Supporting Statement A for:

Information Program on Clinical Trials: Maintaining a Registry and Results Databank (NLM)

(OMB Control #:0925-0586)

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LIST OF ATTACHMENTS:

A.1 Circumstances Making the Collection of Information Necessary

This information collection request seeks approval of a revision of the existing Paperwork Reduction Act clearance for the collection of Clinical Trial Registration and Results Information via the ClinicalTrials.gov web site operated by the National Library of Medicine (NLM) under the authority of the Director of the National Institutes of Health (NIH). This supporting statement provides additional information about the request for processing the information collection request, Information Program on Clinical Trials: Maintaining a Registry and Results Databank (NLM), to update the existing Paperwork Reduction Act (PRA) clearance. The Office of Management and Budget (OMB) Notice-of-Action authorizing the current 3-year approval of the information collection (OMB No. 0925-0586) was issued November 25, 2015 and is due to expire on November 30, 2018.

Compelling reasons exist for the collection of updated clinical trial registration and results information by ClinicalTrials.gov. This information collection is necessary to implement statutory requirements of Section 801 of the Food and Drug Administration Amendments Act of 2007 (FDAAA) and the Clinical Trials Registration and Results Information Submission final rule (42 CFR Part 11), issued by the Department of Health and Human Services (HHS) on September 21, 2016 (81 FR 64981). The rule expands and clarifies the statutory requirements as required and authorized by FDAAA, following publication of a notice of proposed rulemaking (NPRM) on November 21, 2014, with 90-day public comment period (79 FR 69566). That comment period was extended for 30 days, as described in the extension notice published on February 13, 2015 (80 FR 8030).

FDAAA amends section 402 of the Public Health Service (PHS) Act (42 U.S.C. 282) to add a new subsection (j) that expands the data bank of clinical trial information, ClinicalTrials.gov, that was established under previous law (Section 113(a) of the Food and Drug Administration Modernization Act of 1997 (FDAMA), which is now subsection (i) of section 402 of the Public Health Service Act (42 U.S.C. 282(i)), and makes available to the public a searchable data bank of information about the results of certain clinical trials of drug products (including biological products) and device products.

Pursuant to section 402(j) of the PHS Act, the Director of NIH is to collect and make available to the public in a searchable data bank information concerning certain clinical trials of drug products (including biological products) and device products that are subject to regulation by the Food and Drug Administration (FDA) under sections 505, 510(k), 515, or 520(m) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355, 360(k), 360e, 360j(m)) and section 351 of the Public Health Service Act (42 U.S.C. 262) (i.e., applicable clinical trials). FDAAA mandates the implementation of the revised and expanded clinical trials registry by December 26, 2007 and the addition of basic results information beginning on September 27, 2008. It specifies a set of requirements for the submission of adverse event information beginning on September 27, 2009. FDAAA requires the responsible party for specified clinical trials of FDA-regulated drug products (including biological products) and device products to submit clinical trial registration and results information (including adverse event information) to ClinicalTrials.gov on specified timelines. The statute permits the NIH to collect information on other types of clinical trials and on applicable clinical trials that were

completed prior to enactment of the law using alternative reporting deadlines established in the law.

This information collection also satisfies the purposes of the original and ongoing clinical trial information collection that was established by FDAMA. That law specifies that "The Secretary, acting through the Director of NIH, shall establish, maintain, and operate a databank of information on clinical trials for drugs for serious or life-threatening diseases and conditions… The Secretary shall establish the databank after consultation with the Commissioner of Food and Drugs, the directors of the appropriate agencies of the National Institutes of Health (including the National Library of Medicine), and the Director of the Centers for Disease Control and Prevention…the Secretary shall collect, catalog, store, and disseminate the information described in such paragraph" (Section 113(a)(2) of FDAMA (42 U.S.C. 282(i)(1)).

The information collection is also necessary to allow researchers and organizations who are not subject to FDAAA or FDAMA to register trials and other clinical studies (e.g., observational studies) optionally as a means of enhancing enrollment or to comply with policies of other organizations. For example, since 2004, the International Committee of Medical Journal Editors (ICMJE) has required the prospective registration of interventional studies as a prerequisite for results to be considered for publication in journals that have adopted the ICMJE policy. Subsequently, the World Health Organization (WHO) published international standards for clinical trial registration. The 2013 Declaration of Helsinki ("Ethical Principles for Medical Research Involving Humans") asserts that "every research study involving human subjects must be registered in a publicly accessible database" (Article 35) and "Researchers have a duty to make publicly available the results of their research … [for] negative and inconclusive as well as positive results" (Article 36). Because it is the largest and most comprehensive clinical trial registry and results database in the world, ClinicalTrials.gov is the registry that many trial sponsors and investigators choose to use to satisfy these obligations.

A.2 Purpose and Use of the Information Collection

This information collection addresses an important public health need by providing patients, family members, clinicians, and researchers with timely access to up-to-date information about clinical trials as well as other types of clinical studies, and their results. The registration information enables patients and their family members to learn about relevant studies and facilitate possible enrollment. Alone or when combined with collected results information, it can also contribute to better-informed decisions about medical treatments. In addition, clinical trial information can reduce inadvertent and unnecessary duplication of clinical research studies, help reviewers detect incomplete reporting of the results of specific trials, allow comprehensive analysis and reporting of the results of many trials of specific therapies, and therefore provide regulators, scientists, health professionals, and the public a more accurate picture of the benefits and potential harms of specific therapies or products and a more solid foundation for decision-making. The NIH and the FDA have encouraged the registration of clinical trials in publicly accessible databanks; as such, information is not otherwise easily accessible to the general public. (For a detailed description of the public health benefits resulting from clinical trial registration and results

information submission, see Section I of the final rule, published on September 21, 2016 (81 FR 64981).

Information is collected via electronic submission to the ClinicalTrials.gov Protocol Registration and Results System (PRS), available at https://clinicaltrials.gov/ct2/manage-recs/register. The information in the databank is available to all members of the public including patients, health care providers, and researchers. FDAAA Section 801 explains that the purpose of the clinical trials registry databank is to enhance patient enrollment and provide a mechanism to track the progress of clinical trials. The information is intended to provide current and reliable information on the broadest possible scale to members of the public, including to physicians and researchers, about the existence, nature, enrollment status, location, eligibility criteria, sponsorship, progress, and outcomes of clinical trials. The registry provides basic information about the studies, their implementation, and how to enroll. Progress of the trials is updated so that individuals have current information on initiatives to intervene to treat, cure, ameliorate or prevent the health conditions with which they are afflicted or at risk. In some instances, registration information is used for the purpose of facilitating enrollment in clinical trials of drug products intended for the treatment of patients with serious or life-threatening diseases and conditions. Facilitating enrollment can hasten completion of clinical trials, leading to faster and potentially more thorough testing of the safety and efficacy of new interventions, accelerating and expanding availability of promising interventions for serious and life-threatening diseases and conditions. The results portion of the databank summarizes the outcomes of the trial, by arm.

This information is of immediate value to patients with a variety of diseases and conditions. Safe and effective treatments are not available for all diseases and conditions (including those that are serious and life-threatening), and clinical trials represent patients' first opportunity to receive new interventions, some of which may ultimately be found to represent therapeutic breakthroughs. Information regarding opportunities to participate in such clinical trials is often not publicly available, and patients who may wish to participate in a clinical trial may have difficulty finding such trials. The databank expands public availability of such information for patients. This expanded patient access to information about clinical trials increases patients' options while enabling them to contribute to development of advances in the treatment, diagnosis, and prevention of diseases and conditions, including those that are serious and life-threatening. The availability of results information helps ensure that scientists have access to the latest scientific information about potential treatments for disease, as much of this information is not published in the scientific literature. The information can help scientists to better plan new research projects, and avoid duplication that can expose human volunteers to unnecessary risks. It can also ensure that treatment decisions are based on a more complete set of scientific evidence.

Data Elements Required for Registration in 42 CFR 11.28(a)(2), (b)(2), and (c)

The required registration data elements for this information collection are listed in Table 2-1 (also see Attachment 1 for data element definitions and Attachment 2 for the registration data entry screenshots). Collection of similar requested information before the final rule

was previously approved under OMB Control Number 0925-0586. The data elements required under the final rule include items of information that are specifically enumerated in FDAAA as authorized and required to be collected for the registration of applicable clinical trials that are subject to FDAAA (section 402(j)(2)(A) of the PHS Act). The collection includes additional data elements required by rulemaking that are necessary to meet other requirements of FDAAA and to enable effective management and operation of the database, and facilitate the registration of other types of studies, not all of which are subject to FDAAA (e.g., observational studies and patient registries). For example, FDAAA requires that the databank enable searching by the location of the clinical trial and by "age group studied in the clinical trial, including pediatric subpopulations" (section 402(j)(2)(B) of the PHS Act). Information is collected to support these functions. FDAAA also establishes compliance and enforcement requirements that apply to mandatory submissions of information under that law. Information is collected to distinguish between mandatory and voluntary submissions. FDAAA requires that the registry be easily used by the public and that entries be easily compared (section 402(j)(2)(B)(iv) of the PHS Act), making necessary the collection of structured data to ensure consistency and completeness of entries (e.g., requiring information on intervention model, number of arms, masking, and allocation as elements of Study Design). The list of items encompasses those that are necessary to fulfill the requirements established by FDAMA, but includes additional data elements to enable to data bank to serve other purposes.

