Guidance for Industry: Oversight of Clinical Investigations - A Risk-Based Approach to Monitoring

0910-[NEW]

SUPPORTING STATEMENT

A. Justification

1. Circumstances Making the Collection of Information Necessary

FDA requests OMB approval to collect information about the above-titled Guidance for Industry that assists sponsors of clinical investigations in developing risk-based monitoring strategies and plans for investigational studies of medical products, including human drug and biological products, medical devices, and combinations thereof. Sponsors are required to provide appropriate oversight of their clinical investigations to ensure adequate protection of the rights, welfare, and safety of human subjects and the quality and integrity of the resulting data submitted to FDA.[1] FDA's regulations require sponsors to monitor the conduct and progress of their clinical investigations.[2, 3] The regulations are not specific about how sponsors are to conduct monitoring and are therefore compatible with a range of approaches to monitoring.

The guidance makes clear that sponsors can use a variety of approaches to fulfill their responsibilities for monitoring investigator conduct and performance in investigational new drug (IND) or investigational device exemption (IDE) studies. The guidance describes strategies for monitoring activities that reflect a modern, risk-based

[1] Part 312 (21 CFR part 312), subpart D generally (Responsibilities of Sponsors and Investigators) and part 812 (21 CFR part 812), subpart C generally (Responsibilities of Sponsors).

[2] Section 312.50 requires a sponsor to, among other things, ensure ''proper monitoring of the investigation(s)'' and ''that the investigations(s) is conducted in accordance with the general investigational plan and protocols contained in the IND.'' 812.40 states that sponsors are responsible for, among other things, "ensuring proper monitoring of the investigation,..."

[3] Also see §§ 312.53(d), 312.56(a), and 812.43(d), and 812.46.

approach that focuses on critical study parameters and relies on a combination of monitoring activities to oversee a study effectively. For example, the guidance specifically encourages greater use of centralized monitoring methods, where appropriate.

FDA currently has OMB approval for the information collection required under Part 812[4] (21 CFR part 812) (OMB control number 0910–0078). Part 812 allows for an Investigational Device Exemption (IDE) for a device, which would otherwise be subject to provisions of the Federal Food, Drug, and Cosmetic Act (the FD&C Act), as amended by the Food and Drug Modernization Act of 1997 (FDAMA), such as premarket notification or premarket approval to be used in investigations involving human subjects in which the safety and effectiveness of the device is being studied. The purpose of Part 812 is to encourage the development of useful medical devices, and allow investigators the maximum freedom possible, without jeopardizing the health and safety of the public or violating ethical standards. Also, FDA currently has OMB approval for the information collection required under Part 312[5] (21 CFR part 312), including certain provisions under subpart D (OMB control number 0910–0014). The Investigational New Drug (IND) regulations in Part 312 contain reporting and recordkeeping requirements that will provide the evidence and data needed for sponsors submitting New Drug Applications (NDA) to FDA for approval. Without the information provided by sponsors in response to the IND regulations, FDA cannot authorize or monitor the clinical investigations which must be conducted prior to authorizing the sale and general use of new drugs. These reports enable FDA to monitor a study's progress, to assure subject

[4] Part 812 (21 CFR Part 812), subpart C, generally (Responsibilities of Sponsors).

[5] Part 312 (21 CFR part 312), subpart D, generally (Responsibilities of Sponsors and Investigators)

safety, to assure that a study will be conducted ethically, and to increase the likelihood that the sponsor will conduct studies that will be useful in determining whether the drug should be marketed and available for use in medical practice. These regulations encourage the development of useful drug and biologic products, and allow investigators the maximum freedom possible, without jeopardizing the health and safety of the public or violating ethical standards.

The collection of information associated with this draft guidance that is not currently approved under OMB control numbers 0910–0014 or 0910–0078 is as follows:

Development of Comprehensive Monitoring Plan: Section IV.D of the guidance recommends that sponsors develop a prospective, detailed monitoring plan that describes the monitoring methods, responsibilities, and requirements for each clinical trial. The plan should provide those involved in monitoring with adequate information to effectively carry out their duties. All sponsor and contract research organization (CRO) personnel who may be involved with monitoring, including those who review and/or determine appropriate action regarding potential issues identified through monitoring, should review the monitoring plan. The components of a monitoring plan are described in the guidance, including monitoring plan amendments (i.e., the review and revision of monitoring plans and processes for timely updates). FDA understands that it is usual and customary practice for sponsors to develop monitoring plans; however, not all monitoring plans contain all the elements described in the guidance.

2. Purpose and Use of the Information Collection

The information collection provides a means for sponsors to document how sponsors will comply with the regulatory requirement to provide oversight of clinical investigations. The information will be used by FDA during FDA inspections, to assess, in part, sponsors' oversight of clinical investigations.

3. Use of Improved Information Technology and Burden Reduction

Monitoring plans are not submitted to FDA for IND studies. However, 21 CFR 812.25(e) requires that written monitoring procedures be submitted as part of the IDE application (OMB No. 0910-0078). Sponsors may use electronic means to create and maintain such plans when practicable.[6]

4. Efforts to Identify Duplication and Use of Similar Information

The IND regulations do not require the development of a monitoring plan, this is a new recommendation. The IDE regulations (21 CFR 812.25(e)) require that written monitoring procedures be submitted as part of the IDE application. This guidance provides detail on the development of the monitoring plan.

