical trial results information as specified in § 11.48(b) not later than 30 calendar days after the date on which the final report of the approved pediatric postmarket surveillance of a device as specified in 21 CFR 822.38 (or any successor regulation) is submitted to FDA.

§ 11.48 What constitutes clinical trial results information?

(a) For each applicable clinical trial other than a pediatric postmarket surveillance of a device that is not a clinical trial for which clinical trial results information must be submitted under § 11.42, the responsible party must provide the following:

(1) *Participant flow.* Information for completing a table documenting the progress of human subjects through a clinical trial by arm, including the number who started and completed the clinical trial. This information must include the following elements:

(i) Participant Flow Arm Information. A brief description of each arm used for describing the flow of human subjects through the clinical trial, including a descriptive title used to identify each arm.

(ii) Pre-assignment Information. A description of significant events affecting the number of human subjects enrolled in the clinical trial but not assigned to an arm, if any.

(iii) Participant Data. The number of human subjects that started and completed the clinical trial, by arm.

(2) *Demographic and baseline characteristics.* Information for completing a table of demographic and baseline measures and data collected by arm or comparison group and for the entire population of human subjects who participated in the clinical trial. This information must include the following elements:

(i) *Baseline Characteristics Arm/Group Information.* A brief description of each arm or comparison group used for describing the demographic and baseline characteristics of the human subjects in the clinical trial, including a descriptive title used to identify each arm or comparison group.

(ii) *Overall Number of Baseline Participants.* The total number of human subjects for whom baseline characteristics were measured, by arm or comparison group, and overall.

(iii) *Baseline Measure Information.* A description of each baseline or demographic characteristic measured in the clinical trial, including age, gender, and any other measure(s) that were assessed at baseline and are used in the analysis of outcome measures in accordance with § 11.48(a)(3). The description of each measure must include the following elements:

(A) Name and Description of the measure, including any categories that are used in submitting the results;

(B) *Measure Type and Measure of Dispersion:* For each baseline measure submitted, an indication of the type of data to be submitted and, the associated measure of dispersion;

(C) *Unit of measure.*

(iv) *Baseline Measure Data.* The value(s) for each submitted baseline measure, by arm or comparison group and for the entire population of human subjects who participated in the clinical trial.

(3) *Outcomes and statistical analyses.* Information for completing a table of data for each primary and secondary outcome measure by arm or comparison group, including the result(s) of scientifically appropriate statistical analyses that were performed on the outcome measure data, if any. This information must include the following elements:

(i) *Outcome Measure Arm/Group Information.* A brief description of each arm or comparison group used for submitting an outcome measure for the

clinical trial, including a descriptive title to identify each arm or comparison group.

(ii) *Analysis Population Information* (A) Number of Participants Analyzed. The number of human subjects for which an outcome was measured and analyzed, by arm or comparison group.

(B) Number of Units Analyzed. If the analysis is based on a unit other than participants, a description of the unit of analysis and the number of units for which an outcome was measured and analyzed, by arm or comparison group.

(C) Analysis Population Description. If the Number of Participants Analyzed differs from the number of human subjects assigned to the arm or comparison group, a brief description of the reason(s) for the difference.

(iii) *Outcome Measure Information.* A description of each outcome measure, to include the following elements:

(A) Name of the specific outcome measure, including the titles of any categories in which Outcome Measure Data are aggregated;

(B) Description of the metric used to characterize the specific outcome measure;

(C) Time point(s) at which the measurement was assessed for the specific metric;

(D) Outcome Measure Type. The type of outcome measure, whether primary, secondary, other pre-specified, or post-hoc;

(E) *Outcome Measure Reporting Status.* Whether data for the outcome measure are included in the present submission and, if not, the anticipated submission date;

(F) *Measure Type.* For each outcome measure for which data are collected, the type of data to be submitted (number or measure of central tendency) and, if a measure of central tendency, the related measure of dispersion or precision;

(G) *Unit of Measure.* For each outcome measure for which data are collected, the unit of measure.