Table 2-1 Information collection for the expanded clinical trials registry under 42 CFR 11.28(a)(2), (b)(2), and (c)

Data Element and Regulatory Citation [42 CFR 11.28(a)(2)]	**Justification** [Statutory References are to section 402(j) of the PHS Act]
(i). Descriptive Information	
(A) Brief Title (*including acronym or abbreviation*)*†	(2)(A)(ii)(I)(aa) specifies a brief title, intended for the lay public
(B) Official Title*†	Collected to help researchers understand the general purpose of the study and to associate the trial with data from other sources. Added using the authority in section 402(j)(2)(A)(iii).
(C) Brief Summary*†	(2)(A)(ii)(I)(bb) specifies a brief summary, intended for the lay public
(D) Primary Purpose	(2)(A)(ii)(I)(cc) specifies the primary purpose
(E) Study Design *For interventional studies, includes:* • *allocation,* • *arm description,* • *arm designation,* • *arm number/label,* • *arm type,* • *interventional study model,* • *masking,* • *number of arms.* *For observational studies, includes:* • *group/cohort description,*	(2)(A)(ii)(I)(dd) specifies study design. Requested information under this heading is intended to meet the statutory and practical requirements to ensure complete and consistent collection of information to describe the design of interventional and observational studies.

group/cohort number or label, • *number of groups/cohorts,* • *observational study model* • *sampling method, and* • *time perspective.*	
(F) Study Phase	(2)(A)(ii)(I)(ee) specifies for an applicable drug clinical trial, the study phase
(G) Study Type (record type)*†	(2)(A)(ii)(I)(ff) specifies "study type"
(H) Pediatric Postmarket Surveillance of a Device Product*	Collected to identify studies that are post-market pediatric surveillances of a device product that are required to be registered, even if they are not interventional or observational studies. Added using the authority in section 402(j)(2)(A)(iii).
(I) Primary Disease or Condition Being Studied in the Trial, or the Focus of Study*†	(2)(A)(ii)(I)(gg) specifies the primary disease or condition being studied, or the focus of the study
(J) Intervention Name(s)*† *Includes (K) other intervention name(s),*† (L) intervention description,*†(M) intervention type (e.g., drug, device, surgical procedure),*† (N) studies a U.S. FDA-regulated device product, (O) studies a U.S. FDA-regulated drug product, (P) device product not approved or cleared by U.S. FDA, (Q) post prior to U.S. FDA approval or clearance, and (R) product manufactured in and exported from the U.S.*	(2)(A)(ii)(I)(hh) specifies intervention name and intervention type. FDA product regulation and approval status collected to determine which trials are required to be registered; to assess eligibility of device trials for delayed public posting in accordance with section (2)(D)(ii) as well as the ability for sponsors to indicate that such device trials to be posted publicly (i.e., opt-out of delayed posting); and to assist in identifying trials for which results information will subsequently be required.
(S) Study Start Date*	(2)(A)(ii)(I)(ii) specifies study start date
(T) Primary Completion Date*	(2)(A)(ii)(I)(jj) specifies expected completion date. Completion date is defined in the statute 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
(U) Study Completion Date	Collected to identify the date the final subject was examined or received an intervention for purposes of final collection of data for the study (e.g., last subject's last visit). Added using the authority in section 402(j)(2)(A)(iii).
(V) Enrollment	(2)(A)(ii)(I)(kk) specifies "the target number of subjects"
(W) Primary Outcome Measure Information (including name, description, and time of assessment)	(2)(A)(ii)(I)(ll) specifies "outcomes, including primary and secondary outcome measures"
(X) Secondary Outcome Measure Information (including name, description, and time point(s))	(2)(A)(ii)(I)(ll) specifies "outcomes, including primary and secondary outcome measures"
(ii). Recruitment Information	
(A) Eligibility Criteria (*includes study population description for observational studies*)†	(2)(A)(ii)(II)(aa) specifies "eligibility criteria"
(B) Sex/Gender†	(2)(A)(ii)(II)(bb) specifies "gender"
(C) Age Limits†	(2)(A)(ii)(II)(cc) specifies "age limits"

(D) Accepts Healthy Volunteers	(2)(A)(ii)(II)(dd) specifies "whether the trial accepts healthy volunteers"
(E) Overall Recruitment Status	(2)(A)(ii)(II)(ee) specifies "overall recruitment status"
(F) Why Study Stopped	Collected to help users understand why a study was "terminated," "suspended," or "withdrawn." Added using the authority in section 402(j)(2)(A)(iii).
(G) Individual Site Status	(2)(A)(ii)(II)(ff) specifies "individual site status"
(H) Availability of Expanded Access (*indication of whether there is expanded access and if, yes, NCT number of expanded access record submitted in accordance with 42 CFR 11.28(c)*)	(2)(A)(ii)(II)(gg) specifies "...whether or not there is expanded access to the drug and how to obtain information about such access"
(iii). Location and Contact Information	
(A) Name of the Sponsor*†	(2)(A)(ii)(III)(aa) specifies "the name of the sponsor"
(B) Responsible Party, by Official Title (type, *name, official title, organizational affiliation*)*†	(2)(A)(ii)(III)(bb) specifies "the responsible party, by official title"*)*
(C) Facility Name (*facility location – city, state, country, zip/postal code*)	(2)(A)(ii)(III)(cc) specifies "the facility name and facility contact information (including the city, State, and zip code for each clinical trial location, or a toll-free number through which such location may be accessed)"
(C) Facility Contact (*name, phone or email*)	(2)(A)(ii)(III)(cc) specifies "the facility name and facility contact information (including the city, State, and zip code for each clinical trial location, or a toll-free number through which such location may be accessed)"
(C) Central Contact (*name, title, toll-free telephone number or email address*)*†	(2)(A)(ii)(III)(cc) specifies " ...or a toll-free number through which such location may be accessed"
(iv). Administrative Data	
(A) Unique Protocol Identification Number*†	(2)(A)(ii)(IV)(aa) specifies "the unique protocol identification number"
(B) Secondary ID (*including ID Type*)*†	(2)(A)(ii)(IV)(bb) specifies "other protocol identification numbers, if any"
(C) U.S. Food and Drug Administration IND or IDE Number (*including grantor name, IND/IDE number, IND/IDE serial number*)†	(2)(A)(ii)(IV)(cc) "the Food and Drug Administration IND/IDE protocol number." IND/IDE grantor, IND/IDE number, and IND/IDE serial number are considered the components of a complete IND/IDE protocol number. (Note: IND/IDE information is not made public.)
(D) Human Subjects Protection Review Board Status*	Collected to ensure users that registered trials conform with relevant human research protection policies. Added using the authority in section 402(j)(2)(A)(iii).
(E) Record Verification Date*†	(2)(A)(ii)(IV)(cc) specifies "record verification date"
(F) Responsible Party Contact Information*†	(1)(B) specifies "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 at the time of submission of clinical trial information under paragraph (2)." (Note: contact information not made public)

*Indicates the subset of information required in 42 CFR 11.28(b)(2) for registration of a pediatric postmarket surveillance of a device product that is not a clinical trial conducted under section 522 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 360l) as specified.

†Indicates the subset of information required in 42 CFR 11.28(c) for registration of each investigational drug product (including a biological product) available through expanded access, as specified in section 561 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 360bbb), and studied in applicable drug clinical trials (i.e., for which Availability of Expanded Access in 42 CFR 11.28(a)(2)(ii)(H) is indicated). Additionally, the following two data elements are only required for expanded access records: Expanded Access Type and Expanded Access Status as specified in 42 CFR 11.28(c)(1)(x) and (2)(iv), respectively. See Attachment 3 for a list of expanded access data element definitions and the data entry screenshots.

In addition to the items listed in Table 2-1, respondents may submit optional data elements in order to provide a more complete record of the clinical trial, meet the requirements of other policies related to the disclosure of clinical trial information (such as that of the ICMJE, which requires registration as a precondition for considering manuscripts reporting clinical research for publication), or facilitate the registration of patient registries (i.e., types of "observational studies"). Optional information consists of those elements listed below.

- links to related Web-based information (e.g., publications regarding the trial, additional enrollment information),
- keywords to facilitate search and retrieval,
- overall study official (required by the ICMJE policy),
- biospecimen retention and biospecimen description (for observational studies only),
- detailed description of the trial/study,
- names of collaborators (required by the ICMJE policy),
- whether or not a data monitoring committee has been established for the trial,
- Patient registry observational study sub-type (required by the Agency for Healthcare Research and Quality (AHRQ) Registry of Patient Registries (RoPR)),
- Information about an Institutional Review Board, other than approval status
- Information about plans for, and the availability of, individual patient data (IPD) for sharing with other researchers (proposed by the 2016 Institute of Medicine report and the ICMJE), and
- Target follow-up duration (for patient registries).

Before registering a study, a data provider must establish an account in the ClinicalTrials.gov data entry system, which is known as the Protocol Registration and Results System (PRS). This will typically be done by an organization that sponsors clinical research. A PRS account does not need to be established each time a study is registered; once an organization has established a PRS account, it may use the account to register, submit results, and update information for any number of clinical studies. Collection of this information allows the NLM to verify the existence of a data submitter's organization and have a designated individual as the point of contact from the submitter's organization.

Establishment of a PRS account also provides a mechanism for organizations to, in turn, authorize individual users (e.g., responsible parties) to enter data for individual studies. The information collected in the PRS Account Application Form is listed in Table 2-2.

Table 2-2 Information collection in the PRS Account Application Form

Data Element	Definition/Description
1. Organization/Sponsor Information	
Type of Organization	May be a Government Agency, Industry, University, Nonprofit Organization, or Other
Country	Country of the sponsoring organization.
Organization Name	Official name of sponsoring organization.
Organization Address	Mailing address for the headquarters of the sponsoring organization, including street address, city, state or province, postal code, and country (if different from the Country information submitted above, e.g., if using a mailing address different from the country of the organization's headquarters).
Organization Abbreviations and Acronyms	Other names used by the sponsoring organization.
Parent Organizations (*if applicable*)	Name(s) of any larger organization(s) with which the sponsoring organization is affiliated and relationship(s), such as subdivision, division, or department.
Official Representative	Name of official contact person at sponsoring organization who is authorized to represent the organization and to verify information about it.
Official Representative Phone	Primary phone number for the official representative, including country code, area code, and extension.
Official Representative Email	Primary email address for the official representative.
Organization URL	Official Web address of the organization.
Funding Organization	Name of the primary funding source for the trials that the organization registers.
2. Administrator Information	
Administrator Name	Full name of person who is authorized by the sponsor to update and maintain data in the PRS.
Affiliation	Official name of organizational affiliation of the Administrator, if different from the sponsoring organization.
Administrator Phone	Primary phone number of the Administrator, including country code, area code, and extension.
Administrator Email	Email address for contacting the administrator.
3. Regulatory Information	
Regulatory Authority	Name of the organization with regulatory authority over the trials that this organization registers, e.g., a national or international health authority or an institutional review board or ethics committee.
Regulatory Authority Address	Mailing address of the regulatory authority, including street address, city, state or province, postal code, and country.

