Supporting Statement A for:

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

April 10, 2012

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A. JUSTIFICATION

A.1 Circumstances Making the Collection of Information Necessary

This information collection request seeks 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 under the authority of the Director, National Institutes of Health. The OMB Notice-of-Action granting 3-year approval of the information collection (OMB No. 0925-0586), became effective April 28, 2009, and is due to expire on April 30, 2012. We are using the revision as an opportunity to make some minor adjustments to the information collection to enhance its utility and allow submission of some additional data elements that will assist users of ClinicalTrials.gov in interpreting submitted adverse event information and to facilitate use of the data bank to register patient registries.

Compelling reasons exist for the continued collection of clinical trial registration and results information by ClinicalTrials.gov. This information collection is necessary to enable compliance with statutory requirements of Section 801 of the Food and Drug Administration Amendments Act of 2007 (FDAAA; Public Law 110-85). Enacted on September 27, 2007, FDAAA amends section 402 of the Public Health Services Act [42 U.S.C. 282] to add a new section (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)] and makes available to the public a searchable data bank of information about the results of certain controlled clinical trials of drugs, biological products, and devices.

Pursuant to section 801 of FDAAA, the Director of NIH is to collect and make available to the public in searchable data bank information concerning certain controlled clinical trials of drugs, biologics, and devices that are subject to regulation by the Food and Drug Administration (FDA). 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 default requirements for the submission of adverse event information that take effect on September 27, 2009. FDAAA requires sponsors and designated principal investigators of specified clinical trials of FDA-regulated drugs, biological products, and devices 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 studies and on trials that were completed prior to enactment of the law or other reporting deadlines established in the law.

This information collection will also satisfy the purposes of the original clinical trial information collection that was established to comply with 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, Information Program on Clinical Trials for Serious or Life-Threatening Diseases, Food and Drug Administration Modernization Act of 1997, Public Law 105-115, 105th Congress).

The information collection is also necessary to allow researchers and organizations who are not subject to FDAAA or FDAMA to voluntarily register trials and other clinical studies (e.g., observational studies) 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 journal. Subsequently, the World Health Organization (WHO) published international standards for clinical trial registration. The 2008 Declaration of Helsinki ("Ethical Principles for Medical Research Involving Humans") asserts that "every clinical trial be registered in a publicly accessible database" [Article 19] and "authors have a duty to make publicly available the results of their research … [for] negative and inconclusive as well as positive results" [Article 30]. 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. In addition, there is interest in using ClinicalTrials.gov as a platform for registering patient registries.

Finally, this information collection is essential to the effective stewardship of Federal Funds. After consultation with other agencies and NIH components, NIH has determined that the information is not currently available in any single, reliable, accessible source. Since the passage of the FDAAA, staff at the National Library of Medicine has worked with other NIH officials, representatives of the U.S. Food and Drug Administration and officials of the Department of Health and Human Services to revise the set of data elements needed to register an applicable clinical trial and to develop the set of data elements necessary to report basic results information in accordance with the law. As described below, public comment was solicited on preliminary versions of the data submission system for basic results information.

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, 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 and a more solid foundation for decision-making. For several years, the National Institutes of Health (NIH) and the Food and Drug Administration (FDA) have initiated efforts to encourage the registration of clinical trials in publicly accessible databanks; as such, information is not otherwise easily accessible to the general public.

Information will be collected via electronic submission to the ClinicalTrials.gov Protocol Registration System, available at http://www.clinicaltrials.gov. The information in the databank will be available to patients, other members of the public, 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 will provide basic information about the trials, their implementation, and how to enroll. Progress of the trials will be updated so that individuals will have current information on initiatives to intervene to treat, cure, ameliorate or prevent the health conditions with which they are afflicted or at risk. The results portion of the databank will summarize the outcomes of the trial, by arm. In some instances, registration information will be used for the purpose of facilitating enrollment in clinical trials of drugs intended for the treatment of patients with serious or life-threatening diseases and conditions. Facilitating enrollment will 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.

This information will be 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 are ultimately 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 will expand public availability of such information for patients. This expanded patient access to information about clinical trials will increase patients' therapeutic 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 will 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. They will be able to better plan new research projects, and avoid duplication that can expose human volunteers to unnecessary risks. It will also ensure that treatment decisions are based on a more complete set of scientific evidence.

Data Elements for Registration

The required registration data elements for this information collection are listed in Table 2-1. Collection of this information was previously approved under an earlier information collection request, OMB No. 0925-0586. The elements 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 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 (e.g., observational studies and patient registries). For example, FDAAA requires that the databank enable searching by "the safety issue, if any, being studied in the clinical trial as a primary or secondary outcome" and by the location of the clinical trial [*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 also 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 collected for expanded clinical trials registry

Data Element		**Justification** [Statutory References are to section 402(j) of the PHS Act, as added by *PL 110-85, Section 801(a)*]
1. Descriptive Information		
	Brief Title	(2)(A)(ii)(I)(aa) specifies a brief title, intended for the lay public
	Brief Summary	(2)(A)(ii)(I)(bb) specifies a brief summary, intended for the lay public
	Primary Purpose	(2)(A)(ii)(I)(cc) specifies the primary purpose
	Study Design *For interventional studies, includes:* • *allocation,* • *arm description,* • *arm designation,* • *arm number/label,* • *arm type,* • *intervention study model,* • *masking,* • *number of arms.* *For observational studies, includes:*	(2)(A)(ii)(I)(dd) specifies study design. Requested information under this heading is intended to meet the statutory and practical requirements ensure complete and consistent collection of information to describe the design of interventional and observational studies.