(iv) *Outcome Measure Data.* The measurement value(s) for each outcome measure for which data are collected, by arm or comparison group, and by category (if specified).

(v) *Statistical Analyses.* Result(s) of scientifically appropriate statistical analyses, if any, including any statistical analysis that is:

(A) Pre-specified in the protocol and/or statistical analysis plan that was performed on the outcome measure data,

(B) Made public by the sponsor or responsible party prior to the date on which results information is submitted for all primary and secondary outcome measures studied in the clinical trial, or

(C) Conducted in response to a request made by the U.S. Food and Drug Administration prior to the date on which complete clinical trial results information is submitted for all of the primary outcome measures studied in the clinical trial. Submitted Statistical Analysis information must include:

(*1*) *Statistical Analysis Overview:* Identification of the arms or comparison groups compared in the statistical analysis, the type of statistical test conducted; and, for a non-inferiority test, a description of the analysis that includes, at minimum, the power calculation and non-inferiority margin;

(*2*) *Statistical Test of Hypothesis:* The p-value and the procedure used for the statistical analysis;

(*3*) *Method of Estimation:* The estimation parameter, estimated value, and confidence interval.

(4) *Adverse event information.* (i) Information for completing two tables summarizing adverse events collected during an applicable clinical trial:

(A) Table of all serious adverse events grouped by organ system, with the number and frequency of each event by arm or comparison group; and

(B) Table of all adverse events, other than serious adverse events, that exceed a frequency of 5 percent within any arm of the clinical trial, grouped by organ system, with the number and frequency of each event by arm or comparison group.

(ii) Information for each table specified in paragraph (a)(4)(i) of this section must include the following elements:

(A) *Adverse Event Arm/Comparison Group Information.* A brief description of each arm or comparison group used for submitting adverse event information from the clinical trial, including a descriptive title used to identify each arm or comparison group.

(B) *Total Number Affected, by Arm or Comparison Group.* The overall number of human subjects affected, by arm or comparison group, by one or more

(*1*) Serious adverse event(s), or

(*2*) Adverse event(s) other than serious adverse events that exceed a frequency of 5 percent within any arm of the clinical trial.

(C) *Total Number at Risk, by Arm or Comparison Group.* The overall number of human subjects included in the assessment, by arm or comparison group, for

(*1*) Serious adverse events, or

(*2*) Adverse event(s) other than serious adverse events that exceed a frequency of 5 percent within any arm of the clinical trial.

(D) *Total Number Affected, by Organ System.* For each organ system that has one or more adverse events listed in either the table of serious adverse events or the table of adverse events other than serious adverse events that exceed a frequency of 5 percent within any arm of the clinical trial, the overall number of human subjects affected, by arm or comparison group, within each table.

(E) *Total Number at Risk, by Organ System.* For each organ system that has one or more adverse events listed in either the table of serious adverse events or the table of adverse events other than serious adverse events that exceed a frequency of 5 percent within any arm of the clinical trial, the overall number of human subjects at risk for the adverse event, by arm or comparison group.

(F) *Adverse Event Information.* A description of each type of serious adverse event and other adverse event that is not a serious adverse event and exceeds a frequency of 5 percent within any arm of the clinical trial, consisting of the following attributes:

(*1*) Descriptive term for the adverse event; and

(*2*) Organ system associated with the adverse event.

(G) *Adverse Event Data.* For each type of adverse event listed in accordance with paragraph (a)(4)(ii)(F) of this section:

(*1*) Number of human subjects affected by such adverse event;

(*2*) Number of human subjects at risk for such adverse event;

(H) *Additional Adverse Event Description.* If the adverse event information collected in the applicable clinical trial is collected based on a different definition of adverse event and/or serious adverse event than defined in this part, a brief description of how those definitions differ.

(iii) Information submitted by organ system must be grouped according to the organ system classification established in ClinicalTrials.gov.