Data Elements Required for Results Information Submission in 42 CFR 11.48

Results information, which has been collected by ClinicalTrials.gov since September 23, 2008, derives from statutory language in FDAAA for "Basic Results" (section 402(j)(3)(C) of the PHS Act) and "Adverse Events" (section 402(j)(3)(I) of the PHS Act). The Act also

requires HHS to consider requiring the submission of results information for certain trials of unapproved products whether approval "was sought of not," specific results information (e.g., "summaries of the clinical trial and its results"), and "Such other categories as the Secretary determines appropriate" by rulemaking (section 402(j)(D) of the PHS Act). In addition to these "Basic Results," the final rule requires the submission of the "full protocol … to help evaluate the results of the trial" as well as other specified data elements within the FDAAA-specified "Basic Results" categories. Thus, the final rule requires the submission of up to seven types of results information for applicable clinical trials of drug products, regardless of approval status under section 505 of the Federal Food, Drug, and Cosmetic Act; biological products, regardless of licensure status under section 351 of the Public Health Service Act; and device products, regardless of clearance status under section 510(k) of the Federal Food, Drug, and Cosmetic Act or approval status under section 515 or 520(m) of the Federal Food, Drug, and Cosmetic Act:

1. *Demographic and Baseline Characteristics of the Patient Sample* – 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, including the number of patients who dropped out of the clinical trial and the number of patients excluded from the analysis, if any. (section 402(j)(3)(C)(i) of the PHS Act)

2. *Primary and Secondary Outcomes and Statistical Analyses* - The primary and secondary outcome measures, 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. (section 402(j)(3)(C)(ii) of the PHS Act)

3. *Adverse Events* – 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 and a table of anticipated and unanticipated adverse events that are not included in the first table that exceed a frequency of five 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)(I) and (II) of the PHS Act). The final rule also requires the submission of information for a third table of all-cause mortality, and about methods used for collecting adverse event information (e.g., the specific period or time frame over which adverse events were collected, whether adverse events were collected systematically or non-systematically).

4. *Protocol and Statistical Analysis Plan (SAP)* – The full protocol or such information on the protocol for the trial as may be necessary to help to evaluate the results of the trial (section 402(j)(3)(D)(iii)(III) of the PHS Act). The final rule also requires the submission of the SAP if it is a separate document.

5. *Results Point of Contact* - A point of contact for scientific information about the clinical trial results. (section 402(j)(3)(C)(iii) of the PHS Act)

6. *Certain Agreements* - Whether there exists an agreement (other than an agreement solely to comply with applicable provisions of law protecting the privacy of

participants) between the sponsor or its agent and the principal investigator (unless the sponsor is an employer of 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. (section 402(j)(3)(C)(iv) of the PHS Act)

7. *Additional Results Information for Applicable Device Clinical Trials of Unapproved or Uncleared Device Products* – 42 CFR 11.42 requires responsible parties to submit results information for all applicable clinical trials, including those studying unapproved, unlicensed, or uncleared drug products, biological products, or device products. However, 42 CFR 11.35(b)(2)(i) specifies that the Director will post publicly submitted registration information for such trials "not earlier than the date of FDA approval or clearance," unless authorized by a responsible party to post the registration as soon as practicable as specified in 42 CFR 11.35(b)(2)(ii). Thus, for an applicable device clinical trial of an unapproved or uncleared device product and for which clinical trial registration information has not been posted publicly at Clinical Trials.gov at the time of results submission, the responsible party must submit additional results data elements that are similar to registration data elements and necessary to enhance access to and understanding of the posted results information. Although these required results data elements were not explicitly specified in FDAAA, they were added by HHS using the authority granted to require by rulemaking "[s]uch other categories as the Secretary determines appropriate." (section 402(j)(3)(D)(iii)(IV) of the PHS Act)

In the information collection under the final rule, the specific information to be submitted for results data elements consists of the following:

For the first item, the information is divided into two parts: 1) information about participant flow, and 2) information about the demographics and baseline characteristics of the patient sample (overall and by each arm of the trial). For participant flow, respondents must indicate the number of subjects that started the trial (overall and by arm), the number of subjects that completed the trial (overall and by arm), and provide more detailed information about activities before the assignment of participants to the different arms of the trial. Optionally, respondents may indicate the number of subjects that reach other important milestones in the clinical trial (as defined by the respondent) or proceed through different periods of the trial. Respondents also have the option of indicating the specific reasons that patients dropped out of the trial and of providing more detailed information about recruitment of patients to different arms of the trial. This optional information provides a more complete description of the trial that can aid in interpreting and understanding the results. This objective is consistent with the statutory requirements to provide information to help ensure that information in the results database does not mislead patients (section 402(j)(3)(B)(iv) of the PHS Act) and enhances patient understanding of the results of clinical trials (402(j)(3)(D)(i) of the PHS Act).

The information collected for demographic and baseline characteristics of the patient population will, by necessity, vary from one clinical trial to another. Respondents must indicate the overall number of baseline participants, overall number of units analyzed (if not human participants), and any clarifying/explanatory information. This information provides users of ClinicalTrials.gov with clear information about the number of subjects that were ultimately enrolled in a trial and for whom baseline measures were collected. While some demographic and baseline characteristics (e.g., gender and age) are common to virtually all clinical trials, many others are trial-specific (e.g., the presence or absence of a particular disease or physiological characteristic). Hence, respondents must submit information on the following specific demographic characteristics only if specified in the protocol: age, sex/gender, and race/ethnicity. Respondents must also submit information on any other baseline characteristics used in the analysis of the primary outcome measure(s), but have the option of specifying additional, trial-specific categories of demographic and baseline information, and providing the corresponding data. To provide additional flexibility and reduce the burden on respondents, demographic and baseline characteristic data can be reported in a variety of ways, consistent with the way it was collected during the study: as raw numbers, measures of central tendency (e.g., means, medians), or by relevant categories (e.g., numbers of patients with or without a particular disease or characteristic), using the measurement units most appropriate to the clinical trial. In order to enable this flexibility, respondents must provide descriptive information about the submitted data, in addition to the numerical data values themselves. For example, they must to provide the name/label for each variable (e.g., baseline blood pressure), the unit of measure (e.g., millimeters of mercury), and indicate whether the submitted data represent a measure of central tendency (e.g., statistical mean or median) or the number of patients in different categories (e.g., high blood pressure, low blood pressure). The PRS uses this information to generate the appropriate row and column headings for the tables into which the data itself will be submitted.

For the second item, (primary and secondary outcome measures and statistical analyses), a similar approach is taken. Respondents must provide explanatory information about the participants analyzed and indicate the number of participants analyzed for each outcome measure specified in their study protocol (the outcome measures will have been submitted to the database during the registration process, but may be modified by the respondent when submitting results). For each outcome measure specified in the protocol, respondents submit both descriptive information and the outcome data itself. Required descriptive information includes the type of outcome measure (primary, secondary, other pre-specified or post-hoc), the name or title of the outcome measure (if different from the name/title submitted to the database during registration), the measurement type (number, measure of central tendency, categorical, etc.) and the units of measurement. Consistent with the statute, respondents are also required to submit information about the statistical analysis used for the outcome measures, such as the p-value or confidence interval for scientifically appropriate tests of statistical analysis significance.

For the third item, adverse event information, the information collection is consistent with the provisions in FDAAA calling for tables of information about serious adverse

events and frequent adverse events, by arm and organized by organ system (section 402(j)(3)(I)(ii) and (iii) of the PHS Act). The submission of this information has been required as part of results information for any trial for which results are submitted on or after September 27, 2009 in accordance with section 402(j)(3)(I)(ii) of the PHS Act.

The general approach taken to collect adverse event information is similar to that for items 1 and 2. For two of the adverse events tables (i.e., serious. and frequent), respondents must indicate the total number of participants affected and the total number of participants at risk, by arm. We have found that such information is necessary to calculate the overall frequency of events within each table. In addition, this information facilitates data entry by allowing data providers to submit the number of participants at risk a single time for all individual adverse events in a table (i.e., data providers only need to provide this information for any individual adverse event that involves a different number of participants at risk). For the frequent adverse events table, the frequency threshold for reporting adverse events must be indicated. FDAAA specifies the submission of all non-serious adverse events which exceed a frequency of 5 percent in any arm; we permit the submission of information exceeding a lower frequency threshold on an optional basis (this approach allows the submission of more data than the minimum required by law). For each adverse event included in one of these two tables, respondents must submit the following information: the name of the adverse event, the organ system to which the adverse event relates, the number of participants affected by that adverse event (by arm), and the number of participants that were at risk (by arm) if different from the total number of participants at risk. Respondents must also submit the following additional descriptive information about the reported adverse events: the time frame during which adverse events were collected (which may differ across events in the same study), a brief description of any adverse event definition(s) used in the trial that differs from the definitions specified in the final rule, the type of collection approach used to collect adverse events (i.e., systematic or non-systematic), and the total number of deaths observed in the trial due to any cause (as a third all-cause mortality table). Respondents may choose to submit the name of any standardized vocabularies used to name the adverse events and the number of occurrences of each adverse event reported (by arm). Our experience in operating ClinicalTrials.gov indicates that such information is helpful to those trying to interpret submitted adverse event information.

For the fourth item, respondents must submit a copy of the full protocol and the SAP (if not included in the protocol), including all amendments approved by the time that results information is initially submitted, that apply to all sites in the trial. Further, the protocol (and SAP, as appropriate) must be submitted, with a cover sheet identifying the Official Title and National Clinical Trial (NCT) number of the study and the date of the protocol and SAP, in a common electronic document format specified at https://prsinfo.clinicaltrials.gov/. For point of contact, the information to be collected consists of the name (or official title) of the point-of-contact, the organization name, telephone number, and email address.

For certain agreements, the respondent is to indicate whether or not the principal investigator (PI) is an employee of the sponsoring organization: if the response is

"yes," then no additional information needs to be provided, consistent with statute's exclusion; if the response is "no," then the respondent is required to indicate whether such an agreement exists and, if so, may optionally indicate whether the restriction lasts for fewer than 60 days, between 60 and 180 days, or some other period of time. Information about the duration of the restriction is intended to distinguish between restrictions that fall within standard industry practice (approximately 60 days) and those that exceed it.

If results information is submitted for an applicable device clinical trial of an unapproved or uncleared device for which registration information has not been posted on ClinicalTrials.gov, then the respondent must provide additional results information for 31 results data elements, as defined in the final rule and listed for item 7 ("Additional Clinical Trial Results Information for Applicable Device Clinical Trials of Unapproved or Uncleared Device Products") in Table 2-3 (below).

Additionally, respondents may provide optional information in a free-text field, as desired, to describe important limitations of the results information (including adverse events) or caveats for interpreting it. Such information is intended to improve the ability of database users to understand the information.

The table below summarizes the information collection for results information. All elements are required to be submitted, except for those marked "optional." See Attachment 4 for the results data element definitions and Attachment 5 for the results data entry screenshots.