5. Impact on Small Businesses or Other Small Entities

FDA's authority and responsibility to ensure the safe use of investigational drugs, biologics, and medical devices applies to small as well as to large businesses involved in sponsoring investigational studies. FDA believes that its responsibility requires the equal application of the regulations to all businesses. While FDA does not believe it can apply different standards with respect to statutory requirements, FDA does provide special help

[6] See Electronic Copies for Pre-Market Submissions: General Information - Questions and Answers at http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/PremarketSubmissions/ucm134508.htm#q7

to small businesses. A small business coordinator has been assigned to the Commissioner's staff to ensure that small businesses have an adequate opportunity to express their concerns and to keep FDA management apprised of how regulatory decisions might impact the small business community. To provide additional assistance to small businesses, FDA has established an office whose exclusive concern is to provide small business with help in dealing with FDA regulatory requirements.

6. Consequences of Collecting the Information Less Frequently

The guidance recommends sponsors develop a comprehensive monitoring plan for each clinical trial and consider what events would indicate a need for revision of the monitoring plan. Less frequent collection of this information would not facilitate sponsors' documentation of how they will provide oversight of clinical investigations or how FDA will assess sponsor's oversight of clinical investigations during FDA inspections.

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

There are no special circumstances.

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

In accordance with 5 CFR 1320.8(d), in the Federal Register of August 29, 2011 (76 FR 53683), a 60-day notice was published for public comment on this information collection. The following is a summary of the comments and FDA's response to the comments for the two collections of information associated with the draft guidance that are not currently approved by OMB.

- *Development of Comprehensive Monitoring Plan:*

FDA received comments that the guidance lacks specific information on development and initialization of risk assessment plans, appropriate mitigation plans, and execution of mitigation plans through the monitoring plan. Addition of use of risk management tools, along with potential applications for using risk-based monitoring strategies would help facilitate implementation.

In response to the comments, FDA included additional detail in the final guidance in an effort to enhance the quality, utility, and clarity of the information collected. Specifically, FDA included additional detail on the development of a monitoring plan, which focuses on the important and likely risks, identified by the risk assessment, to critical data and processes. In addition, FDA included additional guidance on the steps involved in performing a risk assessment and references to tools and methodologies that can be used to perform a risk assessment. FDA clarified that the guidance does not provide comprehensive detail on how to perform a risk assessment.

FDA received several comments that the guidance should specify that it is acceptable for monitoring plans to reference existing standard operating procedures (SOPs) or other documents.

The draft guidance specifies that a monitoring plan may reference existing policies and procedures in order to minimize the burden of the collection of information.

- *Voluntary Submission of Monitoring Plans to FDA:*

FDA received numerous comments that the lack of specific details about FDA review of the monitoring plans early enough in the investigational new drug (IND)

process could delay startup of clinical trials. In addition, numerous comments requested a detailed process or procedure.

Although the draft guidance stated that CDER was considering establishing processes through which sponsors could voluntarily submit monitoring plans for CDER feedback, CDER has concluded that CDER does not have the resources necessary to commit to such a review at this time. CDER is exploring the possibility of a pilot program in this area in the future.

9. Explanation of Any Payment or Gift to Respondents

No remuneration has been provided.

10. Assurance of Confidentiality Provided to Respondents

Information in IDEs will only be released in accordance with FDA regulations implementing the Freedom of Information Act, 21 CFR Part 20 and the Investigational Device Exemptions regulations, 21 CFR 812. Information will be protected from inappropriate disclosure.

The information obtained during an investigation may be used to support an application for marketing the device (i.e. premarket approval application or premarket notification). A summary of the safety and effectiveness data from the investigation and other information, except for trade secret, production and distribution information, will be available for public disclosure if the premarket approval application is approved, abandoned, or denied, and if the premarket notification is found substantially equivalent.

11. Justification for Sensitive Questions

There are no questions of a sensitive nature.

12. Estimates of Annualized Burden Hours and Costs

Annualized Hour Burden Estimate

FDA understands it is usual and customary practice for sponsors to develop monitoring plans; however, not all monitoring plans contain all the elements described in the guidance. Therefore, our following burden estimate provides the additional time that a sponsor would expend in developing a comprehensive monitoring plan based on the recommendations in the guidance. We estimate that approximately 88 sponsors will develop approximately 132 comprehensive monitoring plans in accordance with the draft guidance, and that the added burden for each plan will be approximately 4 hours to develop, including the time needed for preparing monitoring plan amendments when appropriate (a total of 528 hours).

TABLE 1—ESTIMATED ANNUAL REPORTING BURDEN [1]

Draft guidance on monitoring clinical investigations	Number of respondents	Number of responses per respondent	Total annual responses	Average burden per response (Hr)	Total hours
Development of Comprehensive Monitoring Plan	88	1.5	132	4	528

[1] There are no capital costs or operating and maintenance costs associated with this collection of information. Burden estimates of less than 1 hour are expressed as a fraction of an hour in the format "[number of minutes per response]/60".

Annualized Cost Burden Estimate

The cost estimate is based on a regulatory manager or director, at a pay rate of $75/hr, who would be responsible for developing the monitoring plan. The Department of Labor website was used to determine an appropriate wage rates for respondents.

Type of Respondent	Total Burden Hours	Hourly Wage Rate (Approximate)	Total Respondent Costs
Regulatory Manager	4	$75.00	$300

These figures do not include start-up, operating, maintenance, or capital costs.

These figures do not include costs of contracting out or paying outside parties for information collection activities in this section.

13. Estimates of Other Total Annual Costs to Respondents and/or Recordkeepers/Capital Costs

Except as described in section 12 above, there are no other costs, including capital and start-up, or operation, maintenance, and purchase costs, associated with this collection of information.

14. Annualized Cost to the Federal Government

There is no additional annualized cost to the Federal Government.

15. Explanation for Program Changes or Adjustments

This is a new collection of information.

16. Plans for Tabulation and Publication and Project Time Schedule

There are no publications or other schedules.

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

There are no forms or expiration dates associated with this information collection.

18. Exceptions to Certification for Paperwork Reduction Act Submission

The FDA does not request an exception to the certification of this information collection.