SUPPORTING STATEMENT FOR

Information Program on Clinical Trials for Serious or Life-Threatening Diseases: Maintaining a Databank

Guidance for Clinical Research Sponsors Conducting Research When Medicare Pays for Items and Services to Register Study Information in a Data Bank

OMB No. 0910-0459

A. Justification

(Each section of the supporting statement will contain separate FDA text and a separate CMS text unless otherwise indicated.)

1. Circumstances Making the Collection of Information Necessary

FDA: Section 113 (a) of the Food and Drug Administration Modernization Act of 1997 (FDAMA) specifies that "The Secretary, acting through the Director of NIH, shall establish, maintain, and operate a data bank of information on clinical trials for drugs for serious or life-threatening diseases and conditions…The Secretary shall establish the data bank 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). FDAMA Section 113 is attached in its entirety.

The proposed extension of an existing collection of information is necessary for maintaining this data bank of information on clinical trials and to satisfy the above statutory requirement. In addition, the information to be collected will address a public health need. Patients may benefit from participation in clinical trials, but only limited information is currently available to the public about opportunities to participate in clinical trials. As discussed below, the National Institutes of Health (NIH) and the Food and Drug Administration (FDA) have initiated efforts to encourage pharmaceutical manufacturers to voluntarily list their clinical trials in publicly-accessible data banks.

The PDQ database was initiated by the National Cancer Institute (NCI) in 1984 to provide information regarding cancer-related clinical trials. While this publicly-accessible data bank provides comprehensive information regarding NCI-sponsored trials, private-sector participation is not mandatory. NCI and FDA have collaborated to encourage pharmaceutical manufacturers to participate in PDQ since 1995, and have modified the

system to address industry concerns. A small number of pharmaceutical manufacturers voluntarily submitted cancer trial information to PDQ for listing.

Other institutes within the National Institutes of Health have also developed publicly-available clinical trial data banks, and one has encountered similar problems with efforts to encourage pharmaceutical firms to participate. The National Institute on Aging and the FDA developed a publicly-accessible data bank of information on trials of new treatments for Alzheimer's disease. Pharmaceutical manufacturers developing new Alzheimer's disease treatments were invited to participate, and few elected to do so on a voluntary basis.

The initiative under FDAMA Section 113 represents an extension of a major existing FDA/NIH clinical trial data bank program involving mandatory submission of information from all HIV/AIDS clinical trial sponsors. The Health Omnibus Programs Extension of 1988 (Public Law 100-607, also known as the HOPE legislation), provided for the Secretary of Health and Human Services to work with NIH and FDA to create a data bank of information about clinical trials of drugs for the treatment of human immunodeficiency deficiency (HIV) virus and acquired immune deficiency syndrome (AIDS). The AIDS Clinical Trials Information Service (ACTIS) was created in 1989, and served as a publicly-available source of information about clinical trials of new treatments for HIV and AIDS.

Participation in ACTIS is mandatory for sponsors of "clinical trials of experimental treatments for AIDS and related illnesses conducted under regulations promulgated pursuant to section 505 of the Federal Food, Drug, and Cosmetic Act...," from the point when a trial to test efficacy begins. Participation in this program is required for sponsors of HIV/AIDS trials in both the public and private sectors, and is enforced by means of a mechanism triggered by FDA receipt of an Investigational New Drug (IND) application for such a study. Similar to the HOPE legislation and the ACTIS data bank, FDAMA provides for mandatory participation from the point "when a trial to test effectiveness begins."

CMS: On September 19, 2000, the Health Care Financing Administration (now the Centers for Medicare & Medicaid Services (CMS)) implemented a Clinical Trial Policy through the NCD process. The Clinical Trial Policy was developed in response to a June 7, 2000 executive memorandum, issued by President Clinton, requiring Medicare to pay for routine patient costs in clinical trials. The original policy suggested that a registry be established into which studies meeting the criteria for coverage under the policy would be enrolled for administrative purposes. This registry was never established.