Table 2-3 Information collection for the expanded clinical trials results database under 42 CFR 11.48

Data Element and Regulatory Citation [42 CFR 11.48(a)]	**Justification** [Statutory References are to section 402(j) of the PHS Act]
(1). Participant Flow (by arm)	(3)(C)(i) "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 *for each arm of 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*"
(i) Arm information for each arm	
(ii) Pre-assignment information	
Period titles, defined by respondent [optional]	
(iii) Number of subjects that started the trial and each defined period (overall and by arm)	(3)(C)(iv) [above]
(iii) Number of subjects that completed the trial and each defined period (overall and by arm)	Allows calculation of number of patients that dropped out of the study.
Number of subjects that reached other trial/period milestones (defined by the respondent) [optional]	
Reasons for not completed (reasons and number of subjects withdrawing for each reason) [optional]	

Recruitment details [optional]	
(2). Demographic and Baseline Characteristics (overall and by arm)	(3)(C)(i) "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"
(i) Arm/group information for each arm	
(ii) Analysis population information (*including overall number of baseline participants, overall number of units analyzed, and any clarifying/explanatory information*)	
(iii) Baseline measure information:	
• Age (mean, median, or by age category)	
• Sex/Gender	
• Race/Ethnicity	
• Other baseline characteristics used in the analysis of the primary outcome measure(s).	
• Other baseline characteristics of importance to the clinical trial (e.g., number or percentage with a relevant medical pre-condition). [optional].	
• Descriptive information about each baseline characteristic.	
• Measurement type, i.e., number, measure of central tendency (e.g., mean, median geometric mean).	
• Measure of dispersion (e.g., standard deviation, full range), if a central tendency reported	
• Names of the categories into which data are divided, if a categorical measurement	
• Unit of measure	
(iv) Baseline measure data	
(v) Number of baseline participants (and units), by arm or comparison group and overall (if applicable)	
(3). Outcomes measures (by arm) and statistical analyses	(3)(C)(ii) "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. . ."
(i) Arm/group information for each arm	
(ii) Analysis population information	
• Number of participants analyzed (per outcome measure, per arm/group) or number of units analyzed (i.e., if the analysis is not based on participants, but on the number of implants, lesions, eyes, etc., examined)	
• Analysis population description (e.g., per protocol, intention to treat, other method)	

(iii) Descriptive information for each outcome measure (as below):	
• Title of the outcome measure	
• Description of the metric used	
• Outcome measure time point(s)	
• Type of outcome measure (primary, secondary, other pre-specified, post-hoc)	
• Outcome measure reporting status (posted or not posted) [optional]	
• Measure type (i.e., number or measure of central tendency) and measure of dispersion (e.g., standard deviation, full range, etc.), if applicable	
• Titles of the categories into which data are divided, if a categorical measure reported	
• Unit of measure and categories of measurement	
• Type of units analyzed (required when the analysis is not based on "participants" – e.g., eyes, lesions, or implants)	
(iv) Outcome measure data	
• Number	
• Descriptive statistics, if applicable	
(v) Statistical analyses (as below):	". . . including the results of scientifically appropriate tests of the statistical significance of such outcome measures."
• Criteria for scientifically appropriate tests of statistical analysis significance	
• Statistical analysis overview, including comparison groups selected	
• Whether or not the analysis is a test of non-inferiority or equivalence [Y/N]	
• P-value or confidence interval (including the level, lower limit and upper limit)	
• Method of estimation – statistical test or estimation parameter and dispersion of confidence interval, required if P-value is reported	
(4). Adverse Event Information (by arm)	(3)(I)(iii)(I) "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." (3)(I)(iii)(II) "A table of anticipated and unanticipated adverse events that are not included in the table described in subclause (I) 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."

(i) Information to describe the methods for collecting adverse events	
• Time frame for adverse event collection	
• Brief description of any adverse event definition(s) used in the trial that differs from the definitions specified in the final rule	
• Adverse event collection additional description	
• Adverse event term (description of the event)	
• Source vocabulary name (if any) [optional]	
• Organ system	"grouped by organ system" [(3)(I)(iii)]
• Collection approach (e.g., systematic assessment or spontaneous report)	
(ii) Information for completing adverse event tables, by arm or comparison group (including frequency threshold for reporting other (non-serious) adverse event and total number of deaths from all causes for the all-cause mortality table)	Tables: (1) all serious adverse events, (2) all adverse events, other than serious adverse events, that exceed a frequency of 5 percent within any arm of the clinical trial; and (3) all-cause mortality, with the number and frequency of deaths due to any cause
(iii) Information for each table	
• Arm/group information for each arm	
• Total number of participants affected	"results information on serious adverse. . . events" and "results information on . . . frequent adverse events" [(3)(I)(i)]
• Total number of participants at risk	
• Adverse event term additional description	
• Adverse event data	
o Number of affected participants	"number and frequency of such event in each arm of the clinical trial" [(3)(I)(iii)]
o Number of events [optional]	
o Number of participants at risk	"number and frequency of such event in each arm of the clinical trial" [(3)(I)(iii)]
(5). Protocol and Statistical Analysis Plan	(3)(D)(iii)(III) "The full protocol… to help evaluate the results of the trial."
(6). Administrative Information	
(i) Results Point of Contact (*including name or official title, organization name, and email address*)	(3)(C)(iii) "a point of contact for scientific information about the clinical trial results"
(ii) Certain Agreements	
• Whether all PIs are employees of the sponsor? [Y/N]. [If *yes*, then no additional information is required].	(3)(C)(iv) . . . "unless the sponsor is an employer of the principal investigator"
• Whether there are results disclosure restrictions on PIs [Y/N]?	(3)(C)(iv) . . . "whether there exists an agreement. . ."
• PI disclosure restriction type (i.e., less than or equal to 60 days; 60-180 days; Other) [optional]	To determine whether the restriction extends beyond standard industry practice (approx. 60 days).
(7). Additional Clinical Trial Results Information for Applicable Device Clinical Trials of Unapproved or Uncleared Device Products	
(i) Consists of the following 31 results data elements, as described in Table 2-1 (above): Brief Title; Official Title; Brief Summary; Primary Purpose; Study Design; Study Type; Primary	Collected to enhance access to and understanding of the posted results information. Added using the authority in section 402(j)(3)(D)(iii)(IV).

Disease or Condition Being Studied in the Trial, or the Focus of the Study; Intervention Name(s); Other Intervention Name(s); Intervention Description; Intervention Type; Device Product Not Approved or Cleared by U.S. FDA, if any studied intervention is a device product; Study Start Date; Primary Completion Date; Study Completion Date; Enrollment; Primary Outcome Measure Information; Secondary Outcome Measure Information; Eligibility Criteria; Sex/Gender; Age Limits; Accepts Healthy Volunteers; Overall Recruitment Status; Why Study Stopped; Name of the Sponsor; Responsible Party; Facility Name and Facility Location, for each participating facility in a clinical trial; Unique Protocol Identification Number; Secondary ID; Human Subjects Protection Review Board Status; and Record Verification Date.	
(ii)An affirmation that any information previously submitted in (i) have been updated and are to be included as clinical trial results information.	
8. Overall Limitations and Caveats [optional free-text field]	

Information collection for results information for a pediatric postmarket surveillance of a device product that is not a clinical trial requires that the responsible party provide to ClinicalTrials.gov a copy of any final report that is submitted to FDA as specified in 21 CFR 822.38, as specified in 42 CFR 11.48(b).

FDAAA provides for responsible parties to delay submission of results information if they submit a certification that they are seeking either initial approval or approval for a new use of the drug or device under investigation in the clinical trial (sections 402(j)(3)(E)(iv) and (3)(E)(v)). The final rule clarified and further modified this process in 42 CFR 11.44(c) and (b), respectively. Respondents must submit directly through the PRS an indication certifying that the trial qualifies for delayed results information submission under either 42 CFR 11.44(b) or (c). See Attachment 6 for certification data element definitions and data entry screenshots.

FDAAA also permits responsible parties to request an extension of the deadline for submitting results if they submit a written request that demonstrates “good cause” for the extension and provides an estimate of the date on which the information will be submitted (section 402(j)((3)(E)(vi)). The provision at 42 CFR 11.44(e), which implements this statutory provision, specifies that all extension requests must be submitted directly through the PRS by entering the following information into the existing record for the trial of interest.

- An indication that a “good cause” extension is requested (a menu option)
- The proposed date on which results information will be submitted
- An explanation (free-text) of the “good cause” for requesting the extension

The extension request data element definitions and data entry screenshots appear in Attachment 7.

Note that not all information submitted as part of a certification or extension request will be publicly displayed in ClinicalTrials.gov. The fact that a responsible party (or associated manufacturer) has submitted a marketing application or premarket notification is considered confidential information. Similarly, we do not intend to post the explanation of the "good cause" for requesting an extension, although we may make available an anonymized list of general reasons for which extension requests have been granted and/or denied. Thus, as specified in the final rule, the posted record for a clinical trial will indicate that results information submission has been delayed in general, but will not specify the particular reason for the delay.

A.3 Use of Improved Information Technology and Burden Reduction

FDAAA itself directs the Director of the NIH to "ensure that the registry databank is made publicly available through the Internet" (section 402(j))(2)(A) of the PHS Act). ClinicalTrials.gov uses the latest software and Internet technologies for submitting registration and results information, and for searching/retrieving such information. Information can be entered manually into electronic forms available in the PRS or can be uploaded automatically (and in batches) from computer systems that put it in a structured format specified in the PRS. To minimize the burden on respondents and ensure data consistency between registration and results sections of study records, relevant clinical trial registration information is imported into results information templates. In addition, the data entry system for results submission in the PRS has been designed to allow respondents considerable flexibility in submitting required data in a way that matches their own data analysis plans and formats common to reporting results in journal articles and other publications.

The final rule requires conforming changes in the PRS. The new data elements will be available in a PRS test system to help responsible parties better understand the new elements and requirements and become familiar with the new structure before the rule's effective date. This test approach will also enable NLM to make adjustments as needed in response to user comments. Other enhancements have been made and are continuing to be made to improve the usability of the system to all stakeholders.

A.4 Efforts to Identify Duplication and Use of Similar Information

ClinicalTrials.gov is a unique information resource, containing registration information on nearly 227,000 clinical studies in more than 190 countries as of September 29, 2016. No comparable public listing of clinical trials exists in the world. While some companies make some clinical trial information available through commercial databases, these efforts are not as comprehensive as ClinicalTrials.gov and contain limited information on only a select subset of trials. Similarly, the results information collected by ClinicalTrials.gov is unique. While a small number of pharmaceutical companies have created public websites containing results of their clinical studies, they are limited to the company's trials and

results are not structured to allow easy comparison among trials in different databases. The industry association PhRMA established a publicly accessible results database for member companies, but submission of information was voluntary and therefore limited. PhRMA decommissioned and removed this results database in 2012.