	• *group/cohort description, group/cohort number or label,* • *number of groups/cohorts,* • *observational study model,* • *sampling method, and* • *time perspective.*	
	Study Phase	(2)(A)(ii)(I)(ee) specifies for an applicable drug clinical trial, the study phase
	Study Type (record type)	(2)(A)(ii)(I)(ff) specifies "study type"
	Primary disease or conditions; Focus of Stud*	(2)(A)(ii)(I)(gg) specifies the primary disease or condition being studied, or the focus of the study
	Intervention Name *Includes FDA approval status, intervention description, other intervention names, and intervention type (e.g., drug, device, surgical procedure)*	(2)(A)(ii)(I)(hh) specifies intervention name and intervention type. FDA approval status collected to determine eligibility of device trials for public posting in accordance with section (2)(D)(ii) and to assist in identifying trials for which results information will subsequently be required.
	Study Start Date	(2)(A)(ii)(I)(ii) specifies study start date
	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
	Target Number of Subjects (Enrollment)	(2)(A)(ii)(I)(kk) specifies "the target number of subjects"
	Primary Outcome Measures (including title, specific measure description, and time of outcome measurement)	(2)(A)(ii)(I)(ll) specifies "outcomes, including primary and secondary outcome measures"
	Secondary Outcome Measures (including title, specific measure description, and time of outcome measurement)	(2)(A)(ii)(I)(ll) specifies "outcomes, including primary and secondary outcome measures"
	Safety Issue? (Yes/No)	(2)(B)(ii) requires the database to enable "searching by safety issue, if any, studied as primary or secondary outcome."
2. Recruitment Information		
	Eligibility Criteria (*includes study population description for observational studies*)	(2)(A)(ii)(II)(aa) specifies "eligibility criteria"
	Gender	(2)(A)(ii)(II)(bb) specifies "gender"
	Age Limits	(2)(A)(ii)(II)(cc) specifies "age limits"
	Healthy Volunteers Acceptance	(2)(A)(ii)(II)(dd) specifies "whether the trial accepts healthy volunteers"
	Overall Recruitment Status	(2)(A)(ii)(II)(ee) specifies "overall recruitment status"
	Individual Site Status	(2)(A)(ii)(II)(ff) specifies "individual site status"
	Expanded Access Information	(2)(A)(ii)(II)(gg) specifies "...whether or not there is expanded

		access to the drug and how to obtain information about such access”
3. Location and Contact Information		
	Name of Sponsor	(2)(A)(ii)(III)(aa) specifies “the name of the sponsor”
	Responsible Party (type, *name, official title, organizational affiliation*)	(2)(A)(ii)(III)(bb) specifies “the responsible party, by official title”;*)*
	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)”
	Facility Contact (*name and 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)”
	Central Contact (*name, title and toll-free telephone number of email address*)	(2)(A)(ii)(III)(cc) specifies “ ...or a toll-free number through which such location may be accessed”
4. Administrative Data		
	Unique Protocol ID	(2)(A)(ii)(IV)(aa) specifies “the unique protocol identification number”
	Other Protocol IDs	(2)(A)(ii)(IV)(bb) specifies “other protocol identification numbers, if any”
	FDA IND/IDE Protocol? (*including grantor name, IND/IDE number and 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*)
	Record Verification Date	(2)(A)(ii)(IV)(cc) specifies “record verification date”
	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*
5. Other Necessary Information		
	Applicable Clinical Trial? (including FDA-Regulated Intervention?, Section 801 Clinical Trial? And FDA approval status of each intervention	Collected to distinguish between mandatory submission of Applicable Clinical Trials [defined in (1)(A)(i)] and voluntary submissions authorized in [(4)(A)], to help data submitters determine if their trial is an applicable clinical trial, and to indicate whether the trial involves approved or unapproved medical products, which is necessary to determine the date on which results information is to be submitted per (3)(E).
	Pediatric Post-market Surveillance	Collected to identify studies that are post-market pediatric surveillance studies that are required to register, even if they are not standard interventional or observational studies.
	Delayed Posting?	Collected to identify trials of unapproved/uncleared devices for which information is to be withheld from public posting in

		accordance with (2)(C)(ii)(I)
	Institutional Review Board Approval Information (including Board Approval, Approval Status, Approval Number, Board Name, Board Affiliation, and Board Contact)	Collected to ensure that registered trials conform with international human research protection policies. This information is not required for federally funded or IND/IDE studies because they are subject to procedures that verify compliance with such polices. (*Note that only the Approval Status is made public*)
	Oversight Authorities	Collected to determine which organization (domestic or international) has authority over the trial, which is essential to verifying that any listed trial conforms with relevant regulations regarding human subjects research.