On July 10, 2006, CMS opened a reconsideration of its national coverage determination on clinical trials. The purpose of the reconsideration is to further refine the policy to rename it the Clinical Research Policy (CRP) to address several ambiguities, including the link between the CRP and the Coverage with Evidence Development concept, and the authority to allow the Agency to pay for the costs of limited investigational items. One requirement to qualify for coverage of clinical costs under the proposed policy is that the study must be enrolled in the NLM clinical studies data bank.

In 1997, the U.S. Congress mandated in the Food and Drug Administration Modernization Act (Section 113) the establishment by the National Institutes of Health (NIH) of a publicly-accessible clinical trials data bank and required sponsors to list eligible trials in the data bank. The NIH, through its National Library of Medicine (NLM) developed the Clinical Trials Data Bank, which has been available to the public since February 2000 at www.clinicaltrials.gov. Eligible trials were originally defined as those intended to treat a life-threatening disease or condition and a phase 2, 3, or 4 trial with efficacy endpoints. Since that time two initiatives by organizations with a great deal of credibility in the development and dissemination of studies of drugs, devices, biologicals and procedures have occurred that support the use of this data bank. In January 2005, the Pharmaceutical Research Manufacturers of America's voluntary disclosure announcement supports the voluntary posting of information about ongoing hypothesis – testing trials of all disease to the NLM site by September 13, 2005. As of July 1, 2005 the International Committee of Medical Journal editors requires trials to be registered (i.e., posted on the NLM website) in order to be considered for publication.

The statutory authority for the Clinical Research Policy is §1862 (a)(1)(E) of the Social Security Act (the Act).

Since the implementation of the Clinical Trial Policy National Coverage Determination in 2000, the Medicare clinical trials registry was never established. The NLM data bank is an ideal registry to fulfill the original intent of the policy for administrative purposes as well as provide a means to allow beneficiaries and family members and providers to be aware of clinical research in which Medicare pays specified clinical costs.

The goals of CMS Proposed Clinical Research Policy (NCD Manual §310.1) are to:

- Allow Medicare beneficiaries to participate in research studies;
- Encourage the conduct of research studies that add to the knowledge base about the efficient, appropriate, effective, and cost-effective use of products and technologies in the Medicare population, thus improving the quality of care that Medicare beneficiaries receive; and,
- Allow Medicare beneficiaries to receive care that may have a health benefit, but for which evidence for the effectiveness of the treatment or service is insufficient to allow for full, unrestricted coverage.

In addition, by requiring posting at this site and specifying mandatory data fields that must be completed, the Agency may be confident that the sponsor meets the following requirements specified in the proposed clinical research policy:

- All clinical studies covered under this policy must include in the protocol a description of how a representative sample of participants appropriate to the disease and item or service being studied will be selected.
- The principal purpose of the study is to test whether the intervention potentially improves the participants' health outcomes;

- The study is well-supported by available scientific and medical information or it is intended to clarify or establish the health outcomes of interventions already in common clinical use;
- The study does not unjustifiably duplicate existing studies;
- The study design is appropriate to answer the research question being asked in the study;
- The study is sponsored by a credible organization or individual capable of executing the proposed study successfully and disseminating the results appropriately;
- The study is in compliance with Federal regulations relating to the protection of human subjects; and
- All aspects of the study are conducted according to the appropriate standards of scientific integrity.

2. How, by Whom, and for What Purpose Information is Used

FDA: Information required under FDAMA Section 113 (a) will be submitted electronically to the Clinical Trials Data Bank.

This information about clinical trials to test effectiveness of drugs for serious or life-threatening diseases and conditions will be entered into the data bank. The information in the data bank will be available to individuals with serious or life-threatening diseases and conditions, to other members of the public, to health care providers, and to researchers (FDAMA, Section 113 (a)).

This 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 also be of immediate value to patients with serious and life-threatening diseases and conditions. Safe and effective treatments are not available for all serious and life-threatening diseases and conditions, 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 data bank 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.