Much of the registration information to be collected under FDAAA and the final rule is currently submitted to FDA in a different format and in considerably more detail by holders of investigational new drug applications (INDs) and investigational device exemptions (IDEs) under federal regulations, but is not publicly available. IND/IDE submissions are confidential and proprietary, and are not subject to release under the Freedom of Information Act (5 U.S.C. 552). Similarly, FDA receives detailed information about the results of clinical trials when the manufacturer of a drug product, biological product, or device product submits an application for approval, licensure, or clearance, but such information is not made public in a systematic fashion, is not comparable across studies, and is heavily redacted. Scientific journals contain selected results for some clinical trials, but results of many clinical studies are never submitted for publication. Recent research indicates that negative or inconclusive trials are particularly underrepresented in the literature. Indeed, the lack of publicly accessible information about clinical trials was one of the factors that motivated the development of Title VIII of FDAAA.

The specific processes developed for submitting trial information by responsible parties under FDAAA provide for public availability of clinical trial registration and results information while being sensitive to the needs of data submitters, e.g., by minimizing reporting burden and protecting FDA submissions from unauthorized release. Considerable attention has been devoted to development of the processes for registering trials with ClinicalTrials.gov to minimize the possibility for duplicate submission of registration information (e.g., registration of a single multi-site trial by more than one trial site). Processes for results reporting have been developed so as to ensure the flexibility to report data from trials with different designs, while providing consistency in the types of information reported. To minimize the burden on respondents further, the required results information tables were designed to be similar to those published in scientific journals and use terminology that is widely used in practice.

A.5 Impact on Small Businesses or Other Small Entities

We believe that the final rule is not likely to have a significant economic impact on a substantial number of small entities. While a number of the responsible parties submitting clinical trial registration and results information are small businesses and entities (e.g., physician practices, start-up or small companies that produce medical devices), we expect that they will also have a small number of ongoing trials at any point in time, limiting their burden. Our economic analysis is detailed in section V.G. of the final rule (starting on 81 FR 65131, Sep 21, 2016). In general, the preparation and submission of the required information for the databank represents a small proportion of the total administrative

burden for any business (large or small) conducting a clinical trial. Organizations involved in conducting clinical trials must sustain a substantial administrative burden (e.g., submissions to the FDA, institutional review boards, funding agencies such as NIH, data monitoring committees). These efforts far outweigh the effort needed to register, summarize results, and update records in the Clinical Trial Registry and Results Databank. Furthermore, of the information to be supplied to ClinicalTrials.gov is, in general, already compiled for the study protocol, scientific and ethical reviews, regulatory reviews, recruitment of subjects to participate in the trials, the preparation of journal publications, and compliance with policies of the ICMJE and World Health Organization (WHO), and submissions to the FDA. Thus, the additional burden of this information collection (on large and small entities) is the time needed to submit the information to ClinicalTrials.gov in the format specified. Many small entities choose to list information in the ClinicalTrials.gov for clinical studies that are not subject to federal law, suggesting that the benefits of registration and results information submission outweigh the costs of the effort involved. Lastly, the efforts that have been made to develop results submission structures that are similar to those used in preparing scientific publications and reports to the FDA should further minimize the burden on small entities.

A.6 Consequences of Collecting the Information Less Frequently

For applicable clinical trials that are subject to the final rule implementing Title VIII of FDAAA (i.e., 42 CFR part 11), registration information must be submitted when trials are initiated and updated periodically to reflect changes in the conduct of the study. In general, the law requires that trials be registered not later than 21 days after enrolling the first subject (section 402(j)(2)(C) of the PHS Act). In general, submitted information must be updated at least once every 12 months if there are any changes to report, but changes in recruitment status and other data elements specified in the final rule (42 CFR 11.64(a)) must be reported within 30 days of such change (section 402(j)(4)(C)(i) of the PHS Act). Results information is required to be submitted to the data bank within 12 months of the primary completion date. The submission deadline can be extended if the responsible party certifies that the manufacturer is seeking or plans to seek FDA approval, licensure, or clearance for an initial or new use for the drug product, biologic product, or device product under study. The responsible party may also request an extension of the submission deadline for "good cause." Less frequent submission and updating of information would be inconsistent with the law and would cause delays, gaps, and errors in the publicly available information about clinical trials, compromising the databank's utility as a resource for patient recruitment and for providing reliable, up-to-date information to the public about ongoing trials and completed trials.

A.7 Special Circumstances Relating to the Guidelines of 5 CFR 1320.5

This collection fully complies with 5 CFR 1320.5.

A.8 Comments in Response to the Federal Register Notice and Efforts to Consult Outside the Agency

In compliance with 5 CFR 1320.8(d), soliciting comments on the information collection prior to submission to OMB, Federal Register Notices were published on November 21, 2014 (79 FR 69566) (90-day comment period) for the NPRM and a 30-day extension notice on February 13, 2015 (80 FR 8030). The preamble of the final rule, published on September 21, 2016 (81 FR 64981), addressed the approximately 900 comments received on the NPRM during the full 120-day expended comment period.

In the NPRM (79 FR 69566, Nov 21, 2014), the Agency invited 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.

Commenters responded to the economic analysis in the NPRM of the estimates of the costs and benefits of the rule. While some commenters found the analysis appropriate overall and considered a 40 hour estimate for results information submission to be accurate, other commenters suggested that the time estimates used to calculate registration, results, and updates burden were lower than they should be. Some argued that the burden of entering information into the database is greater for smaller research institutions because, unlike larger research organizations, they are less likely to have dedicated and trained personnel to manage clinical trial information reporting. Others suggested the rule will be equally burdensome to small and large organizations. We recognize that some members of the regulated community may spend more hours than others to develop, process, and maintain clinical trial records. However, we believe our estimates of 8 hours for registration information, 40 hours for results information and 16 hours for updates of information, are a reasonable representation of the overall average time required to complete all registration and results requirements by all respondents.

Commenters also suggested that ClinicalTrials.gov harmonize its clinical trial reporting requirements with existing international regulations in order to decrease the burden on institutions. It was suggested that reporting unique numbers of individuals with adverse events by organ system differs from the EU reporting standards and increases the burden of the rule. In consideration of the commenters' concerns, the final rule no longer requires the reporting of numbers of people with adverse events at the organ system level. We anticipate that this change will decrease the burden of the rule.

One commenter suggested that the rule would also have an economic impact on biopharmaceutical development because of competitive harms associated with premature disclosure of confidential commercial information. As discussed in section III.B of the preamble of the final rule (starting on 81 FR 64992, Sep 21, 2016) and 42 CFR 11.44, this rule requires only summary level results information to be submitted, and it allows for delayed submission with certification in order to minimize any perceived competitive disadvantages for unapproved, unlicensed, or uncleared products (see 42 CFR 11.44(b) and

(c)) and delayed posting of registration information for unapproved or uncleared device products (see 42 CFR 11.35(b)(2)(i)). Submission of clinical trial results information for applicable clinical trials of approved, licensed, or cleared products and applicable clinical trials of unapproved, unlicensed, or uncleared products, according to deadlines established by the final rule, ensures consistent and timely public access to comprehensive summary results for all applicable clinical trials. Furthermore, we are not persuaded that economic harms will result from the public posting of the required data elements.

Commenters also suggested that the cost estimates understated the burden associated with bringing previously submitted registration information into compliance with the final rule. One commenter suggested that the cost of compliance will not go down over time, while another suggested that in order to decrease this burden, the rule should only apply to those trials that had their First Subject First Visit or Primary Completion Date after the effective date of the rule. In consideration of commenters' concerns, the final rule eliminates virtually all additional burden associated with updating previously submitted trial information by requiring only registration as specified in the final rule for applicable clinical trials for which the date of initiation is after the effective date of the final rule and by only requiring results information submission as specified in the final rule for applicable clinical trials that reach their primary completion date after the effective date of the final rule. In light of these changes, which are discussed in more detail in Section IV.E of the preamble of the final rule (starting on 81 FR 65117, Sep 21, 2016), there are very few applicable clinical trials registered or submitted partial results prior to the effective date of the final rule that will need to be updated as a consequence of the rule. As such, we expect the burden associated with such situations to be minimal because they will arise relatively infrequently. In addition, we anticipate that the occurrence of such situations will decrease over the next three years because, ultimately, there will be very few ongoing applicable clinical trials that were initially registered prior to the effective date of the final rule.

Another commenter suggested that the correction procedures in § 11.66 of the NPRM could cause further economic burden because they thought that no clear distinction in the definitions of errors and falsifications was provided, which they said could lead to unnecessary and costly preemptive actions by the responsible party. The final rule no longer distinguishes between different types of errors (see 42 CFR 11.64), and, thus, the potential economic burden of differentiating the type of error has been eliminated.

Commenters also suggested that the Agency should calculate actual burden and include other costs such as reprograming of institutional systems, increased medical review, and management oversight. They suggested that we had not sufficiently considered the costs associated with activities carried out by organizations that may invest substantial resources to avoid the negative consequences of violating the legal and regulatory requirements, e.g., loss of federal grant support and/or monetary penalties. We agree that our cost estimate did not attempt to isolate the cost and burden that an institution as a whole might absorb in order to facilitate and monitor compliance among clinical investigators subject to the rule who are employed by the institution. Because overhead costs (i.e., costs not related to direct labor or direct materials) varies among different industries and occupations, we attempted to approximate those overhead costs by doubling the average hourly wages in

the personnel cost calculations. We took this approach in part because the cost of this rule is likely to vary significantly among institutions and organizations due to differences in institution's sizes, frequency of clinical trials performed per year and variation in the need to update or create information technology tools or application used to support clinical trial registration and results information submission and also because of the lack of data on the cost of institutional compliance. Nonetheless, in response to public comments, we have developed a separate estimate of the costs that institutions may assume in order to facilitate and monitor compliance among employees with responsibilities under the rule. The estimate is described in Section V.E of the preamble of the final rule (starting on 81 FR 65125, Sep 21, 2016).

Commenters suggested that the NIH should allow financial burden of registration and results reporting to be covered as a direct cost in grants, whether incurred by the investigator or shared with a central administration unit. The Agency has previously clarified for NIH awardees that "[g]iven the nature of registration and result information report requirement and that the project staff will generally be in the best position to submit and maintain these data, the costs of compliance with section 402(j) of the PHS Act will be generally allowable as direct charges to NIH grants. While it is expected that these costs will be covered by the funds provided with the grant, administrative supplements could also be considered."

