Supporting Statement A for:

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

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LIST OF ATTACHMENTS:

A. Justification

The Food and Drug Administration Amendments Act of 2007 [FDAAA, Public Law 110-85] was enacted on September 27, 2007. The statute modified 42 USC 282 to add a new

section (j) that expands the databank of clinical trials registration information that was established under previous law and makes available to the public a searchable databank of information about the results of certain controlled clinical trials of drugs, biologics and devices, as provided for in the statute. The law mandated 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.

Effective March 10, 2008, the information collection request for the pre-existing collection of clinical trial registry information, the "Information Program on Clinical Trials for Serious or Life-Threatening Diseases: Maintaining a Databank," (OMB No. 0910-0459) was transferred from the FDA to NIH. The new OMB No. is 0925-0586. [See OMB Notice of Action dated 03/10/2008, ICR Reference Number 200803-0925-002]. Along with this transfer, the title of the information collection request has been revised to reflect the expansion in the scope of the clinical trials databank that resulted from enactment of the Food and Drug Administration Amendments Act of 2007. The new title is "Information Program on Clinical Trials: Maintaining a Registry and Results Databank." The expanded program will include registration and results information on certain clinical trials of drugs, biologics, and devices, whether or not they relate to serious and life-threatening diseases. Emergency clearance approval of the information collection was requested to ensure the effective implementation of this new law by expanding the prior information collection to reflect the broader scope of clinical trials that are required to submit registration information under FDAAA and the additional data elements that are needed to comply with the new law. In accordance with 5 CFR 1320.8(d), NIH published an emergency clearance request with a 15-day comment period for this information collection on March 21, 2008 (Vol. 73, No. 56, page 15163). The OMB Notice-of-Action granting approval of the emergency clearance became effective July 3, 2008 with the revision of the currently approved collection due to expire on January 31, 2009. This proposed information collection was published in the Federal Register on October 8, 2008 (Vol. 73, No. 196, p. 58973) and allowed 60 days for public comment. One public comment was received.

This new information collection request is intended to: (1) finalize the information request for the expanded registry, which was approved in emergency form; and (2) request expansion of the prior information collection to reflect the statutory requirement to collect basic results information.

Compelling reason exists for the collection of required information for successful implementation of the expanded Clinical Trial Registry, as described in Public Law 110-85. 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 law, 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. In addition, as outlined below,

public comment was solicited on preliminary versions of the data submission system for basic results information.

A.1 Circumstances Making the Collection of Information Necessary

This information collection is necessary to comply with new statutory requirements contained in Section 801 of the Food and Drug Administration Amendments Act of 2007 (FDAAA; Public Law 110-85). FDAAA, enacted on September 27, 2007, instructs the Director of NIH to expand the databank of the Clinical Trials Registry that was established under previous law [Section 113(a) of the Food and Drug Administration Modernization Act of 1997 (FDAMA)] and to establish a results databank. Pursuant to the new law [codified in 42 USC 282(j)(2)(A)(ii)] the Director of NIH is to collect and make available to the public in a searchable data base information concerning certain controlled clinical trials of drugs, biologics, and devices that are subject to regulation by the Food and Drug Administration (FDA). The statute permits the NIH to collect information on other types of clinical trials and on trials that were completed prior to enactment of the law or other reporting deadlines established in the law. FDAAA mandates the implementation of the revised and expanded registration of clinical trials by December 26, 2007. It also requires, beginning on September 27, 2008, the collection of information describing the results of clinical trials. This request addresses the collection of both registration and results information authorized by FDAAA Section 801.

The original information collection was established to comply with the requirements of the FDAMA, which 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).

In complying with these statutes, the proposed 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 and their results. The collection of information about clinical trials enables patients and their family members to learn about relevant clinical trials and facilitate possible enrollment. It can also contribute to making 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.