(5) *Administrative information.* (i) *Results Point of Contact.* Point of contact for scientific information about the clinical trial results information, including the following:

(A) Name or official title of the point of contact;

(B) Name of affiliated organization; and

(C) Telephone number and email address of the point of contact.

(ii) *Certain Agreements.* An indication of whether the principal investigator is an employee of the sponsor and, if not, whether there exists any agreement (other than an agreement solely to comply with applicable provisions of law protecting the privacy of human

subjects participating in the clinical trial) between the sponsor or its agent and the principal investigator that restricts in any manner the ability of the principal investigator, after the completion date of the clinical trial, to discuss the results of the clinical trial at a scientific meeting or any other public or private forum, or to publish in a scientific or academic journal information concerning the results of the clinical trial.

(6) *Additional clinical trial results information for applicable device clinical trials of unapproved or uncleared devices.* (i) For an applicable device clinical trial of an unapproved or uncleared device, the responsible party must provide the following data elements, as the data elements are defined in § 11.10(b): Brief Title; Official Title; Brief Summary; Primary Purpose; Study Design; Study Type; Primary Disease or Condition Being Studied in the Trial, or the Focus of the Study; Intervention Name; Other Intervention Name; Intervention Description; Intervention Type; U.S. FDA Approval, Licensure, or Clearance Status; Study Start Date; Completion Date; Enrollment; Primary Outcome Measure Information, as previously submitted to ClinicalTrials.gov; Secondary Outcome Measure Information as previously submitted to ClinicalTrials.gov; Eligibility Criteria; Gender; Age Limits; Accepts Healthy Volunteers; Overall Recruitment Status; Why Study Stopped; Actual Enrollment; Name of the Sponsor; Responsible Party by Official Title; Facility Name and Facility Location, for each participating facility in a clinical trial; Unique Protocol Identification Number; Secondary IDs; Human Subjects Protection Review Board Status; and Record Verification Date.

(ii) The responsible party shall submit the results information specified in paragraph (a)(6)(i) of this section by submitting an affirmation that the information previously submitted to ClinicalTrials.gov for the data elements listed in paragraph (a)(6)(i) of this section have been updated in accordance with § 11.64(c) and are to be included as clinical trial results information.

(b) *Pediatric postmarket surveillance of a device that is not a clinical trial.* For each pediatric postmarket surveillance of a device that is not a clinical trial, the responsible party must submit a copy of any written final report that is submitted to FDA as specified in 21 CFR 822.38 (or any successor regulation). The final written report must be in a common electronic document format specified at *http://prsinfo.clinicaltrials.gov.* The responsible party must redact names, addresses, and other personally identifiable information or commercial confidential information contained in the final written report prior to submission to NIH. Redacted information may not include any information specified in §§ 11.28(a) or 11.48(a) of this part.

§ 11.52 When will NIH post submitted clinical trial results information?

The Director will post publicly clinical trial results information submitted under this subpart at ClinicalTrials.gov not later than 30 calendar days after the date of submission.

§ 11.54 What are the procedures for waiving of the requirements of this subpart?

(a) Waiver request.

(1) A responsible party may request a waiver from any applicable requirement(s) of this subpart by submitting a waiver request in the form of a written letter to the Secretary or delegate prior to the deadline specified in § 11.42(a) for submitting clinical trial results information.

(2) The waiver request must contain:

(i) The NCT number, Brief Title, and Name of the Sponsor of the applicable clinical trial for which the waiver is requested;

(ii) The specific requirement(s) of this subpart for which the waiver is requested; and

(iii) A description of the extraordinary circumstances that the responsible party believes justify the waiver and an explanation of why granting the request would be consistent with the protection of public health or in the interest of national security.

(3) The responsible party will not be required to comply with the specified requirements of this subpart for which a waiver is granted.

(4) The responsible party must comply with any requirements of this subpart for which a waiver is not granted or must submit an appeal as set forth in paragraph (b) of this section. The deadline for submitting any required clinical trial results information will be the later of the original submission deadline or 15 calendar days after the notification of the denial is sent to the responsible party.