In addition to the comments received during the NPRM comment period, the agency made numerous refinements to the PRS based on feedback from users during the development of results database and its subsequent operation (73 FR 29525, May 21, 2008), and will continue to make further enhancements based on operational experience. Numerous other steps have also been taken to consult outside the agency. As required by FDAAA, the agency convened a public meeting in April 2009 to solicit stakeholder input on development of the registry and results data bank (74 FR 12138, Mar 23, 2009). More than 200 participants registered for the event, and the agency received more than 70 written comments that were taken into consideration in the development of the NPRM for implementing the expanded system. Discussions were also held with the FDA's Risk Communication Advisory Committee. In addition, the National Library of Medicine's Board of Regents established a Working Group on Clinical Trials to help guide its implementation of the required Clinical Trial Registry Data Bank. The working group includes members from industry, academic medical centers, and patient groups, among other constituencies. It held its first meeting on February 11, 2008 and met again on September 15, 2008 to discuss the information collection system for results information. Additional information about the working group and its membership is available online at https://www.nlm.nih.gov/od/bor/bor.html. NLM also organized two workshops to solicit expert input on clinical trials registration and results reporting. Both events included representatives of the affected stakeholder communities. The first was held in Warrenton, Virginia on November 8-9, 2006; the second in Bethesda, Maryland on July 16-17, 2007. Between June and September 2008, a number of webinars and other demonstrations of the results reporting system were arranged for a wide range of affected communities and stakeholders. In 2013, NLM contracted a usability expert to study and evaluate the PRS and implemented an online survey of PRS users via the American Consumer Satisfaction Index (ASCI) survey, which is widely used across the public and private sectors. Based on

feedback from users of the PRS, an initial update of the user interface was implemented to help streamline the data submission process and additional improvements are in progress. A second phase in 2014, based on usability study findings and expert evaluation, further streamlined the data submission process for protocol and results information, including access to enhanced resource materials for data providers and improved portfolio management functions. NLM also plans to incorporate some of the stakeholder feedback provided in the nearly 900 responses received by the agency during the NPRM public comment period.

Development of this information collection has benefited from other forms of public consultation, as well. The FDAMA and FDAAA legislation that established and expanded the clinical trials registry resulted from extensive Congressional hearings that included input from a range of stakeholders. The preceding information collections have been in effect for nearly 16 years and have won wide acceptance from the affected communities. NIH staff participates regularly in conferences, meetings, conferences, and other discussion forums with affected stakeholders in industry, academia and the general public. Staff has published articles about ClinicalTrials.gov, PRS, and their requirements in widely disseminated peer-reviewed journals. Since enactment of FDAAA, NIH staff has redoubled efforts to consult with affected stakeholders, participating in meetings and conferences with representatives of the drug and device industries, FDA law community, academic medical centers, and the library community, among others. The agency has fielded numerous questions about ClinicalTrials.gov from those submitting clinical trial information and those accessing that information; such feedback on the operation of the system has been taken into consideration in developing this information collection.

A.9 Explanation of Any Payment or Gift to Respondents

No gifts or payments are to be offered in regard to this information collection.

A.10 Assurance of Confidentiality Provided to Respondents

Respondents or data providers establish accounts in the data entry system, the PRS, through which they register and submit results information. The information they submit includes the name and contact information of the individual who is authorized to update and maintain data in the PRS. Information about these individuals is not posted on the data bank or otherwise made publicly available.

Information about the sponsor or responsible party for the trial must be submitted at the time of trial registration, including the name of the sponsor and contact information. The name and title of the sponsor or responsible party is publicly posted, but contact information is not. At the time of results information submission, the name and contact information of the individual who has knowledge of the results must be submitted. The information is posted in order to enable members of the public with questions about the results to seek additional information.

Information about trial participants is submitted to the data bank and made publicly available. The information is submitted in aggregate form; none is individual level

information. The information falls into two categories. The first is demographic information consists of age, sex/gender, and race/ethnicity. The second is information on the participants' experiences in the trial, i.e., outcomes, including any adverse outcomes.

For clinical trials of common diseases or that recruit large numbers of participants and/or recruit participants from multiple locations, it is highly unlikely that the aggregate participant information could contain characteristics that would enable re-identification of study participants. In small clinical trials designed to develop interventions for rare diseases and that have few recruitment sites or recruit subjects from small, well-defined populations, there is a small risk of re-identification. If a sponsor/responsible party believes that the submission of summary results information could lead to the re-identification of participants, under section 402(j)(3)(H) of the PHS Act and in 42 CFR 11.54, they may request a waiver of results submission requirements. The agency would expect to grant a waiver if it were determined that the results could only be submitted in a way that would likely enable participants to be re-identified.

The NIH Privacy Act Officer has reviewed the information collection and the manner in which the information is maintained and has determined that the Privacy Act does not apply because the personally identifiable information that is collected is not retrieved through the individual's identity (see Attachment 8). The analysis also recognizes that most of the information submitted to the data bank is required by law (402(j) of the Public Health Service Act) to be made public order to accomplish certain policy objectives. The Privacy Impact Assessment for the collection and storage of this information is currently under review and will be submitted separately.

A.11 Justification for Sensitive Questions

No questions of a sensitive nature are included in this data collection.

A.12 Estimates of Annualized Burden Hours and Costs

The burden associated with this information collection is calculated in two parts: the burden associated with registration and subsequent updates; and the burden associated with the submission of results information, including adverse events, and subsequent updates. These information collections will occur at different times, but the registration and results information will be integrated into a single record for each clinical trial, which is entered through the PRS account.

Registration: Initial Submission and Updates

Before submitting registration information, an organization must establish a PRS account once and use that account to register all of its trials. We consider the creation of the PRS account a one-time burden on respondents, and thus do not include it in this annual burden analysis. The burden associated with registration includes the time and effort necessary for the data provider to extract the data elements from the study protocol, format them for submission, and enter the information into the databank. A number of clinical trials of

drug products, biological products, and device products are registered with ClinicalTrials.gov pursuant to the mandatory and voluntary submissions provisions of the Food and Drug Amendments Act of 2007 (FDAAA). The registration databank also receives a large number of submissions of information from registrants who, though not subject to FDAAA, wish to make information about other clinical studies public for purposes of recruitment or compliance with other policies (e.g., International Committee of Medical Journal Editors). Voluntary registration is explicitly authorized in P.L. 110-85 (section 402(j)(4)(A) of the PHS Act) and 42 CFR 11.60, and the statute and final rule place certain requirements on parties that voluntarily register clinical trials of drug products, biological products, and device products that are subject to FDA regulation but not subject to the mandatory reporting requirements of the law. Nevertheless, all submissions of registration information is collected in accordance with the specifications established for mandatory registrations.

Mandatory Submissions

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 final rule. Using the approach described below, we estimate that a total of 7,400 applicable clinical trials of drug products (including biological products) and device products per year would be subject to the registration requirement of this final 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 for an applicable clinical trial but do not appear to have been conducted under an IND or IDE, e.g., because they are exempt from the requirement to submit an IND or IDE. 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 will be subject to the registration requirement of this final rule each year.

To calculate the burden associated with registering 7,400 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 1 hour more than the estimate used in the 2015 OMB Paperwork Reduction Act clearance for the ClinicalTrials.gov data collection (80 FR 50297, Aug 19, 2015) to account for the time needed to submit the additional data elements required by the final 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 will 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 will 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. This figure is the same as the estimate used in the 2015 OMB Paperwork Reduction Act clearance for the ClinicalTrials.gov data collection (80 FR 50297, Aug 19, 2015). 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. These estimates include the time involved in addressing any issues identified during quality control review of submitted registration information.

Voluntary and Non-regulated Submissions

A number of trials studies will likely be registered in ClinicalTrials.gov as voluntary submissions under 42 CFR 11.60 (e.g., phase 1 clinical trials of FDA-regulated drug products or biological products) or that are not subject to 42 CFR Part 11 at all (e.g., clinical trials that do not involve any FDA-regulated drug products, biological products, or device products or are conducted entirely outside the US and are outside of FDA's jurisdiction). Investigators may choose to register such studies in order to assist in the recruitment of subjects or to comply with medical journal policies that make registration in a publicly accessible repository a condition of publication. In addition, starting in 2017, clinical trial registration and results information will also be collected from all NIH-funded trial investigators whether or not they are subject to 42 CFR Part 11, which will lead to an increase in the number of both voluntary and non-regulated submissions.

NIH Policy

In tandem with the release of the Clinical Trials Registration and Results Information Submission final rule, the NIH issued a complementary policy, NIH Policy on Dissemination of NIH-Funded Clinical Trial Information, that establishes registration and reporting expectations for all NIH funded clinical trials regardless of study phase, type of intervention, or whether they are subject to the 42 CFR part 11 (81 FR 64922, Sep 21, 2016). In order to estimate the added impact of the NIH Policy, we began by determining that 526 NIH-funded trials that were first registered in 2015 are likely not applicable clinical trials. This figure represents the likely number of additional trials for which investigators will have the burden of registration and submitting results per year under the NIH policy. In addition, we estimated that approximately 25 percent of NIH-funded trials that are not applicable clinical trials have not been registered in the past (despite encouragement from NIH and the ICMJE policy). This leads to an estimate of an additional 131 NIH-funded trials per year for which registration and results information need to be submitted under the NIH policy. The total number of non-applicable clinical trials that will be registered and for which results will be submitted under the NIH policy is estimated to be 657 per year. Investigators subject to the NIH policy will be expected to

submit the same registration information within the same timeframes as responsible parties subject to 42 CFR 11.28(a)(2). We, thus, use the assumptions to estimate the burden for applicable clinical trials, i.e., 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.

All Others

In order to estimate the burden for all other clinical trial registrations, we examined registrations to ClinicalTrials.gov in 2015 and found that a total of 19,170 clinical trials were registered that year. Because we estimate that 7,400 of these are applicable clinical trials subject to mandatory registration under 42 CFR Part 11, the remaining 11,770 trials can be considered to be either voluntary submissions under 42 CFR 11.60 or not fall under the rule (i.e., non-regulated). Of these, 526 were the NIH–funded trial subject to the NIH policy (see above). This leaves an estimated 11,244 trials registered per year that do not fall under either the mandatory submission requirements of the rule or the NIH policy.