Data Elements for Clinical Trials Data Bank

FDAMA Section 113 (a) requires the Department of Health and Human Services, through the National Institutes of Health (NIH), to establish a registry of clinical trials for both federally and privately funded trials "of experimental treatments for serious or life-threatening diseases or conditions." The Act specifies that the Data Bank should, for each trial, contain the purpose of the trial, eligibility criteria for participation, the location of the trial sites, and a point of contact for those wanting to enroll in the trial. The data should be in a form that is readily understandable by members of the public. FDAMA Section 113 (a) also notes that the Data Bank may include information pertaining to the results of clinical trials.

Based on these legislative requirements, discussions with NIH collaborating Institutes and other groups, and comments submitted to Docket 98D-0293 "Section 113 NIH Data Bank—Clinical Trials for Serious Diseases," data elements were developed for the *Clinical Trials Data Bank.* These elements fall into several areas: descriptive information, recruitment information, location and contact information, and administrative data.

Descriptive Information
Brief Title
Brief Protocol Summary
Study Design/Study Phase/Study Type
Condition or Disease
Intervention

Recruitment Information
Study Status Information
Eligibility Criteria/Gender/Age

Location and Contact Information
Location of Trial/Site Status information
Contact information

Administrative Data
Study ID Number
Data Provider/Study Sponsor
Date Last Modified

CMS: For CMS purposes, the statutory authority for the Clinical Research Policy is §1862 (a)(1)(E) of the Social Security Act. The end users of the NLM registry data bank include sponsors of studies (i.e., industry, federal agencies), patients and their families seeking opportunities to participate in studies, and editors of the International Committee of Medical Journal.

3. Use of Improved Information Technology and Burden Reduction

FDA: Sponsors will be required to submit information to the data bank electronically by means of electronic media including internet-based forms, thereby reducing their administrative burden.

CMS: The collection of this information is through electronic means over the Internet.

4. Efforts to Identify Duplication and Use of Similar Information

FDA: Nearly all of the information to be collected under FDAMA Section 113 (a) is currently submitted to FDA in a different format by sponsors of Investigational New Drug (IND) applications under Federal Regulations (21 C.F.R. Section 312). IND submissions are confidential and proprietary, and are not subject to release under section 552 of title 5, United States Code, popularly known as the Freedom of Information Act. The specific processes for submission of information under FDAMA Section 113 (a) by clinical trial sponsors provide for public availability of clinical trial information while being sensitive to the needs to minimize study sponsors' duplication of effort and protect IND submissions from unauthorized release.

Information about clinical trials previously accessible through other NIH-supported data banks is now available through the *ClinicalTrials.gov* website (e.g. ACTIS, PDQ, the Rare Diseases Clinical Research Database and others). Some NIH institutes continue to maintain their own clinical trial site and provide the data to ClinicalTrials.gov (cancer.gov). Others use their own site to help users find disease specific clinical trials in *ClinicalTrials.gov.* For example, when a user seeks information from the AIDSinfo search screen *(*http://www.aidsinfo.nih.gov*)*, each search of *ClinicalTrials.gov* is automatically limited to trials studying HIV/AIDS.

Some companies make clinical trial information available through commercial databases and choose to designate the organization as a data provider for the company. For example, *CenterWatch.com* maintains a public clinical trials data base and serves as a data provider for one or more companies.

CMS: This information collection does not duplicate any other effort since most clinical research studies already enter study protocol information into this data bank in accordance with Section 113 of the Food and Drug Administration Modernization Act (the Modernization Act) (Public Law 105-115)).