In addition to the items listed in Table 2-1, respondents may submit optional data elements to provide a more complete record of the clinical trial or meet the requirements of other policies related to the disclosure of clinical trial information (such as that of the International Committee of Medical Journal Editors, which requires registration as a precondition for considering research papers for publication). 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]
- official title of the trial (in contrast to the "brief title" required by law) and acronym [required by the ICMJE],
- study completion date [formerly completion date] (as opposed to primary completion date as specified in FDAAA)
- study classification [formerly endpoint] (e.g., safety, efficacy, bioequivalences -- for interventional studies only)
- biospecimen retention and biospecimen description (for observational studies only)
- detailed description of the trial/study
- names of collaborators [required by the ICMJE],
- whether or not a data monitoring committee has been established for the trial, and
- why recruitment stopped?

In addition, to facilitate the registration of patient registries, as part of an initiative being conducted with the Agency for Healthcare Research and Quality (AHRQ), the information collection is being modified to enable the collection of additional data elements that describe patient registries, including the duration of participation, registry procedures, and quality factors. This information was not contained in the previous information collection under OMB 0925-0586).

Before registering a study, a data provider must establish an account in the ClinicalTrials.gov protocol registration system (PRS). This will typically be done by an organization that sponsors clinical trials. 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 National Library of Medicine to verify the existence of a data submitter's organization and have a designated point of contact from the submitter's organization. Establishment of an organizational account also provides a mechanism for organizations to, in turn, authorize individual users (e.g., responsible parities) 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.

Information collected for results

Results information, which has been collected since September 23, 2008, derives from statutory language included in FDAAA. The Act requires the submission of the five types of information for applicable clinical trials of drugs that are approved under section 505 of the Federal Food, Drug, and Cosmetic Act or licensed under section 351 of the Public Health Services Act and devices that are cleared under section 510(k) of the Federal Food, Drug, and Cosmetic Act or approved under section 515 or 520(m) of such Act:

1. *Point of Contact* - A point of contact for scientific information about the clinical trial results.

2. *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.

3. *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.

4. *Primary and Secondary Outcomes* - 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.

5. *Adverse Events* – (1) A table of anticipated and unanticipated serious adverse events grouped by organ system, with number and frequency of such event in each arm of the clinical trial and (2) 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.

For the first item, 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 the second item, the respondent 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, 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.

The information collection for the third item is divided into two parts: information about participant flow and 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) and the number of subjects that completed the trial (overall and by arm). 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 phases 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 and pre-assignment 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. This information was not previously

required, but is added during this revision to provide 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 only two demographic characteristics: age and gender. Respondents 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 enable this flexibility, respondents will be required to provide descriptive information about the submitted data, in addition to the numerical data values themselves. For example, they will be required 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 information collection system uses this information to generate the appropriate row and column headings for the tables into which the data itself will be submitted.

A similar approach is taken to collect information describing the primary and secondary outcome measures (item 4 above). Respondents must 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). Additional explanatory information about the analysis population may also be provided (optionally). For each outcome measure specified in the protocol, respondents are required to 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 will have the option to submit additional information about the statistical analysis used for the outcome measures, such as the p-value or confidence interval.

For 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]. This information was collected as voluntary in the previous information collection description, but in accordance with section 402(j)(3)(I)(ii) of the PHS Act it is required to be submitted as part of results information for any trial for which results are submitted on or after September 27, 2009. While most of the adverse events information to be collected was included in the previous PRA clearance, we are revising the

information collection to add a small number of data elements (most of them optional) that allow for a more complete description of the adverse events that will help users better interpret the information.

The general approach taken to collect adverse event information is similar to that for items 3 and 4. For each 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. Of these elements, the latter was not collected previously. 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 a voluntary basis (this approach allows the submission of more data than the minimum required by law). For each adverse event included in a table, 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. We have also made it possible for respondents to voluntarily 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), additional descriptive information, the name of any standardized vocabularies used to name the adverse events, the methodology used to assessment adverse events (i.e., designating whether adverse event information is collected systematically or spontaneously), and the number of occurrences of each adverse event reported (by arm). Of these elements, only the time frame and additional descriptive information were not collected previously. Our experience in operating ClinicalTrials.gov indicates that such information is helpful to those trying to interpret other submitted adverse event information.

Respondents may provide additional information, 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. Only those elements marked with an asterisk are required to be submitted; optional information is also identified.

Table 2-3 Information collected for clinical trial results

[items marked with an asterisk are required to be submitted; others are optional]

Data Element		**Justification** [References are to section 402(j) of the PHS Act as added by *PL 110-85, Section 801(a)*]
1. Point of Contact for Results*		(3)(C)(iii) "a point of contact for scientific information about the clinical trial results
	Name or official title*	
	Organization name*	
	Phone number* (and extension, if any)	
	Email address*	
2. Certain Agreements*		
	Whether all PIs are employees of the sponsor? [Y/N]. [If *yes*, then no additional information is required under item 2]. *	(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* • less than or equal to 60 days • 60-180 days • Other	To determine whether the restriction extends beyond standard industry practice (approx. 60 days).
3. Participant Flow (by arm)*		(3)(C)(iv) "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*"
	Arm/Group title* and description [optional] for each arm	
	Period titles [defined by respondent]*	
	Number of subjects that started the trial and each defined period (overall and by arm)*	(3)(C)(iv) [above]
	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]	
	Pre-assignment details [optional]	
4. Baseline Characteristics (overall and		(3)(C)(iv) "A table of the demographic and baseline