We expect that sponsors and investigators for these clinical trials will submit the same clinical trial registration information as is submitted for applicable clinical trials that are subject to mandatory submission under the rule in 42 CFR 11.28(a)(2). We expect that information submitted for such clinical trials will be updated as frequently as information for applicable clinical trials that are subject to mandatory submission under the rule. Therefore, for calculating the registration burden associated with these clinical trials, we use the same assumptions as for applicable clinical trials required to register under 42 CFR 11.22, i.e., 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.

These figures would be expected to decline over time as registrants become more familiar with the registration processes and refine their data submission systems. The Internet-based data entry system developed by NIH incorporates features that decrease the data provider's time requirements for quality control procedures. The Clinical Trials Registry Databank is set up to receive protocol information transmitted electronically by sponsors. If the sponsor chooses to manually enter the protocol information, the data entry system allows it to be entered in a uniform and efficient manner primarily through pull-down menus. Some data providers lack information system capabilities enabling efficient collection of company-wide information on clinical trials subject to reporting requirements under FDAAA. The estimation of burden reflects the relative inefficiency of this process for these firms. As a sponsor's familiarity with the data entry system increases, the hourly burden will continue to decrease.

Triggered Submissions Following Voluntary Submissions

42 CFR 11.60 implements section 402(j)(4)(A) of the PHS Act and stipulates that if a responsible party voluntarily registers or submits results information for a clinical trial of an FDA-regulated drug product or device product that is not an applicable clinical trial subject to the mandatory clinical trial information submission requirements, 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 include phase 1 trials of drug products and small feasibility studies of device products (neither of which is considered to be applicable clinical trial) 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 will trigger a requirement to submit clinical trial information for other applicable clinical trials that are included in the marketing application for a drug product or device product only if the entity submitting the marketing application or premarket notification is the same as the responsible party for those other trials and still has access to and control over the necessary data.

In practice, we expect that the requirement under 42 CFR 11.60 to submit clinical trial information for applicable clinical trials not otherwise registered in ClinicalTrials.gov will 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 be registered in ClinicalTrials.gov consistent with section 402(j)(2)(C) of the PHS Act and 42 CFR 11.60. For example, the voluntary submission of information for a phase 1 trial of an unapproved drug product would trigger the submission of information for an applicable clinical trial that was not previously submitted only if the responsible party for the voluntarily-submitted trial is the same as the entity submitting the marketing application, the applicable clinical trial is required to be submitted in that marketing application, and the marketing application is for the same use studied in the voluntarily submitted trial. 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 19,170 clinical trials that are registered every year, on average, with ClinicalTrials.gov, we estimate that 11,770 submissions are either voluntary under FDAAA or non-regulated (all but the 7,400 that are applicable clinical trials). Using 1 percent estimate and this figure, we calculate that voluntary registrations will trigger the required submission of clinical trials information for an estimated 118 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 (88 total) registration information only will need to be submitted; for the other quarter, results information will need to be submitted. For those clinical trials for which only registration information is required, we estimate that it will take a data submitter 8 hours to register the clinical trial. Submitted information will not generally need to be updated because the clinical trial will, in general, have reached its primary completion date by the time the requirement to submit clinical trial information is triggered.

Results Information Submission and Updates

Mandatory Submissions

To estimate the burden associated with submission of clinical trial results information, we started with the premise that every clinical trial required to be registered under 42 CFR Part 11 in a given year would be subject subsequently to mandatory results information submission. While the statute requires results information submission for all applicable clinical trials that study drugs (including biological products) or devices that are approved, cleared, or licensed by FDA, the rule additionally requires the submission of clinical results information for applicable clinical trials of drug products (including biological products) and device products that are not approved, cleared, or licensed by FDA. We, therefore, estimate that the burden associated with results information submission applies to a total of 7,400 applicable clinical trials of drug products (including biological products) and device products per year (see calculations under "Mandatory Submissions" under the "Registration and Updates" subsection, above), recognizing that in most cases, such clinical trial results information will not be submitted in the same year as the associated clinical trial registration information, but in accordance with the results information submission deadlines specified in 42 CFR 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 will 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 information submission times, comments made at the April 2009 public meeting, responses to the burden estimates included in the 2015 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 the study design, number of outcome measures (primary and secondary), statistical analyses, and adverse event information. The estimates 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 calculated and 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 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 2015 OMB Paperwork Reduction Act clearance for the ClinicalTrials.gov data collection (80 FR 50297, Aug 19, 2015) and reflects the additional information that is required to be submitted under this final rule. We

expect the hour burden will decline as responsible parties become more familiar with ClinicalTrials.gov and implement procedures for streamlining data collection, analysis, and formatting.

The provision at 42 CFR 11.48(a) requires submission of the full protocol and SAP (if a separate document) at the time results are submitted and allows redaction by the responsible party if confidential commercial information or personally identifiable information is included. Because protocol and SAP documents already exist, we do not expect that the requirement to upload them will impose a significant burden that is not already accounted for in the results submission burden. In addition, we anticipate that the need for redaction will be very rare, so those costs should also be minimal.

Under the final rule, results information is required to be submitted for all applicable clinical trials that are subject to the registration requirement and that reach their completion date after the effective date of the final rule (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. We also estimate that, on average, each results record will 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 will take 10 hours, on average. 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 (2 updates per trial). 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 information submission under the final rule of 444,000 hours. These estimates include the time involved in addressing any issues identified during quality control review of submitted results information.

Voluntary and Non-regulated Submissions

NIH Policy

As discussed under the “Registration and Updates” subsection (above), we estimate that the impact of the NIH policy, over and above that for mandatory submissions under 42 CFR Part 11, to be 657 NIH-funded trials that are likely not applicable clinical trials per year. Additionally, we use the same assumptions as for mandatory submissions to estimate the burden, namely that initial results submission will take on average 40 hours with two expected updates requiring an average of 10 hours total.

All Others

To estimate the number results information submissions over and above that for mandatory submissions under 42 CFR Part 11, we looked at results information submitted to ClinicalTrials.gov in 2015 and found that 1,580 submissions were for clinical trials that were neither applicable clinical trials subject to mandatory submissions nor funded by NIH. We estimate that this number will grow slightly, secondary to various other funder policies (e.g., PCORI). We, therefore, estimate that we will receive approximately 2,000

results information submissions per year that are not subject to either to mandatory submission requirements under the final rule or the NIH policy. We estimate that the time required to submit clinical trial results information for such clinical trials would be equivalent to that for mandatory results information submission for applicable clinical trials under 42 CFR 11.48(a).

Triggered Submissions Following Voluntary Submissions

As discussed under the "Registration and Updates" subsection (above), based on experience, we estimate that 30 trials per year (a quarter of the 118 clinical trials submitted to ClinicalTrials.gov per 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. Additionally, we estimate that the hourly burden would equal the 40 hours estimated for results information submission for other applicable clinical trials plus 5 hours to account for the additional data elements that are specified in 42 CFR 11.60(b)(2)(i)(B) and (c)(2)(i)(B).

Delayed Submission of Results via Certification or an Extension Request

We also have estimated the average time and cost associated with the submission of certifications and extension requests to delay results information submission, consistent with 42 CFR 11.44(b), (c), and (e). Responsible parties for applicable clinical trials may submit a certification to delay results information submission for an applicable clinical trial provided that initial approval, licensure, or clearance or approval, licensure, or clearance of a new use is or will be sought. We estimate that the number of clinical trials that will qualify for delayed submission of results in a given year will not exceed the estimated number of newly initiated applicable clinical trials per year that are conducted under an IND or IDE. Such clinical trials study drug products (including biological products) and device products that are unapproved, unlicensed, or uncleared or that are already approved, licensed, or cleared for one use, but for which approval, licensure, or clearance of a new use is or will be sought. While some responsible parties might elect to submit clinical trial results information 1 year after the primary completion date instead of certifying for delayed submission, for purposes of this estimate, we assume that they all will elect to submit a certification to delay results information submission. Using the same FDA data we used to estimate the number of applicable clinical trials subject to the registration requirements under the "Registration and Updates" subsection (above), we estimate that certifications will be submitted for 5,150 trials per year. We estimate that it will take no more than 30 minutes for a responsible party to determine that an applicable 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 to ClinicalTrials.gov. Using this figure produces an estimated annual hour burden of 2,575 hours for certifications.

Regarding extension requests for good cause, 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 2008 and 2015. A total of 192 requests were submitted during those 8 years. Many of these requests were not needed in order to delay results information submission because the estimated primary completion date of the

applicable clinical trial had changed. An extension request is not needed in such these situations because a responsible party need only update the estimated primary completion date to reflect changes in the progress of the trial. Other extension requests were submitted for clinical trials that were not applicable clinical trials subject to section 402(j) of the PHS Act. Under the final rule, the approach outlined in 42 CFR 11.22(b) can be used to determine that the clinical trial is not an applicable clinical trial that is subject to this final rule. When these unnecessary requests are excluded, we received about 20 requests per year to delay results information submission for applicable clinical trials for which the actual primary completion date had passed.

Under the final rule, we expect that the number of extension requests will increase as responsible parties gain 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 3 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 7,400). It would also represent approximately 10 percent of the applicable clinical trials that do not certify for delayed results information submission. While responsible parties may request an extension request even after they have filed a certification, we do not expect this to happen frequently. Moreover, as explained in Section IV.C.3. of the final rule (starting on 81 FR 65066, Sep 21, 2016), we expect that extensions will be granted in only a limited set of circumstances where "good cause" has been demonstrated. In cases where an extension request is denied, the responsible party will 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, we expect to receive 50 appeals per year.

We estimate that the time required for gathering the information for a good-cause extension request or appeal and submitting it to ClinicalTrials.gov will be no more than 2 hours. Using this figure, we estimate that the annualized hourly burden for extension requests and appeals will be 500 hours.

We note that under 42 CFR 11.54, responsible parties may also seek a waiver from any applicable results information submission requirement under 42 CFR Part 11. Such waivers are available only under extraordinary circumstances that must be consistent with the protection of the public health or in the interest of national security. We expect the need for such waivers to be exceedingly rare. As such, we are subsuming the costs of waiver requests in the extension request estimates.