A.2 Purpose and Use of the Information Collection

Information will be submitted electronically at the Website 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 treatments, accelerating and expanding availability of promising treatments 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 treatments, 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 therapeutic advances in the treatment of serious and life-threatening diseases and conditions. 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 volunteers to unnecessary risks. It will also ensure that treatment decisions are based on a more complete set of scientific evidence.

Data Elements for Clinical Trials Registration

The required registration data elements for this information collection are listed in Table 2-1. Collection of much of this information was previously approved under an earlier information collection request, OMB No. 0910-0459 (items included in the earlier clearance request are marked with an asterisk). The elements include items of information that are specifically enumerated in FDAAA as authorized and required to be collected for the registry *[PL 110-85, Section 801(a), adding new 42 U.S.C. 282(j)(2)(A)*]. 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. 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 [*PL 110-85, Section 801(a), adding new 42 U.S.C. 282(j)(2)(B)]* Information is collected to support these functions. FDAAA also establishes compliance and enforcement requirements that apply to mandatory submissions of information. Information is collected to distinguish between mandatory and voluntary submissions. The Law also requires that the registry be easily used by the public and that entries be easily compared [*PL 110-85, Section 801(a), adding new 42 U.S.C. 282(j)(2)(B)(iv)],* 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.

Table 2-1 Information collected for expanded clinical trials registry

Data Element	**Justification** [Statutory References are to 42 USC 282(j) 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:* • *group/cohort description, group/cohort number or label,*	(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.

	• *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 Study*	(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
	Expected 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 specific measure and time of outcome measurement)	(2)(A)(ii)(I)(ll) specifies "outcomes, including primary and secondary outcome measures"
	Secondary Outcome Measures (including specific measure 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 (*name, organization, contact information*)	(2)(A)(ii)(III)(bb) specifies “the responsible party, by official title” [*Note*: *contact information not made public)*
	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.
	Record Verification Date*	(2)(A)(ii)(IV)(cc) specifies “record verification date”
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 [not required for federally funded or IND/IDE studies because they are subject to procedures that verify compliance with such polices].
	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.

* Data element was included in OMB No. 0910-0459

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 to enable compliance with the requirements of other clinical trial reporting policies (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. Those optional elements that were previously approved for collection under OMB 0910-0459 are indicated with an asterisk.

- 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?

The Clinical Trials Registry Databank, ClinicalTrials.gov has been in operation since 2000 and has incorporated elements and features to facilitate use by affected stakeholders with each successive OMB approval. Effective March 10, 2008, the information collection request for the pre-existing collection of clinical trial registry information, the "Information Program on Clinical Trials for Serious or Life-Threatening Diseases: Maintaining a Databank," (OMB No. 0910-0459) was transferred from the FDA to NIH. The new OMB

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Information collected for reporting basic results

The information collected for reporting basic results derives from statutory language included in FDAAA. The Act requires the submission of the four types of information for 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.

For the first of these items, 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 of these items, the respondent will be asked 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 [42 USC 402(j)(3)(B)(iv)] and enhances patient understanding of the results of clinical trials [42 USC 402(j)(3)(D)(i)].

The information to be collected for demographic and baseline characteristics of the patient population will, by necessity, vary from one clinical trial to another. 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 are required to 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: 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.

Respondents may provide additional information, as desired, to describe important limitations of the data or caveats for interpreting it. Such information is intended to improve the ability of database users to understand the information.

The data collection also includes information about adverse events. FDAAA requires the Secretary to determine by regulation “the best method for including in the registry and results databank appropriate results information on serious adverse and frequent adverse events” [paragraph (3)(I)(i)]. Such regulations are to be issued within 18 months of enactment, or default provisions in FDAAA take effect at 24 months requiring the submission of tables of information about adverse events by arm and organized by organ system [(3)(I)(ii), (iii)]. In order to test different methods for collecting information on serious and adverse events, the data collection permits respondents to submit such information in a form consistent with the default provisions of the law and to provide information about the method by which such information is collected and the threshold for reporting an event (e.g., the threshold frequency above which events are reported). Respondents submitting adverse event information (which will be voluntary until the statutory requirements take effect) will be required to provide certain elements of information (designated by double asterisks below), including: 1) the name of the adverse event, the organ system to which it relates; 3) the assessment type (designating whether

adverse event reports are generated systematically or spontaneously); 4) the total number of subjects affected by a serious adverse event; 5) the threshold frequency for reporting non-serious adverse events; 6) the total number of subjects affected by non-serious adverse events; and 8) a breakout by arm of the number of affected participants for each reported event. Additional information may be provided about specialized vocabularies used to name adverse events.