by arm)*		data collected overall and for each arm of the clinical trial to describe the patients who participated in the clinical trial
	Arm/Group title* and description [optional] for each arm	
	Overall number of baseline participants*	
	Baseline measure names(s)*	
	• Age (mean, median, or by age category)*	Common demographic variable for clinical trials
	• Gender*	Common demographic variable for clinical trials
	• 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*	
	Baseline characteristic data*	
	• Number (if applicable)*	
	• Descriptive statistics* (central tendency value and dispersion value)	
5. Outcome measures (by arm)*		(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. . . “
	Arm/Group title* and description [optional] for each arm	
	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) [optional]	
	Descriptive information for each outcome measure (as below):*	
	• Type of outcome measure (primary, secondary, other pre-specified, post-hoc)*	
	• Outcome measure reporting status* (posted or not posted)	
	• Title of the outcome measure*	
	• Outcome measure time frame*	
	• Outcome measure related to a safety issue [Y/N]?*	
	• Description of the outcome [optional]	
	• Measure type (i.e., number or measure of central tendency,) and measure of dispersion (e.g., standard deviation, full range, etc.), if applicable	
	• Measure of dispersion (e.g., standard deviation, full range) if a central tendency reported.*	
	• 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)*	
	Outcome data*	
	• Number*	
	• Descriptive statistics,* if applicable	
	Statistical analysis [optional]	“. . . including the results of scientifically appropriate tests of the statistical significance of such outcome measures.”
	• Comparison groups selected [optional]	
	• Whether or not the analysis is a test of non-inferiority or equivalence [Y/N] [optional]	

	• P-value or confidence interval (including the level, lower limit and upper limit) [optional]	
	• Method – statistical test or estimation parameter and dispersion of confidence interval [optional], required if P-value is reported	
6. Overall Limitations and Caveats [optional]		
7. Adverse Event Information (by arm)*		(3)(I)(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)(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.
	Arm/Group title* and description [optional] for each arm	
	Time frame for adverse event collection [optional]	
	Adverse event collection additional description [optional]	
	Adverse event term (description of the event)*	
	Source vocabulary name (if any) [optional]	
	Organ system*	“grouped by organ system” [(3)(I)(iii)]
	Assessment type (e.g., systematic assessment or spontaneous report) [optional]	
	Total number of participants affected by any serious adverse event*	“results information on serious adverse. . . events” [(3)(I)(i)]
	Adverse event term additional description	
	Total number of participants at risk for serious adverse event*	
	Frequency threshold for reporting other (non-serious) adverse event*	
	Total number affected by other (non-serious) adverse events*	“results information on . . . frequent adverse events” [(3)(I)(i)]
	Total number of participants at risk for other (non-serious) adverse event*	
	Adverse event data*	
	• Number of affected participants*	“number and frequency of such event in each arm of the clinical trial” [(3)(I)(iii)]

	• Number of events [optional]	
	• Number of participants at risk*	"number and frequency of such event in each arm of the clinical trial" [(3)(I)(iii)]

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 [(3)(E)(iv) and (3)(E)(v)]. To simplify this process, the ClinicalTrials.gov has been modified to allow the submission of certifications directly through the Protocol Registration System. The responsible party must submit the following information:

- An indication (a menu option) certifying that the trial qualifies for delayed submission under either the "seeking initial approval" or "seeking approval of a new use" provisions of FDAAA
- The name of the intervention(s) that are unapproved, unlicensed, or uncleared or for which new use approval will be sought (to resolve ambiguity if a trial involves multiple interventions with different approval status).
- The marketing application or premarket notification number assigned by the FDA (to permit subsequent linking of approval packages to trial records in ClinicalTrials.gov).

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 [(3)(E)(vi)]. To simplify the process, extension requests are submitted directly through the ClinicalTrials.gov Protocol Registration System 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.

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 reasons for which extension requests have been granted and/or denied.

A.3 Use of Improved Information Technology and Burden Reduction

FDAAA itself directs the Director, NIH to make the information available via the Internet, stating that "The Director of NIH shall ensure that the registry databank is made publicly available through the Internet." [section 402(j))(2)(A) of the PHS Act].
ClinicalTrials.gov utilizes the latest software and Internet technologies for submitting registration and results information, and

searching/retrieving such information. Information can be entered manually into electronic forms available on the ClinicalTrials.gov website or can be uploaded automatically (and in batches) from computer systems that put it in a structured format specified in ClinicalTrials.gov. To minimize the burden on respondents and ensure data consistency between registration and results records, relevant clinical trial registration information is imported into results information templates. In addition, the data entry system for results submission 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 system can be viewed at http://clinicaltrials.gov/. A Privacy Impact Assessment was conducted for this information collection and it was determined that the Privacy Act will not apply.