5. Impact on Small Business or Other Small Entities

FDA: This activity is anticipated to have minimal impact upon small business. In addition to required trials, small manufacturers are voluntarily listing their clinical trials in the Clinical Trials Data Bank. Manufacturers developing a new drug conduct clinical trials to demonstrate safety and efficacy of that treatment, as the basis for a marketing application. A clinical trial of a new drug represents a very resource-intensive activity. The sponsor must sustain a

substantial administrative burden related to development of a protocol, review by a local institutional review board and the Food and Drug Administration, patient informed consent, documentation of receipt, storage, and administration of the investigational drug, documentation of adherence to the protocol, and recording of data from repeated assessments of disease and overall patient status. Preparation and submission of the required information for the data bank is anticipated to represent a very small proportion of the total administrative burden for any sponsor with resources sufficient to undertake a clinical trial of a new drug.

CMS: This collection of information does not impact small businesses or other small entities.

6. Consequences of Collecting the Information Less Frequently

FDA: Sponsors will be required to submit information to the data bank within 21 days of initiation of recruitment, upon amending of the study protocol with respect to one of the required informational elements in the data bank, and when recruitment for the study is interrupted, resumed, or completed. If data were collected less frequently, information in the data bank regarding the recruitment status of a study would be subject to inaccuracies. These inaccuracies could reduce efficiency of patient recruitment, increasing the burden for sponsors as a result of patients continuing to contact a sponsor to inquire about participation in a study for which enrollment has been completed. Such inaccuracies would also diminish patients' capacity to access timely and accurate information regarding opportunities to participate in clinical trials.

CMS: The collection of the majority of the data occurs one time only for each study, but updates to the study protocol will require updates to data in the data bank. Updates may be changes related to the addition and deletion of investigational sites, and changes in eligibility criteria.

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

FDA: This collection fully complies with 5 CFR 1320.5.

CMS: The sponsor is required to register the research study in the data bank for payment from the Medicare program.

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

FDA/CMS: In accordance with 5 CFR 1320.8(d), on May 14, 2007, (72 FR 27140), FDA published a 60 day notice for public comment in the Federal Register. No comments were received from the public.

9. Explanation of Any Payment or Gift to Respondents

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

CMS: No payment or gift will be provided to respondents, other than remuneration for the clinical items and services covered under the Medicare program and provided to the beneficiary in the clinical study.

10. Assurance of Confidentiality Provided to Respondents

FDA: No personally identifiable information will be sent to the data bank.

CMS: All applicable patient confidentiality, privacy, and other Federal laws must are complied with, including the Standards for Privacy of Individually Identifiable Health Information (Privacy Rule).

11. Justification for Sensitive Questions

FDA/CMS: There are no questions of a sensitive nature included in this data collection.

12. Estimates of Annualized Burden Hours and Costs

FDA: The information required under section 113(a) of the Modernization Act is currently submitted to FDA under 21 CFR part 312, and this collection of information is approved by OMB under Control Number 0910-0014 until May 31, 2009, and, therefore, does not represent a new information collection requirement. Instead, preparation of submissions under section 113 involves extracting and reformatting information already submitted to FDA. Procedures (where and how) for the actual submission of this information to the Clinical Trials Data Bank are addressed in the final guidance. The chart below provides an estimate of the annual reporting burden for the submission of information to satisfy requirements of Section 113.

The FDA Center for Drug Evaluation and Research (CDER) received 4,858 new protocols in 2005. CDER anticipates that protocol submission rates will remain at or near this level in the near future. Of these new protocols, an estimated two-thirds[1] are for serious or life-threatening diseases and would be subject to either voluntary or mandatory reporting requirements under section 113 of the Modernization Act. Two-thirds of 4,858 protocols per year is 3,239 new protocols per year. An estimated 50 percent[1] of the new protocols for serious or life-threatening diseases submitted to CDER are for clinical trials involving assessment for effectiveness, and are subject to the mandatory reporting requirements under section 113 of the Modernization Act. Fifty percent of 3,239 protocols per year is 1,620 new protocols per year subject to mandatory reporting. The remaining 3,238 new protocols per year are subject to voluntary reporting.