The table below summarizes the information collection for submitting basic results information. Only those elements marked with an asterisk are required to be submitted; optional information is also identified. For adverse event data, those elements marked with two asterisks are required for those respondents who elect to submit adverse event information.

Table 2-2 Information collected for reporting basic results

Data Element		**Justification** [Statutory References are to 42 USC 282(j) 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*	
	Email*	
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 and milestones [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]	
	Preassignment details [optional]	
4. Baseline Characteristics (overall and 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
	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), categorical.	
	• Measure of dispersion (e.g., standard deviation, full range), if a central tendency reported*	
	• the names of the categories into which data are divided, if a categorical measurement*	
	• Units of measure*	
	Baseline characteristic data*	
	• Number (if applicable)*	
	• Descriptive statistics* (central tendency value and dispersion value)	
5. Outcome measures (overall and 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. . . “
	Number of participants analyzed (per outcome measure, per arm/group)*	
	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, measure of central tendency, categorical) and measure of dispersion (e.g., standard deviation, full rante, 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*	
	• Units of measurement and categories of measurement*	
	Outcome data	
	• Number	
	• Descriptive statistics	
	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]	
6. Overall limitations and caveats [optional]		
7. Adverse event information [optional]		
	Adverse event term (description of the event)**	
	Source vocabulary name (if any)	
	Organ system**	"grouped by organ system" [(3)(I)(iii)]
	Assessment type** (e.g.,systematic assessment or spontaneous report)	
	Total number affected by serious adverse event*	"results information on serious adverse. . . events" [(3)(I)(i)]
	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)]
	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	
	• Number of participants at risk**	"number and frequency of such event in each arm of the clinical trial" [(3)(I)(iii)]

FDAAA provides for data submitters 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)]. The submission of a certification is being integrated into the data entry system, allowing the submitter to verify (or update as needed) the FDA approval status of the product(s) involved in the study and to indicate that they are certifying that they are seeking either initial approval or approval for a new use of the product. As a temporary measure (until that feature is integrated into the system) responsible parties wishing to submit a certification are asked to submit via email the following information to NIH: ClinicalTrials.gov identifier of the trial to which the certification applies; unique protocol ID (to verify that the NCT number refers to the correct trial); type of certification (seeking initial approval or seeking approval of a new use); name of the product for which approval is being sought; the existing FDA approval number for the product, if seeking new-use approval (to allow verification with FDA information); name and contact information of the responsible party submitting the certification (to verify that it is the responsible party for the trial being certified)

FDAAA also provides a mechanism whereby data submitters can 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)]. For extension requests, respondents will be required to submit to NIH the following information:

- ClinicalTrials.gov identifier (NCT number) of the applicable clinical trial to which the request for extension applies
- Unique Protocol ID (to verify that the NCT number refers to the correct trial)
- Explanation that demonstrates good cause for the extension
- An estimated date on which results information will be submitted
- Name and contact information of the responsible party

A.3 Use of Improved Information Technology and Burden Reduction

The Clinical Trials Registry Databank utilizes the latest software and Internet technologies for registration, results reporting, and searching capabilities. Information can be uploaded automatically or entered into electronic forms available on the ClinicalTrials.gov website. Relevant information from registration records is imported into results reporting templates to minimize the burden on respondents and ensure data consistency between registration and results records. In addition, data entry system for results reporting has been designed to allow respondents considerable flexibility in reporting required data in a way that matches their own data analysis plans and common formats for reporting results in journal articles and other official publications. The system can be viewed at http://clinicaltrials.gov/. The Law 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." [*PL 110-85, Section 801(a)*, adding new 42 U.S.C. 282(j))(2)(A)].