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

ClinicalTrials.gov is a unique information resource. The registry contains registration information on more than 121,000 clinical studies in more than 170 countries. No comparable publicly 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 (http://www.clinicalstudyresults.org/), 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 is currently submitted to FDA in a different format 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 section 552 of Title 5, United States Code (Freedom of Information Act). Information about non-IND/IDE or IND/IDE-exempt studies is typically contained in clinical trial protocol documents, which are not generally submitted to the FDA nor made available to the public. Similarly, FDA receives information about the results of clinical trials when the manufacturer of a drug or device submits an application for approval, but such information is not made public in a systematic fashion, is not comparable across studies, and is heavily redacted. Scientific journals contain results information 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 further minimize the burden on respondents, the required results 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

This activity is anticipated to have minimal impact upon small business. 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 the burden on them. 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**,** much (if not all) of the information to be supplied to ClinicalTrials.gov is 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, compliance with policies of the International Committee of Medical Journal Editors (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 list their clinical trial information voluntarily in the ClinicalTrials.gov, suggesting that the benefits of registration and results submission outweigh the costs of the effort involved**.** 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 Title VIII of FDAAA, 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 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 study completion date, but only if the product is approved, licensed, or cleared by the FDA. The submission deadline can be extended if the responsible party certifies that the manufacturer is seeking initial FDA approval for the drug, biologic, or device under study or FDA approval for a new use. 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

The information collection proposed in this statement was originally published in the Federal Register on February 9, 2012 (Vol. 77, No. 27, p. 6808) and allowed 60-days for public comment. One public comment was received which was not germane to the specific purpose of the notice. The agency made numerous refinements to the results data entry system based on feedback from users during its development and subsequent operation (as described above), and will continue to make further enhancements based on operational experience. The agency believes its burden estimates are consistent with the experience of users and reflect wide variation in the time necessary to submit information for trials of varying size and complexity. The burden estimate for results submissions were increased from those included in the original submission to account for additional estimates by various industry groups and other data submitters. We expect that the burden will decline as users gain greater familiarity with the system.

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. More than 200 participants registered for the event, and the agency received more than 70 written comments that will be taken into consideration in future development of a Notice of Proposed Rulemaking 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 <http://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.

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 12 years and have won wide acceptance from the affected communities. NIH staff participates regularly in conferences, meetings, monthly conferences, and other discussion forums with affected stakeholders in industry, academia and the general public. Staff has published articles about the system and its 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 data and those accessing data; 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

Most information submitted to the data bank is required by law to be made public, in keeping with the policy objectives of FDAAA and FDAMA. Consistent with the authority provided in the law, the agency does not publicly post certain administrative information that is submitted, including IND or IDE numbers (which are considered confidential) and names, affiliations, and contact information of human subject review boards. In addition, the contact information of the responsible party is not made public (although the name and official title are made public). Confidential information regarding the submission of marketing applications or premarket notifications to the FDA is also withheld from public posting.

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 three parts: the burden associated with the one-time process of applying for a PRS account; the burden associated with registration; and the burden associated with the submission of results information, including adverse events. 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.

PRS Account Application

The burden associated with applying for a PRS account includes the time and effort necessary to collect and enter the information into the PRS Account Application Form. To determine the annual reporting burden, estimates were made of the total number of new applications for PRS accounts that are submitted each year. As noted above, an organization can establish an account once and use that account to register all of its trials. In recent years, approximately 5,500 new applications have been submitted per year. We expect this rate to continue unchanged in coming years. Based on past experience with organizational accounts, we estimated that the time necessary to collect the required information and enter it into a new application form requires no more than 15 minutes. Applying these figures to the anticipated number of new account applications produces a burden estimate of 1,375 hours per year (5,500 applications times 0.25 hours per application). This estimate is summarized in Table 12-1.

Table 12-1 Estimated Burden for New PRS Account Applications

Type	Respondents	Frequency	Total Responses	Average Time per Response	Annual Hour Burden
Application	5,500	1 per applicant	5,500	0.25 hrs	1,375

Registration

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. References below to mandatory and voluntary submissions refer to the requirements of FDAAA. The burden estimates capture both those submissions that are mandatory under FDAAA and those that are done voluntarily.

To determine the annual reporting burden for mandatory submissions of registration information under FDAAA, estimates were made of the number of applicable trials of drugs, biologics, and devices. It was estimated that approximately 5,000 applicable clinical trials of drugs and biologics and 500 applicable trials of devices would be registered annually in accordance with FDAAA. The annual drug and biologic trial estimates were based on information from the FDA indicating that, between 2004 and 2008, the Center for Drug Evaluation and Research (CDER) received an average of 3,670 new clinical trial protocols per year for studies of drugs (excluding biological products) and the Center for Biologics Evaluation and Research (CBER) received an average of 449 new protocols per year for trials of biological products that would be considered applicable drug clinical trials. We reduced the number of drug trial protocols by 30 percent (to 2,569 trials) to exclude phase I trials, which are not subject to registration under the proposed rule. We added to these figures another 1,380 trials, which is equal to the number of trials that were registered at ClinicalTrials.gov between September 2009 and August 2010 that appeared to meet the criteria of an applicable drug clinical trial, but for which protocols were not submitted to the FDA under an investigational new drug application (IND), e.g., because they were IND-exempt. The sum of these figures (i.e., 4,398) provides an estimate of the number applicable drug clinical trials that would be subject to the registration requirement of the proposed rule each year. We rounded up this figure to 5,000 applicable drug clinical trials to account for additional non-IND trials that might not have been captured by our estimation technique. To estimate the number of applicable device clinical trials, we used information from the FDA Center for Devices and Radiological Health (CDRH), which indicated that between 2004 and 2008, an average of 363 new protocols were submitted each year for trials of devices. We added to this figure the 131 trials of devices that were registered with ClinicalTrials.gov between September 2009 and August 2010 but did not indicate that they were conducted under an IDE. Adding this number to the number of device protocols submitted to CDRH yielded an estimate of 494 applicable device clinical trials per year that would be subject to registration under the proposed rule. We rounded up this figure to 500 to account for additional non-IDE trials that might not have been captured by our estimation technique. Adding the estimated number of applicable device clinical trials to the estimated number of applicable drug clinical trials produces a total of 5,500 applicable clinical trials that would be subject to the mandatory submission requirements under FDAAA.