The FDA Center for Biologics Evaluation and Research (CBER) received 474 new protocols in 2005. CBER anticipates that protocol submission rates will remain at or near this level in

[1] Estimate obtained from a review of 2062 protocols submitted to CDER between January 1, 2002 and September 30, 2002.
[1]

the near future. An estimated two-thirds[2] of the new protocols submitted to CBER are for clinical trials involving a serious or life-threatening disease, and would be subject to either voluntary or mandatory reporting requirements under section 113 of the Modernization Act. Two-thirds of 474 new protocols per year is 316 new protocols per year. An estimated 50 percent[2] of the new protocols for serious or life-threatening diseases submitted to CBER are for clinical trials involving assessments for effectiveness. Fifty percent of 316 protocols per year is an estimated 158 new protocols per year subject to the mandatory reporting requirements under section 113 of the Modernization Act. The remaining 316 new protocols per year are subject to voluntary reporting.

The estimated total number of new protocols for serious or life-threatening diseases subject to mandatory reporting requirements under section 113 of the Modernization Act is 1,620 for CDER plus 158 for CBER, or 1,778 new protocols per year. The remainder of protocols submitted to CDER or CBER will be subject to voluntary reporting, including clinical trials not involving a serious or life-threatening disease as well as trials in a serious or life-threatening disease but not involving assessment of effectiveness. Therefore, the total number of protocols 5,332 minus the protocols subject to mandatory reporting requirements 1,778 will be subject to voluntary reporting, or 3,554 protocols.

Our total burden estimate includes multi-center studies and accounts for the quality control review of the data before it is submitted to the data bank. The number of IND amendments submitted in 2002 for protocol changes (e.g. changes in eligibility criteria) was 7,597 for CDER and 855 for CBER. The number of IND amendments submitted in 2002 for new investigators was 11,287 for CDER and 532 for CBER. The number of protocol changes and new investigators was apportioned proportionally between mandatory and voluntary submissions. We recognize that single submissions may include information about multiple sites.

Generally, there is no submission to FDA when an individual study site is no longer recruiting study subjects. For this analysis, we assumed that the number of study sites closed each year is similar to the number of new investigator amendments received by FDA (11,287 CDER and 532 CBER).

Generally, there is no submission to FDA when the study is closed to enrollment. We estimate the number of protocols closed to enrollment each year is similar to the number of new protocols submitted (4,858 CDER and 474 CBER).

The hours per response is the estimated number of hours that a respondent would spend preparing the information to be submitted under section 113(a) of the Modernization Act, including the time it takes to extract and reformat the information. FDA has been advised that some sponsors lack information system capabilities enabling efficient collection of company-wide information on clinical trials subject to reporting requirements under section 113(a) of the

[2] Estimate obtained from a review of 2062 protocols submitted to CDER between January 1, 2002 and September 30, 2002.

[2]

Modernization Act. The estimation of burden under section 113(a) reflects the relative inefficiency of this process for these firms.

Based on its experience reviewing INDs, consideration of the above information, and further consultation with sponsors who submit protocol information to the Clinical Trials Data Bank, FDA estimated that approximately 4.6 hours on average would be needed per response. The estimate incorporates 2.6 hours for data extraction and 2.0 hours for reformatting based on data collected from organizations currently submitting protocols to the Clinical Trials Data Bank. We considered quality control issues when developing the current burden estimates of 2.6 hours for data extraction and the 2.0 hours estimated for reformatting. Additionally, the internet-based data entry system developed by NIH incorporates features that further decrease the sponsor's time requirements for quality control procedures. The Clinical Trials Data Bank was set up to receive protocol information transmitted electronically by sponsors. Approximately 10 percent of sponsors transmit information to the Clinical Trials Data Bank electronically. 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. As sponsor's familiarity with the data entry system increases, the hourly burden will continue to decrease.

A sponsor of a study subject to the requirements of section 113 of the Modernization Act will have the option of submitting data under that section or certifying to the Secretary that disclosure of information for a specific protocol would substantially interfere with the timely enrollment of subjects in the clinical investigation. FDA has no means to accurately predict the proportion of protocols subject to the requirements of section 113 of the Modernization Act that will be subject to a certification submission. To date, no certifications have been received. It is anticipated that the burden associated with such certification will be comparable to that associated with submission of data regarding a protocol. Therefore, the overall burden is anticipated to be the same regardless of whether the sponsor chooses data submission or certification for nonsubmission.