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

The Clinical Trials Registry Databank is unique and encompasses registration information on nearly 60,000 clinical trials in more than 150 countries. No comparable listing of clinical trials exists in the world. While some companies make clinical trial information available through commercial databases and choose to designate the organization as a data provider for the company, these efforts are not as comprehensive as ClinicalTrials.gov and contain limited information on only a select subset of trials. Similarly, the basic results information proposed for collection in ClinicalTrials.gov will be a unique resource. A small number of pharmaceutical companies have created public Web sites containing results of their clinical studies, but they are limited to the company's trials and results are not structured to allow easy comparison among databases. The industry association PhRMA has also established a publicly accessible results database for member companies, but submission of information is voluntary and therefore limited.

Much of the registration information to be collected under FDAAA is currently submitted to FDA in a different format by sponsors of Investigational New Drug (IND) and Investigational Device Exemption (IDE) applications 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 for multi-site trials. Processes for results reporting have been developed so as to ensure the flexibility to report data from different trials, while providing consistency in the types of information reported. To further minimize the burden on respondents, the required results tables were designed by to 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 parties registering clinical trial information will be small businesses and entities (e.g., physician practices, start up or small companies that produce medical devices), the preparation and submission of the required information for the databank is anticipated to represent 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. These efforts far outweigh the effort needed to register, summarize results, and update records in the clinical trial registry databank. Because much of the information to be supplied to the registry is already compiled for the study protocol, scientific and ethical reviews, other regulatory purposes, and recruitment of subjects to participate in the trials – or to comply with policies of the International Committee of Medical Journal Editors (ICMJE) and World Health Organization, the additional burden of this information collection (on large and small entities) is greatly

reduced. The fact that many such organizations list their clinical trial information voluntarily in the ClinicalTrials.gov registry further suggests that the benefits of registration outweigh the costs of the effort involved**.** The efforts that have been made to develop results reporting 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

Reporting of registration information is conducted on an ongoing basis as new trials are initiated and conducted. In general, the law requires that trials be registered within 21 days of recruiting the first patient [*PL 110-85, Section 801(a), adding new 42 U.S.C. 282(j)(2)(C)]*. Information must be updated at least once every 12 months if there are any changes to report; changes in recruitment status must be reported within 30 days of such change [*PL 110-85, Section 801(a), adding new 42 U.S.C. 282(j)(4)(C)(i)]*. Results information is required by the Act be submitted to the databank within 12 months of the study completion date. The deadline can be extended if the responsible party certifies that it is seeking initial FDA approval for the drug, biologic, or device under study, or that it is seeking FDA approval for a new use. Less frequent reporting is inconsistent with the Congressional mandate 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 accordance with 5 CFR 1320.8(d), NIH published an emergency clearance request with a 15-day comment period for the clinical trials registration portion of this information collection on March 21, 2008 (Vol. 73, No. 56, page 15163). A single public comment was received in response to the Federal Register Notice, but the comment was not directly related to this information collection request and did not address any of the items contained in the notice. No further action in responding was taken subsequent to the initial acknowledgement to the sender that the comment had been received and would be reviewed for further consideration. In addition, FDA published a 60 day notice for public comment in the Federal Register on May 14, 2007 (72 FR 27140) to request an extension of the pre-existing clearance for the information collection under FDAMA. No comments were received on that notice.

As agreed with Department officials and OMB, a Federal Register Notice was issued on May 21, 2008 to announce the availability of preliminary versions of the basic results information collection system, and a listserv was established to inform subscribers of the availability of revised materials. Comments received on these materials were taken into

account in designing the information collection system for results that is described in this statement. The comments were particularly helpful in identifying information that could be imported directly from the registration record to the results record and vice-versa (thereby reducing the data submission burden on respondents), in determining which information should be submitted about "other agreements" and statistical tests, and in ensuring the information collection system can accommodate a broad range of clinical trial designs.