The registration databank also receives a large number of voluntary submissions of information from registrants who wish to make their information 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 the statute places certain requirements on parties that voluntarily register clinical trials of drugs and devices that are subject to FDA regulation but not subject to the reporting requirements of the law. Nevertheless, for all voluntary submissions, information is collected in accordance with the specifications established for mandatory registrations. The number of voluntary registrations is estimated by subtracting the anticipated annual number of mandatory registrations from the total number of trial registrations expected during the year, based on historical averages. From calendar year

2008 to 2011, there was an average of approximately 17,000 new trials registered in the ClinicalTrials.gov per year, of which some 9,000 were trials with drugs or biologics as an intervention, 1,700 were trials with a device as an intervention, and 6,300 were other types of studies (e.g., observational studies, trials of procedural interventions or behavioral interventions). Subtracting the estimated annual number of mandatory trial registrations from this 4-year period produces estimated 11,500 voluntary registrations, which includes approximately 4,000 trials of drugs and biologics, 1,200 trials of devices, and 6,300 trials of other intervention types and observational studies.

The hour burden accounts for time required to register trials and provide necessary updating over the course of the study. Based on previous experience, it is estimated that each new registration record will be updated an average of 8 times during the course of the study (e.g., to reflect protocol changes, additions of investigational sites, updates of recruitment status, trial completion). This estimate is consistent with the statutory requirement in FDAAA that clinical trial information be updated at least once annually if there were any changes in the previous 12-month period and within 30 days of any change in the recruitment status of individual sites. The time to complete an initial (new) registration for trials of drugs, biologics, or devices is estimated to be 7 hours (including time to extract, reformat and submit information which has already been produced for other purposes), an increase of 50% above the 4.6 hours that was estimated for the smaller set of information collected under previous law (FDAMA), and which was based on FDA's experience reviewing INDs and consultation with sponsors who submit protocol information to the Clinical Trials Databank. The estimate incorporates 4 hours for data extraction and 3 hours for reformatting, consistent with the proportions that were used in the estimates for the smaller data collection under FDAMA, which were, in turn, based on data collected from organizations submitting protocols to the Clinical Trials Registry Databank. The time required for subsequent updates of registration information is expected to be significantly less than for the original registration (as less information must be provided), and is estimated at 2 hours per update.

Applying these figures to the anticipated numbers of trials produces a burden estimate for mandatory and voluntary, new trial registrations of 391,000 hours. Of this total, 126,500 hours are associated with mandatory registration requirements and 264,500 hours are associated with voluntary reporting. These estimates are summarized in Table 12-2. 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 sponsor's familiarity with the data entry system increases, the hourly burden will continue to decrease.

Table 12-2 Estimated Burden for Newly Registered Trials

Type	Respondents	Frequency	Total Responses	Average Time per Response	Annual Hour Burden
Mandatory Submissions					
Drug & Biologic	5,000	1 Initial	5,000	7 hrs	35,000
		8 Updates	40,000	2 hrs	80,000
Device	500	1 Initial	500	7 hrs	3,500
		8 Updates	4,000	2 hrs	8,000
Subtotal	5,500		49,500		126,500
Voluntary Submissions					
Drug & Biologic	4,000	1 Initial	4,000	7 hrs	28,000
		8 Updates	32,000	2 hrs	64,000
Device	1,200	1 Initial	1,200	7 hrs	8,400
		8 Updates	9,600	2 hrs	19,200
Other	6,300	1 Initial	6,300	7 hrs	44,100
		8 Updates	50,400	2 hrs	100,800
Subtotal	11,500		103,500		264,500
Total	17,000		153,000		391,000

Results Submission

The burden associated with submission of results information consists of the time and effort needed to summarize information from the clinical trial and enter it into the databank. Much of this data is collected and summarized for other purposes, including for inclusion in marketing approval applications to the FDA or for publication in scientific journals.