(b) Appealing a denied waiver request

(1) A responsible party may appeal a denied waiver request by submitting a letter in writing to the Secretary or delegate not later than 15 calendar days after the date on which the letter in paragraph (a)(iii) of this section denying the request is transmitted.

(2) The responsible party is not required to comply with any requirements of this subpart for which the waiver is granted upon appeal.

(3) The responsible party must submit clinical trial results information to comply with any requirements of this subpart that are not waived upon appeal by the later of the original submission deadline or 15 calendar days after the written notice of the denial upon appeal is sent by the Secretary.

(c) If a waiver is granted under paragraph (a) or (b) of this section,

(1) The Director will include a notation in the clinical trial record that specified elements of the requirements of this part have been waived.

(2) The Secretary will notify, in writing, the appropriate committees of Congress and provide an explanation for why the waiver was granted, not later than 30 calendar days after any part of a waiver is granted.

Subpart D—Additional Submissions of Clinical Trial Information

§ 11.60 What requirements apply to the voluntary submission of clinical trial information for clinical trials of FDA-regulated drugs and devices?

(a) If a responsible party voluntarily submits clinical trial information for a clinical trial described in paragraph (a)(1) of this section, the responsible party must meet the conditions specified in paragraph (a)(2) of this section.

(1) Clinical trials to which this section applies. The requirements of this section apply to the following types of clinical trials:

(i) A clinical trial of an FDA-regulated drug or device that is not an applicable clinical trial, and

(ii) An applicable clinical trial that is not required to submit clinical trial registration information under § 11.22(a).

(2) Conditions for voluntary submission of certain clinical trials. The following conditions must be met by a responsible party who voluntarily submits clinical trial information for a clinical trial that is described in paragraph (a)(1) of this section.

(i) The responsible party must submit the information in (A) or (B) for the clinical trial being submitted voluntarily.

(A) If the responsible party voluntarily registers a clinical trial, the responsible party must submit complete clinical trial registration information specified in § 11.28(a). The responsible party may, but is not required to, submit

complete clinical trial results information in § 11.48(a).

(B) If the responsible party voluntarily submits clinical trial results information for a clinical trial for which the clinical trial registration information specified in § 11.28(a) has not been submitted, the responsible party must submit the data elements specified in § 11.48(a), as well as the data elements listed below, as those the data elements are defined in § 11.10(b) and apply to the clinical trial and the interventions studied: Brief Title; Official Title; Brief Summary; Primary Purpose; Study Design; Study Phase, for a clinical trial of a drug; Study Type; Whether the Study is a Pediatric Postmarket Surveillance of a Device; Primary Disease or Condition Being Studied in the Trial; or the Focus of the Study; Intervention Name, for each intervention studied; Other Intervention Name, for each intervention studied; Intervention Description, for each intervention studied; Intervention Type, for each intervention studied; U.S. FDA Approval, Licensure, or Clearance Status, for each intervention studied; Product Manufactured in the U.S., for each intervention studied; Studies an FDA-regulated Device; Studies an FDA-regulated Drug; Study Start Date; Completion Date; Enrollment; Eligibility Criteria; Gender; Age Limits; Accepts Healthy Volunteers; Overall Recruitment Status; Why Study Stopped; Actual Enrollment; Availability of Expanded Access; Name of the Sponsor; Responsible Party by Official Title; Facility Name and Facility Location, for each participating facility; Unique Protocol Identification Number; Secondary IDs; Food and Drug Administration IND or IDE Number; Human Subjects Protection Review Board Status; Record Verification Date; and Responsible Party Contact Information.