The information collection proposed in this statement was previously published in the Federal Register on October 8, 2008 (Vol. 73, No. 196, p. 58973) and allowed 60-days for public comment. One public comment was received that proposed the collection and display of additional information that could improve the tracking of the progress of clinical trials, encouraged further refinements to the system to simplify data entry, and indicated that it had required more time to respond to the collection of results information than the agency had estimated. The agency made numerous refinements to the results data entry system based on feedback from test users during its development (as described above), and expects to make further improvements based on operational experience. The agency believes its original burden estimates were consistent with the experience of test users and notes that those figures accounted for the time necessary for data extraction, quality control and approval, in addition to the submission process itself. The burden estimate in this document was increased to account for the burden association with submission of extension requests and certifications for delayed submission, both of which involve time to track the study compliance timeline and to prepare the necessary submissions. Further increases in the burden estimate should be based on operational experience of a larger number of uses as they continue to gain experience with the system.

Other steps have also been taken to consult outside the agency. 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 10 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 have published articles about the system and its requirements in widely disseminated peer-reviewed journals. Since enactment of FDAAA, NIH staff have 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.

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

No personally identifiable information is to be sent to the databank, other than contact information for designated points-of-contact. This information is required by law to be made public, in keeping with the policy objectives of FDAAA and FDAMA.

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 of clinical trials; and the burden associated with the reporting of results information. These information collections will occur at different times, but the information will be integrated into a single record for each clinical trial.

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, reformat them and enter the information into the databank. References below to mandatory and voluntary reporting refer to the requirements of FDAAA, but all necessary reporting in response to other laws and policies is captured in the estimates.

To determine the annual reporting burden for mandatory submissions of registration information, estimates were made of the number of applicable trials of drugs, biologics, and devices. It was estimated that approximately 3,000 applicable clinical trials of drugs and biologics and 445 applicable trials of devices would be registered annually in accordance with FDAAA. The drug and biologic estimates were based on information showing that in 2005 some 4,858 new clinical trial protocols were submitted to the FDA Center for Drug Evaluation and Research (CDER) and 474 new protocols were submitted to the Center for Biologics Evaluation and Research (CBER). FDA expects that submission rates will remain at or near this level in the near future. Of the drug and

biological protocols received in 2005, an estimated 50% -- or 2,666 protocols -- were for trials involving assessments of effectiveness, which would be subject to the provisions of FDAAA. This figure was raised to 3,000 drug and biological trials per year to account for IND-exempt trials that are required to register in the expanded registration databank, but for which a protocol might not be sent to FDA. For devices, the estimated 445 new applicable device clinical trials per year includes trials related to pre-market applications (approximately 50 applications to FDA containing 75 clinical trial protocols in 2005), 510(k) submissions (approximately 360 submissions to FDA containing clinical trial protocols in 2005), humanitarian device exemptions (9 in 2005). The estimates of drug, biologic, and device trials computed using this approach are consistent with the numbers of relevant trials that were registered with the ClinicalTrials.gov registry in calendar year 2007.

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 [*PL 110-85, Section 801(a), adding new 42 U.S.C. 282(j)(4)(A)]*, 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. In calendar year 2007, there were approximately 13,300 new trials registered in the ClinicalTrial.gov registry databank, of which some 8,000 were trials with drugs or biologics as an intervention, 900 were trials with a device as an intervention, and 4,400 were other types of trials (e.g., observational studies, procedural interventions, behavioral interventions). These figures are consistent with the numbers of trials registered during calendar year 2005. Subtracting the anticipated number of mandatory trial registrations (from Table 12-2) from the anticipated number of total registrations (2007 statistics) produces estimated numbers of voluntary registrations of 5,000 trials of drugs and biologics, 445 trials of devices, and 4,400 trials of other intervention types. To account for a possible increase in voluntary submissions resulting from the heightened level of attention being devoted to clinical trials information, these estimates were raised by 20 percent to 6,000 trials of drugs and biologics, 545 trials of devices, and 5,280 trials of other intervention types.