The number of responses per year for submission of results information will be fewer than that for registration information. Results submission is required only for those applicable clinical trials of drugs, biologics, and devices that were required to register with ClinicalTrials.gov under FDAAA and for which the product(s) under study have been initially approved or cleared by the FDA (i.e., submission of information on pre-marketing trials can be delayed until the drug, device, or biologic is approved or cleared by FDA). Hence, the burden estimate consists primarily of the submission of results information for trials of products that had been approved/cleared by the FDA prior to their registration (e.g., phase 4 trials of approved drugs) and for pre-market trials of products that are approved in a given year (e.g., phase 2 and 3 drug trials, premarket device trials). An additional, smaller burden is associated with the submission of request for extensions of the deadline for reporting results and for the submission of certifications that initial or new-use approval is being sought for the products under investigation in the trial

For drugs and biologics, FDA statistics indicate that CDER and CBER approved approximately 100 new drug applications (NDA) and biological license applications (BLAs) in 2010. This figure is not expected to increase substantially in the near future. FDA estimates that each NDA references, on average, 10 applicable clinical trials. Assuming that a similar number of trials is referenced in each BLA, the number of results submissions to the clinical trials data bank resulting from new product approvals/clearances would be 1,000 per year (10 trials per NDA/BLA times 100 NDAs/BLAs per year). In addition, FDA statistics indicate that 40 supplemental NDA and BLA applications (for new use) are approved each year, with a typical supplemental application referring to 1 or 2 applicable clinical trials. Using the larger of these figures produces an estimate of another 80 submissions per year of results information. To estimate the annual number of results submissions from completed trials of previously approved/licensed drugs and biological products, the ClinicalTrials.gov database was searched for phase 4, interventional studies of drugs and biologics with at least one site in the United States. Approximately 420 such trials were registered in 2010. Thus, it is estimated that 420 additional trials will have results information submitted each year. Adding this number to the previous figures produces an estimate of 1,500 (1,000 + 80 + 420) trials of drugs and biological products that would be required submit results information each year.

For medical devices, FDA statistics indicate that 20 original pre-market applications were approved in 2010. This number is expected to remain at or around its current levels. Most original PMAs refer to one applicable clinical trial, suggesting that original PMA approvals will contribute to the submission of results information for approximately 20 applicable device clinical trials each year. In addition, FDA approves approximately 650 supplemental PMAs, of which about 10 to 20 per year contain applicable clinical trials that would be expected to submit results. Approximately 5% of the 2,500 annual 510(k) reports submitted to FDA contain applicable clinical trials, for an additional 125 medical device trials submitting results each year. The combined number of submissions that would result from these approvals and clearances totals some 165 per year (20 + 20 + 125). To account for submission of information about trials of devices that have already been cleared or approved by FDA, the ClinicalTrials.gov database was searched for interventional trials of devices that are registered each year as phase 4 studies (even though phase terminology applies to drug trials, over half of all registered device studies indicate a phase) with at least one site in the United States. Data for 2010 indicate approximately 90 such trials per year. This figure was doubled (to 180) to account for the fact that slightly over half of all registered device studies provide information about study phase. Using this latter figure, the total number of device trials estimated to submit results information is 345 (165 + 180) trials per year.

To estimate an average amount of time required to submit results information, we reviewed a variety of data sources, including publicly available information from various organizations about results submission times (e.g., McCarthy, K., and Godlew, B. J., "ClinicalTrials.gov: a questionnaire of industry experiences and perceptions," Drug Information Journal. 44: 233-41, 2010), comments made at the April 2009 Public Meeting

and in response to the original burden estimates from OMB clearance documents (73 FR 58972, Oct. 8, 2008), and feedback from respondents who tested preliminary versions of the databank's data entry system during the summer of 2008. These sources contain a wide-range of estimates, from as little as 6 hours to as long as 60 hours. We believe the differences in these estimates reflect a number of factors, including the significant variation in the complexity of applicable clinical trials, in terms of their study design, number of outcome measures (primary and secondary), statistical analyses , and adverse event information. They also reflect differences in the responsible party's familiarity with the 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 has already assembled (and analyzed) the results information for purposes of preparing a journal article or other summary report, while longer estimates may assume the information needs to be compiled. We expect that in most situations, the responsible party would have ready access to the necessary information because it is information that the clinical trial is conducted to collect and analyze (i.e., most of the information we propose for submission would have been collected during the trial, as specified in the protocol). For purposes of this analysis, we selected an average time of 25 hours for initial submission of results information, which corresponds to the higher range of estimates contained in several industry surveys and in other comments the agency received. This figure is well above the 10 hour estimate that was included in the original OMB Paperwork Reduction Act clearance for the ClinicalTrials.gov data collection and includes additional time necessary for the submission of adverse event information (which was voluntary prior to September 2009). We expect the average results submission time would decline as responsible parties become more familiar with ClinicalTrials.gov and implement procedures for streamlining data collection, analysis, and formatting. We also estimate that each results record will be updated twice after the initial submission to reflect changes in the data analysis, additional results from other pres-specified outcome measures, or additional adverse event information. We estimate that such updates would take 8 hours. This figure is higher than the 5-hour estimate used in the previous OMB Paperwork Reduction Act clearance for ClinicalTrials.gov and reflects ongoing experience with data submission and updates to ClinicalTrials.gov, including updates to adverse event information.

It is estimated that the number of trials for which respondents will submit certifications indicating that they are seeking initial or new-use approval from FDA in a given year will be no greater than the number of trials that are subject to the mandatory registration requirement (5,500) less the number of trials for which results information is submitted (1,845), or 3,655 trials. Submission of a certification entails the submission of minimal information about the trial. We expect that it would take no more than 30 minutes for a responsible party to determine that a certification is required and to submit the necessary information through ClinicalTrials.gov.