(ii) If, on or after September 27, 2007, a manufacturer submits an application or premarket notification to FDA for approval, licensure, or clearance of a drug or device under sections 505, 510(k), 515, or 520(m) of the Federal Food, Drug, and Cosmetic Act or section 351 of the Public Health Service Act for the use studied in the clinical trial submitted under paragraph (a)(1) of this section, the Responsible Party specified in paragraph (a)(1) of this section must also submit the information specified in paragraph (a)(2)(iii) of this section by the deadline specified in paragraph (a)(2)(iv)(B) of this section for any applicable clinical trial that has not been submitted to ClinicalTrials.gov and that meets the following criteria:

(A) The applicable clinical trial is required to be submitted to FDA under sections 505, 510(k), 515, or 520(m) of the Federal Food, Drug, and Cosmetic Act or section 351 of the Public Health Service Act in an application or premarket notification for approval, licensure, or clearance to market the drug or device for the use studied in the clinical trial specified in paragraph (a)(1) of this section; and

(B) The manufacturer of the drug or device studied in the applicable clinical trial is also the responsible party for the clinical trial specified in paragraph (a)(1) of this section.

(iii) Information to be submitted for clinical trials described in paragraph (a)(2)(ii) of this section:

(A) If the clinical trial information voluntarily submitted for a clinical trial described in paragraph (a)(1) of this section consists only of the clinical trial registration information specified in § 11.28(a), then the information to be submitted in accordance with paragraph (a)(2)(ii) of this section must consist, at minimum, of the clinical trial registration information specified in § 11.28(a).

(B) If the clinical trial information voluntarily submitted for a clinical trial described by paragraph (a)(1) of this section consists of the clinical trial results information specified in § 11.60(a)(2)(i)(B), then the information to be submitted in accordance with paragraph (a)(2)(ii) of this section must consist of the clinical trial results information specified in § 11.60(a)(2)(i)(B).

(C) If the clinical trial information voluntarily submitted for a clinical trial described by paragraph (a)(1) of this section consists of both the clinical trial registration information specified in § 11.28(a) and the clinical trial results information specified in § 11.48(a), then the information to be submitted in accordance with paragraph (a)(2)(ii) of this section must consist of the clinical trial registration information specified in § 11.28(a) and the clinical trial results information specified in § 11.48(a).

(iv) Submission deadlines:

(A) Secondary outcome measure(s) for voluntarily-submitted clinical trials under paragraph (a) of this section. If data collection for the secondary outcome measure(s) for a voluntarily-submitted clinical trial under paragraph (a) of this section, which submission consists of clinical trial results information, is not completed by the completion date of the voluntarily-submitted clinical trial, then clinical trial results information for the secondary outcome measure(s) must be submitted by the later of the date that the clinical trial results information is voluntarily submitted for the primary outcome measure(s) or 1 year after the date on which the final subject was examined or received an intervention for the purposes of final collection of data for the secondary outcome(s), whether the clinical trial was concluded according to the pre-specified protocol or was terminated.

(B) The clinical trial information specified in paragraph (a)(2)(iii) of this section must be submitted not later than the later of the date on which the application or premarket notification to FDA for approval, licensure, or clearance to market a drug or device under section 351 of the Public Health Service Act or sections 505, 510(k), 515, or 520(m) of the Federal Food, Drug, and Cosmetic Act for the use studied in the clinical trial specified under paragraph (a)(1) of this section is submitted to FDA; or, the date on which the clinical trial information specified in paragraph (a)(2)(i) of this section for the clinical trial specified under paragraph (a)(1) of this section is submitted to ClinicalTrials.gov.

(v) All submissions of clinical trial information under paragraph (a) of this section are subject to the update requirements specified in § 11.64 and the corrections requirements specified in § 11.66.

(b) Statement to accompany applicable clinical trials submitted under paragraph (a) of this section. Each applicable clinical trial for which clinical trial information is submitted under paragraph (a) of this section and posted at ClinicalTrials.gov will include the statement ''Clinical trial information for this applicable clinical trial was submitted under section 402(j)(4)(A) of the Public Health Service Act and 42 CFR 11.60 and is not subject to the deadlines established by sections 402(j)(2) and (3) of the Public Health Service Act or 42 CFR 11.24 and 11.44.''