FDA believes the estimate, 196,667 hours per year (42,754 responses x 4.599 hours per response) accurately reflects the burden. We recognize that companies who are less familiar with the data entry system and the Clinical Trials Data Bank will require greater than 4.6 hours per response. However, as sponsor familiarity with the system increases, the hourly estimate will decrease.

FDA estimates the burden of this collection of information as follows in Table 1:

Table 1--Estimated Annual Reporting Burden for FDA

	Mandatory Submissions		Voluntary Submissions		Total Responses	Hours per Response	Total Hours
	CDER	CBER	CDER	CBER			
New Protocols	1620	158	3238	316	5332	4.6	24527.2
Recruitment Complete	1620	158	3238	316	5332	4.6	24527.2
Protocol Changes	2507	282	5090	573	8452	4.6	38879.2
New Investigators	3725	176	7562	356	11819	4.6	54367.4
Sites Closed	3725	176	7562	356	11819	4.6	54367.4
Total Responses	13197	950	26690	1917	42754	4.6	196,667

*There are no capital costs associated with this collection of information.

CMS: The burden associated with this requirement is the time and effort necessary for the provider to extract the data elements from the study protocol and reformatting and entering the information into the data bank. We estimate that approximately 745 clinical research studies will register on the NLM data bank. The number was derived from a search of the database on September 1, 2006 restricting the search by age (e.g., > 65 years of age); sponsor (e.g., NIH, industry, other federal agency, university/organization); Phase II, III or IV; and by type of study (e.g., cancers and other neoplasms, diagnosis, and devices). The age, sponsor and study phase was applied to each of the three separate searches by type of study. The following number of studies by study type, including trials no longer recruiting was 562 for diagnosis, 164 for cancers and other neoplasms, and 19 for devices. In determining the total number of hours requested, the CMS estimate uses the same assumptions used by the FDA to estimate its total number of burden hours. Therefore, the total annual burden associated with this requirement is 4,172 hours (745 responses x 5.6 hours per response).

CMS estimates the burden of this collection of information as follows in Table 2:

Table 2--Estimated Annual Reporting Burden

CMS	Total Responses	Hours per Response	Total Hours
Study Registration	745	5.6	4,172
Total			4,172

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

FDA/CMS: There are no capital costs associated with this collection.

14. Annualized Cost to the Federal Government

FDA: The estimated cost to the Federal Government for this information is unknown at this time.

CMS: No annualized cost to the Federal government will be incurred.

15. Explanation for Program Changes or Adjustments

Including new burden for CMS represents a revision to an already approved information collection held by FDA. The total increase in burden to OMB Control Number 0910-0459 is 23,674. This estimated increase also includes a burden adjustment for FDA.

FDA: We believe the previous burden estimate of 177,165 hours per year underestimated the burden. The new estimate of 196,667 hours per year more accurately reflects the burden.

CMS: While there are no changes to the actual data being collected, there is an additional requirement being imposed on the responding public. CMS's use of the information collection totals an estimated 4,172 burden hours. As discussed earlier in this document, to qualify for coverage of clinical costs under the proposed Clinical Research Policy (CRP), a clinical research study must be enrolled in the NLM clinical studies data bank.

16. Plans for Tabulation and Publication and Project Time Schedule

FDA: The data submitted is made available to the public through a data bank maintained by the National Institutes of Health, and is subject to public search and review. Data from NIH institutes were made available for search on February 29, 2000. Information regarding non-NIH studies was made available for public search and review during the year 2000.

CMS: There are no publication or tabulation dates.

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

FDA/CMS: No exemption is requested.

18. Exceptions to Certification for Paperwork Reduction Act Submissions

FDA/CMS: No exceptions are requested.