For extension requests, we estimate that approximately 200 requests will be submitted each year. Between September 2008 and September 2010, some 70 extension requests were submitted to ClinicalTrials.gov through a mechanism that had been established for handling such requests. In many of these situations, responsible parties did not need to

submit a request because the request indicated that the estimated completion date for the trial had changed or that the trial was not an applicable clinical trial and therefore results submission was not required. In neither of these situations would we expect an extension request to be submitted: responsible parties will be instructed to update their estimated completion date to reflect changes in the progress of the trial, and there will be other mechanisms in ClinicalTrials.gov to demonstrate that a trial is not subject to results submission under the final rule. Excluding such unnecessary requests and considering only those submitted for applicable clinical trials for which the actual completion date had passed, we received approximately 20 requests per year. We expect that the number of extension requests will increase once a final rule is published and responsible parties have more clarity about the deadlines for submitting 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 4 percent of all applicable clinical trials for which results are to be submitted in a given year (i.e., 200 out of 5,500). It would also represent more than 10 percent of the applicable clinical trials that do not delay results submission via certification. While responsible parties may request an extension request even after they have filed a certification, we expect this would happen infrequently. Moreover, we expect that extensions will be granted in only a limited set of circumstances where "good cause" has been demonstrated. We intend to provide responsible parties with additional guidance about circumstances that the agency will and will not consider to be good cause, which we expect will limit the number of requests to those most likely to be granted by the agency. We estimate that the time required gathering the required information and submitting it to ClinicalTrials.gov would be no more than 2 hours. Using this figure, we estimate that the annualized hourly burden for extension requests will be 400 hours.

Using these figures, it is estimated that the annualized hourly burden associated with reporting of results information to the data bank will be 77,872.5 hours. It is expected that organizations that conduct large numbers of clinical trials will develop information technology systems to automatically extract the required data from their clinical research systems and upload it directly to the clinical trial databank once the submission requirements are finalized. Use of such systems will dramatically reduce the amount of time required to submit information and the burden on respondents.

Table 12-3 Estimated Burden Related to Submission of Basic Results Information

Type of Product	Responses	Frequency	Total Response	Average Time per Response	Annual Hour Burden
Results for drugs & biologics	1,500	1 initial	1,500	25 hrs	37,500
		2 updates	3,000	8 hrs	24,000
Results for devices	345	1 initial	345	25 hrs	8,625
		2 updates	690	8 hrs	5,520
Certifications	3,655	1 per year	3,655	0.5 hrs	1,827.5

		(1 per trial)			
Extension Requests	200	1	200	2 hrs	400
Total	5,700		9,390		77,872.5

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 operating budget for the Clinical Trials Registry Databank in FY2011 is approximately $4 million, which includes NIH staff salaries, costs of software development and maintenance, and quality assurance.

A.15 Explanation for Program Changes or Adjustments

The program reflected in this request responds to ongoing statutory requirements contained in Section 801 of Public Law 110-85 and to NLM's broader authority. Since approval of the previous OMB Paperwork Reduction Act clearance request, the information collection has been modified (1) to make mandatory the submission of adverse event information, consistent with legal requirements of FDAAA (as it modifies section 282(j)(3)(I) of the PHS Act) that took effect on September 27, 2009 (submission of such information was previously voluntary) and (2) to add a small number of data elements (most of them optional) that allow for a more complete description of the adverse events that will help users better interpret the information. We have increased the average hourly burden estimates for the initial submission of results information from 10 hours to 25 hours to reflect the many more submissions that include adverse event information (now required) and to reflect the results of several industry surveys and user feedback regarding results submission times. Of the overall 15 hour difference, a few minutes also account for the collection of the few new data elements related to adverse events. We have also increased our estimate of the number of applicable clinical trials that are subject to the registration requirement of the law to more closely track recent trends. The result is an increased annual burden estimated for registration of 39,790 hours above the previous information collection and an increased estimated annual burden of 16,652.5 hours for the submission of basic results information.

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

Submitted data is made available to the public via a website operated and maintained by NIH: <http://www.clinicaltrials.gov>. Deadlines for public posting of such information are established in FDAAA. Most registration information is posted within 30 days of receipt,

but information for applicable clinical trials of devices that are indicated to be unapproved or uncleared is not posted publicly until after the device is cleared or approved. The databank is subject to public search and review, and the statute 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, study phase, and safety issue being studied as a primary or secondary outcome.

The overall project has proceeded in accordance with statutory milestones. The expanded registry be operational less than 90 days after enactment of FDAAA [i.e., before December 26, 2007]. The expansion of the databank to include basic results information related to the demographic and baseline characteristics of the patient sample and to primary and secondary outcome measures was completed not more than 1 year after enactment [i.e., prior to September 27, 2008]. The collection of adverse event information was made mandatory not later than 2 years after enactment [i.e., prior to September 27, 2009].. FDAAA also requires that the Secretary of HHS further expand the registry and results databank by regulation within 3 years of enactment (i.e., September 27, 2010). The regulations are to consider several topics, including the scope of trials for which mandatory reporting will be necessary and the types of information to be provided. Implementation of these regulations would therefore entail additional collections of information. Appropriate steps will be taken to provide public notice of such changes and to update this information collection documentation.

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.