§ 11.62 What requirements apply to applicable clinical trials for which submission of clinical trial information has been determined by the Director to be necessary to protect the public health?

(a) A responsible party who receives notification that the Director has determined that posting of clinical trial information for an applicable clinical trial described in paragraph (b) of this section is necessary to protect the public health must submit clinical trial information as specified in paragraph (c) of this section.

(b) An applicable clinical trial subject to this section must be either:

(1) An applicable clinical trial of an approved, licensed, or cleared drug or

device that has a completion date on or after September 27, 1997; or

(2) An applicable clinical trial that is subject to registration under § 11.22(a) and studies a drug or device that is unapproved, unlicensed, or uncleared.

(c) Deadline for submission of clinical trial information.

(1) *General.* Except as provided in paragraphs (c)(2) and (c)(3) of this section, a responsible party for an applicable clinical trial that is subject to this section must submit clinical trial registration information specified in § 11.28(a) and clinical trial results information specified in § 11.48(a) to ClinicalTrials.gov not later than 30 calendar days after the submission date specified in the notification described in paragraph (a) of this section.

(2) *Exception.* If a responsible party submits a certification consistent with § 11.44(b) or (c) not later than 30 calendar days after the submission date specified in the notification described in paragraph (a) of this section, the responsible party must submit clinical trial results information specified in § 11.48(a) not later than the deadline specified in § 11.44(b) or (c), as applicable.

(3) If a responsible party submitted clinical trial registration information describing the applicable clinical trial specified in the notification described in paragraph (a) of this section prior to the date on which the notification is sent to the responsible party, the responsible party must update such clinical trial information to reflect changes, if any, in the applicable clinical trial not later than 30 calendar days after the submission date specified in the notification described in paragraph (a) of this section, irrespective of the deadline for updates specified in § 11.64.

§ 11.64 When must clinical trial information submitted to ClinicalTrials.gov be updated?

(a) *General.* (1) Except as provided in paragraphs (b) and (c) of this section, the responsible party for an applicable clinical trial or other clinical trial must submit updates to reflect changes to previously-submitted clinical trial information not less than once every 12 months, unless there are no changes to the clinical trial information during the preceding 12-month period.

(2) Updates to the estimated Completion Date must be submitted not less than once every 12 months, unless there is no change to the estimated date during the preceding 12-month period.

(3) A responsible party must continue to submit updates as specified in this section until the date on which complete clinical trial results information specified in § 11.48 has been submitted for all primary and secondary outcomes and all adverse events that were collected in accordance with the protocol.

(b) *Items Requiring More Rapid Updates.* (1) A responsible party must submit updates to reflect changes to the following clinical trial information data elements not later than 30 calendar days after the change has occurred:

(i) If the first human subject was not enrolled in the clinical trial at the time of registration, the Study Start Date data element must be updated not later than 30 calendar days after the first human subject is enrolled.

(ii) Intervention Name(s) must be updated to a non-proprietary name not later than 30 calendar days after a non-proprietary name is established for any intervention included in the Intervention Name(s) data element.

(iii) *Availability of Expanded Access.* (A) If expanded access to a drug becomes available after a clinical trial of that drug has been registered, the responsible party must, not later than 30 calendar days after expanded access becomes available, update the Availability of Expanded Access data element for that clinical trial and, unless an expanded access record has already been created as required by § 11.28(a)(2)(ix), submit the data elements listed in § 11.28(c) to create an expanded access record.

(B) Upon receipt of an NCT number for an expanded access record created for a clinical trial under § 11.28(a)(2)(ix), the responsible party must update the Availability of Expanded Access data element by entering in the clinical trial record the NCT number of the expanded access record no later than 30 calendar days after the date on which the responsible party receives such NCT number.

(C) Upon termination of an expanded access program, the responsible party must, not later than 30 calendar days after the date of termination, update the Availability of Expanded Access data element to indicate that expanded access is no longer available.