Expanded Access Records

As specified in 42 CFR 11.28(a), if an expanded access record is available for an investigational drug product (including a biological product) that is studied in an applicable drug clinical trial, the responsible party for that applicable clinical trial must, if it is both the manufacturer of the investigational product and the sponsor of the applicable clinical trial, include the NCT number of the expanded access record with the clinical trial information submitted at the time of registration. If an expanded access record for the investigational drug product (including a biological product) being studied in the

applicable clinical trial has not yet been submitted to ClinicalTrials.gov, and if the responsible party is both the manufacturer of the investigational product and the sponsor of the applicable clinical trial, the responsible party must create an expanded access record by submitting data elements in 42 CFR 11.28(c). To determine the cost and burden associated with the creation of this record, we relied on information from FDA. Each year, an estimated 135 investigational drug products (including biological products) that were not previously available for expanded access use will be made available for individual patient expanded access (including emergency use) by responsible parties who are required to create an expanded access record. FDA estimates that 10 treatment INDs or treatment protocols are initiated annually and that expanded access use for intermediate size patient populations is initiated 68 times annually. These are the three types of expanded access for which information in 42 CFR 11.28(c) must be submitted to ClinicalTrials.gov under this final rule for an expanded access record. Thus, we estimate a total of 213 expanded records will need to be submitted per year. 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. Compared to the number of data elements required under the rule for applicable clinical trials, only about half as many data elements are required for an expanded access record for expanded access use under treatment INDs, treatment protocols and for intermediate-size patient populations, and still fewer for expanded access records for individual patient expanded access use. The rule also 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 also estimate an average of two updates per expanded access record per year, each taking which 15 minutes. We estimate the total hour burden associated with expanded access records to be 533 hours per year.

Combining the estimates for submitting and updating registration information (including voluntary and non-regulated submission), submitting and updating results information (including voluntary and non-regulated submission), submitting certifications and extension requests for delayed results submission, and submitting and updating information on expanded access records, we estimate the total burden of the ClinicalTrials.gov information collection to be 1,072,306 hours per year. The total associated cost is estimated to be $100,346,998.

A.12-1 Estimated Annualized Burden Hours

Form Name	Type of Respondent	Number of Respondents	Number of Responses per Respondent	Average Burden Per Response (in hours)	Total Annual Burden Hour
Registration (See Attachment 2)					
Initial	Data Entry Personnel	7,400	1	8	59,200
Updates	Data Entry Personnel	7,400	8	2	118,400

Registration Triggered by Voluntary Submission	Data Entry Personnel	88	1	8	704
Initial Registration of Non-regulated Submissions related to the NIH Policy	Data Entry Personnel	657	1	8	5,256
Updated Registration of Non-regulated Submissions related to the NIH Policy	Data Entry Personnel	657	8	2	10,512
Initial Registration of Voluntary and Non-regulated Submissions	Data Entry Personnel	11,244	1	8	89,952
Updated Registration of Voluntary and Non-regulated Submissions	Data Entry Personnel	11,244	8	2	179,904
Results Information Submission (See Attachment 5)					
Initial	Medical Scientist	7,400	1	40	296,000
Updates	Medical Scientist	7,400	2	10	148,000
Results Triggered by Voluntary Submission	Medical Scientist	30	1	45	1,350
Initial Results Information of Non-regulated Submissions related to the NIH Policy	Medical Scientist	657	1	40	26,280
Update Results Information of Non-regulated Submissions related to the NIH Policy	Medical Scientist	657	2	10	13,140
Initial Results Information of Non-regulated Submissions	Medical Scientist	2,000	1	40	80,000
Update Results Information of Non-regulated Submissions	Medical Scientist	2,000	2	10	40,000
Other					
Certification to Delay Results (See Attachment 6)	Medical Scientist	5,150	1	30/60	2,575

Extension Requests and Appeals (See Attachment 7)	Medical Scientist	250	1	2	500
Expanded Access Records – Initial (See Attachment 3)	Data Entry Personnel	213	1	2	426
Expanded access records- Updates (See Attachment 3)	Data Entry Personnel	213	2	15/60	107
Total		**64,600**	**210,037**		**1,072,306**

A.12-2 Annualized Cost to the Respondents

Type of Respondent	Number of Respondents	Number of Responses per Respondent	Average Burden Per Response (in hours)	Hourly Wage Rate* (doubled)	Respondent Cost
Data Entry Personnel	19,602	4.46	2.66	$72.04	$33,459,734
Medical Scientist	15,487	1.39	17.07	$110.04	$66,887,264
Total					**$100,346,998**

***Source**: U.S. Bureau of Labor Statistics. *For data entry personnel*, based on the median hourly wage of Life, Physical, and Social Science Occupations (19-0000) workers in the pharmaceuticals and medicine manufacturing industries in 2015. *For medical scientist*, based on the average wage of Medical Scientists, Except Epidemiologists (19-1042) in pharmaceuticals and medicine manufacturing industries . (http://www.bls.gov/oes/current/oes190000.htm and http://www.bls.gov/oes/current/oes191042.htm)

A.13 Estimates of Other Total Annual Cost Burden to Respondents and Record Keepers

There are no capital costs associated with this collection.

A.14. Annualized Cost to the Federal Government

The annualized cost to the Federal Government for the proposed data collection effort is estimated to be approximately $6,190,784 for ClinicalTrials.gov activities.

Staff	Grade/Step	Salary & Benefits	% of Effort	Fringe (if applicable)	Total Cost to Gov't
Federal Oversight					
Senior Staff Scientist	Title 42	$263,854	100	N/A	$263,854
Staff Scientist	Title 42	$199,845	100	N/A	$199,845
Staff Scientist	Title 42	$199,271	100	N/A	$199,271
Policy Analyst (Biologist)	14/10	$187,602	100	N/A	$187,602
Information Research	13/10	$150,441	100	N/A	$150,441

Specialist					
Staff Scientist	Title 42	$153,904	100	N/A	$153,904
Information Research Specialist	13/10	$156,991	100	N/A	$156,991
Sub-total					**$1,311,908**
Contractor Cost					
7 Software Developers	N/A	$1,838,097	100	N/A	$1,838,097
21 Quality Assurance Reviewers 1 Administrative Staff	N/A	$2,688,403	100	N/A	$2,688,403
Evaluation, Updates and Training	N/A	N/A	N/A	N/A	$300,000
Sub-total					**$4,826,500**
Travel					
Sub-total					**$12,376**
Other Operational Costs					
Supplies, equipment, maintenance, etc.	N/A	N/A	N/A	N/A	**$40,000**
Total					**$6,190,784**

N/A, not applicable

A.15 Explanation for Program Changes or Adjustments

The NPRM on Clinical Trials Registration and Results Submission was issued on November 21, 2014 (79 FR 69566, Nov. 21, 2014) for public comment. The NPRM proposed several modifications to the information collection, including the scope of trials for which results reporting is required and the types of information to be provided. The initial 90 day public comment period was extended and the public comment period on the NPRM closed on March 23, 2015 (80 FR 8030, Feb 13, 2015). Nearly 900 public comments were received, some of which addressed the Paperwork Reduction Act of 1995 (Section VI of the preamble of the final rule starting on 81 FR 65132, Sep 21, 2016), and which are also discussed in the above Section (see A.8).

The program changes reported in this supporting statement reflect the requirements under the final rule (42 CFR part 11), promulgated to further the implementation of FDAAA. The final rule clarifies, modifies, and expands the information collection requirements that were previously cleared by OMB. Additionally, this supporting statement includes adjustments to the burden estimates to reflect increases in average burden per response due to the new regulatory requirements in section A12-1 (i.e., initial registration increased by 1 hour, from 7 hours to 8 hours; initial results submission increased by 15 hours, from 25 hours to 40 hours) and hourly wage increases in section A12-2, reflecting updated, 2015 data from the BLS (from $64.88 per hour to $72.04 per hour for Data Entry Personnel and from $98.52 per hour to $110.04 per hour for Medical Scientists). It also includes increases in registration and results information from voluntary and non-regulated submissions following the NIH Policy on Dissemination of NIH-Funded Clinical Trial Information.

Per the terms of clearance of the current clearance that expires on 11/30/2018: "Approved consistent with previous terms of clearance: This collection is approved consistent with the agreement that NIH will continue to work with OMB and other interested agencies as they move forward with the rule making process that will eventually define the adverse event reporting framework in response to U.S. Public Law 110-85 (i.e., determining the best method for including in the registry and results databank appropriate results information on serious adverse and frequent adverse events.) These terms of clearance do not preclude the option of NIH using the FDAAA default as a starting point for adverse event reporting. OMB understands that NIH will seek public comments through rulemaking and incorporate prior experience with the optional reporting system to ensure that the default elements are incorporated and displayed in an appropriate and meaningful way."

A.16 Plans for Tabulation and Publication and Project Time Schedule

Submitted information is made available to the public via the ClinicalTrials.gov website, which is operated and maintained by NIH: https://clinicaltrials.gov/. In general, registration information is posted within 30 days of receipt, but consistent with FDAAA, information for applicable clinical trials of devices that are indicated to be unapproved or uncleared for any use is not posted publicly until after the device is cleared or approved by the FDA for marketing in the U.S., unless the responsible party authorizes NIH to post the registration information for that trial as specified in 42 CFR 11.35(b)(2)(ii). Results information is also posted within 30 days of receipt, whether or not it has passed quality review. The databank is subject to public search and review, and FDAAA identifies certain criteria by which the databank must be searchable by the public, including by disease or condition being studied, location of the clinical trial, and study phase.

ClinicalTrials.gov was first launched as a registry in February 2000. Its development since 2007 has followed legislative requirements specified in FDAAA, including the following statutory milestones: The expanded registry was operational in December 2007 (less than 90 days after enactment of FDAAA), and the "basic results" databank by September 2008 (less than 1 year after enactment). The collection of adverse event information became mandatory in September 2009 (2 years after enactment). FDAAA requires the Secretary of HHS to further expand the registry and results databank by regulation. The NPRM on Clinical Trials Registration and Results Submission was issued on November 21, 2014 (79 FR 225, Nov. 21, 2014) for public comment. The NPRM proposed several modifications to the information collection, including the scope of trials for which results reporting is required and the types of information to be provided. The public comment period on the NPRM closed on March 23, 2015, and the agency reviewed and considered all the public comments in drafting the final rule. The final rule for Clinical Trials Registration and Results Information Submission at 42 CFR 11 was issued on September 21, 2016 (81 FR 64981). The effective date is January 18, 2017 and the compliance date is 90 days after publication of the final rule in the Federal Register. The information collection described in this supporting statement reflects the requirements specified in the final rule and this information collection documentation is intended to provide public notice of all changes resulting from the recent rulemaking.

A.17 Reason(s) Display of OMB Expiration Date is Inappropriate

No exemption is requested.

A.18 Exceptions to Certification for Paperwork Reduction Act Submissions

No exceptions are requested.