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, new trial registrations of 351,210 hours. Of this total, 79,235 hours are associated with mandatory registration requirements and 271,975 hours are associated with voluntary reporting. These estimates are summarized in Table 12-1. 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 12-1 Estimated Burden for Newly Registered Trials

Type	Respondents	Frequency	Total Responses	Average Time per Response	Annual Hour Burden
Mandatory Submissions					
Drug & Biologic	3,000	1 Initial	3,000	7 hrs	21,000
		8 Updates	24,000	2 hrs	48,000
Device	445	1 Initial	445	7 hrs	3,115
		8 Updates	3,560	2 hrs	7,120
Subtotal	3,445		31,005		79,235
Voluntary Submissions					
Drug & Biologic	6,000	1 Initial	6,000	7 hrs	42,000
		8 Updates	48,200	2 hrs	96,000

Device	545	1 Initial	545	7 hrs	3,815
		8 Updates	4,360	2 hrs	8,720
Other	5,280	1 Initial	5,280	7 hrs	36,960
		8 Updates	42,240	2 hrs	84,480
Subtotal	11,825		106,025		271,975
Total	15,270		137,130		351,210

During the first year after enactment of FDAAA [i.e., between September 27, 2007 and September 27, 2008] there is an additional mandatory reporting burden associated with the collection of information for applicable trials of drugs, biologics, and devices that were ongoing as of December 26, 2007 and had been previously registered with ClinicalTrials.gov. These respondents already provided information under the previous OMB clearance, but must provide the additional elements required by FDAAA that are subject to this clearance. It was estimated that there were 7,650 entries in the ClinicalTrials.gov registry in December 2007 for ongoing, interventional Phase 2-4 studies of drugs, biologics, and devices that would need to have updated information. Of this total, 7,000 were previously registered trials of drugs and biologics and 650 were previously registered trials of devices. It is anticipated that information collection required to bring these trials into compliance with the new information collection requirements will be significantly less than for a new trial registration and is estimated as 3 hours. The number of updates for these trials is estimated to be 4, which is half of the updates estimated for new registrations. Each update is estimated to require 2 hours, consistent with the updates for newly registered trials. The total burden associated with the updating of information for ongoing trials is 84,150 hours, as shown in Table 12-2.

Table 12-2 Estimated Burden for Mandatory Updating of Information for Ongoing Trials

Type of Respondents	Number of Respondents	Frequency of Response	Average Time per Response	Annual Hour Burden
Drugs and Biologics	7,000	1 Compliance Update	3 hrs	21,000
		4 Subsequent Updates	2 hrs	56,000
Devices	650	1 Compliance Update	3 hrs	1,950
		4 Subsequent Updates	2 hrs	5,200
Total	7,650			84,150

Results Reporting

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 reporting is required only for those applicable clinical trials of drugs, biologics, and devices that are subject to the mandatory registration requirements of 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 an average of approximately 100 new drug applications (NDA) and biological license applications (BLAs) per year between 2004 and 2006. 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 expanded use) are approved each year, with a typical supplemental application referring to 1-2 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 drugs and biologicals, the ClinicalTrials.gov database was searched for phase 4, interventional trials of drugs and biologics with at least one site in the United States. Approximately 470 such trials were registered annually 2006 and 2007. This figure was raised by 20 percent to account for a possible increase in trial registrations following passage of FDAAA (a 20% increase is consistent with the approach used above for estimating trial registrations), yielding an estimate of 565 additional trials that will submit results information each year. Adding this number to the previous figures produces an estimate of 1,645 (1,000 + 80 + 565) trials of drugs and biological products that would submit results information each year. This represents 55% of the estimated number of mandatory registrations of clinical trials, which is consistent with FDA statistics showing that 56% of all actions on NDAs and BLAs are approvals.