(iv) Expanded Access Status, under § 11.28(c)(2)(iv), must be updated not later than 30 calendar days after a change in the availability of access to an investigational drug or investigational device under section 561 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 360bbb).

(v) Overall Recruitment Status must be updated not later than 30 calendar days after any change in overall recruitment status. At the time Overall Recruitment Status is changed, the responsible party must also make the following updates, as applicable:

(A) If Overall Recruitment Status is changed to ''suspended,'' ''terminated,'' or ''withdrawn,'' the Why Study Stopped data element must be submitted.

(B) If Overall Recruitment Status is changed to ''terminated'' or ''active, not recruiting,'' the Actual Enrollment data element must be submitted.

(vi) Individual Site Status must be updated not later than 30 calendar days after a change in status of any individual site.

(vii) Human Subjects Protection Review Board Status must be updated not later than 30 calendar days after a change in status.

(viii) Completion Date must be updated not later than 30 calendar days after the clinical trial reaches its actual completion date;

(ix) Responsible Party, by Official Title must be updated not later than 30 calendar days after a change in the responsible party or the official title of the responsible party;

(x) Responsible Party Contact Information must be updated not later than 30 calendar days after a change in the responsible party or the contact information of the responsible party;

(2) Updates to the U.S. FDA Approval, Licensure, or Clearance Status data element must be submitted not later than 15 calendar days after a change in status has occurred.

(3) If a protocol is amended in such a manner that changes are communicated to human subjects in the clinical trial, updates to relevant clinical trial information data elements must be submitted no later than 30 calendar days after the protocol amendment is approved by a human subjects protection review board.

(4) Record Verification Date must be updated any time the responsible party reviews the complete set of submitted clinical trial information for accuracy, even if no other updated information is submitted at that time.

(c) Irrespective of update requirements established in paragraphs (a) and (b) of this section, upon submission of clinical trial results information for an applicable clinical trial or other clinical trial, a responsible party must submit updates to the clinical trial registration information submitted previously to ClinicalTrials.gov for that applicable clinical trial or other clinical trial, unless there are no changes to the clinical trial registration information.

(d) Public availability of updates.

(1) Updates to clinical trial registration information and clinical

trial results information will be posted in accordance with § 11.35 and § 11.52, respectively.

(2) The Director will retain prior clinical trial registration information and clinical trial results information and make it publicly available in accordance with § 11.35 and § 11.52, respectively, through ClinicalTrials.gov so that the updates do not result in the removal of any information from the original submission or any preceding update.

§ 11.66 What are the requirements for corrections of clinical trial information?

(a) *Correction of errors.* A responsible party who becomes aware of errors in any clinical trial information submitted under this part or is informed by NIH that such clinical trial information contains errors shall correct such errors not later than 15 calendar days after the date on which the responsible party becomes aware of the errors or on which NIH informs the responsible party of the errors, whichever is earlier.

(b) *Correction of falsified data.* A responsible party who becomes aware that clinical trial information submitted under this part was falsified or based on falsified information, shall notify the Director that such information was determined to be falsified or based on falsified information and either:

(1) Submit corrected clinical trial information not later than 15 calendar days after corrected information becomes available; or

(2) Notify the Director not later than 15 calendar days after determining that such information cannot be corrected or is correct as submitted.

(c) *Other corrections of clinical trial information.* A responsible party who becomes aware or is informed by NIH that corrections other than those specified in paragraphs (a) or (b) of this section are needed to any clinical trial information submitted under this part, shall correct such clinical trial information as soon as possible, but not later than 15 calendar days after the date on which the responsible party becomes aware, or is informed by NIH that such clinical trial information is in need of correction, whichever is earlier.

Dated: October 7, 2014.

Francis S. Collins,

Director, National Institutes of Health.

Approved: October 28, 2014.

Sylvia Mathews Burwell,

Secretary.

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