For medical devices, FDA statistics indicate that between 25 and 30 original pre-market applications per year were approved between January 2006 and July 2008. 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 30 applicable device clinical trials each year. In addition, FDA approves approximately 650 supplemental PMAs, of which about 10-20 per year contain applicable clinical trials that would be expected to report results. Approximately 5% of the 2,500 annual 510(k) reports submitted to FDA contain applicable clinical trials, for an additional 125 trials reporting results each year. The combined number of submissions that would result from these approvals and clearances totals some 175 per year. 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, about half of all registered device studies indicate a phase) with at least one site in the United States. Data for 2006 and 2007 indicate an average of 70 such trials per year. In the first nine months of 2008, 76 such studies were registered, suggesting that the rate of registration has increased post-FDAAA to approximately 100 such trials per year. This figure was doubled (to 200) to account for the fact that only 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 375 trials per year.

To calculate the average amount of time per response, we examined the feedback from respondents who tested preliminary versions of the databank's data entry system during the summer of 2008, as well as results of preliminary testing of the data entry system by the agency and its contractors. These studies indicated that results information could take as long as 6-8 hours to manually enter into the system, but that the time decreased as users became more familiar with the data entry system. For purposes of this request, the highest estimated is used. It was further raised to 10 hours to account for verification and quality control processes that might be used by submitting organizations (but would not have been used during the preliminary testing). It was estimated that respondents would update results records twice to provide additional information or revised analyses. Such updates were estimated to take half the time required for the initial submission of information, or 5 hours.

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 equal to the number of trials that are subject to the mandatory registration requirement less the number of trials for which results information is submitted, or 1,425 trials (3,445 minus 2,020). The number of trials for which extension requests will be submitted in a given year is expected to be a small fraction of all the trials that would be otherwise be required to submit results information. For this submission an estimate of 200 extension requests is used, which represents a high estimate of one-tenth of the 2,020 trials that would otherwise submit results. The burden associated with submission of certifications or requests for an extension is estimated at 1 hour, reflecting the limited set of information that must be submitted.

Using these figures, it is estimated that the annualized hourly burden associated with reporting of results information to the data bank will be 42,025 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	Average Time per Response	Annual Hour Burden
Results for drugs & biologics	1,645	1 initial	10 hrs	16,450
		2 updates	5 hrs	16,450
Results for devices	375	1 initial	10 hrs	3,750
		2 updates	5 hrs	3,750
Certifications & Extensions	1,625	1 per year (1 per trial)	1 hr	1,625
Total	4,365			42,025

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 FY2009 is approximately $3 million, which includes NIH staff salaries, costs of software development and maintenance, and quality assurance. Additional costs will be entailed in operating the expanded registry and the results database due to the increased volume of information to be processed. Such costs are expected to be on the order of $2 million to $3 million per year for the first few years of operation.

A.15 Explanation for Program Changes or Adjustments

The program changes reflected in this request respond to new statutory requirements contained in Section 801 of Public Law 110-85. For registration information, the law expands the types of clinical trials that must be registered in the registration databank and

increase the number of data elements that must be submitted. It also requires the submission of basic results information for trials of products that have been approved or cleared by the FDA. The result is an increased annual burden for registration of approximately 152,250 hours above the previous information collection and an additional annual burden of 39,500 hours for the reporting 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 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 will proceed in accordance with statutory milestones. FDAAA requires that the expanded registry be operational 90 days after enactment [i.e., by December 26, 2007]. The Act further requires that the registry databank be expanded using a phased approach to include results information. Starting 90 days after enactment (i.e., December 26, 2007), links are to be established from registry records to specified FDA and NIH results information. Such linking is not expected to entail additional collections of information. Not later than 1 year after enactment [i.e., not later than September 27, 2008], FDAAA requires 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. This request covers the collection of such basic results information. 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 this regulation could therefore entail additional collections of information. Appropriate steps will be taken to provide public notice of such changes at the proper time.

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.