Guidance for Clinical Trial Sponsors: Establishment and Operation of Clinical Trial Data Monitoring Committees

0910-0581

SUPPORTING STATEMENT

Justification

1. Circumstances Making the Collection of Information Necessary

The Food and Drug Administration (FDA) is requesting an extension of Office of Management and Budget (OMB) Control No. 0910-0581 and OMB approval of the information collection provisions contained in a document entitled "Guidance for Clinical Trial Sponsors: Establishment and Operation of Clinical Trial Data Monitoring Committees." The information collection provisions are summarized below:

Sponsor reporting to FDA on DMC recommendations related to safety	Reporting	Recommends that sponsors inform FDA about all recommendations related to the safety of the investigational product whether or not the adverse event in question meets the definition of "serious."
Standard Operating Procedures (SOPs) for DMCs	Recordkeeping	Recommends that sponsors establish certain procedures.
DMC meeting records	Recordkeeping	Recommends that the DMC or the group preparing the interim reports to the DMC maintain all meeting records.
Sponsor notification to the DMC regarding waivers	Disclosure	Recommends that sponsors notify DMCs about any waivers granted by FDA for expedited reporting of certain serious events.
DMC reports of meeting minutes to the sponsor	Disclosure	Recommends that the DMC issue a written report to the sponsor based on the meeting minutes. Reports to the sponsor should include only those data generally available to the sponsor. The sponsor may convey the relevant information in this report to other interested parties such as study investigators.

Sponsors are required to monitor studies evaluating new drugs, biologics, and devices (21 CFR 312.50 and 312.56 for drugs and biologics, and 21 CFR 812.40 and 812.46 for devices). Various individuals and groups play different roles in clinical trial monitoring. One such group is a Data Monitoring Committee (DMC), appointed by a sponsor to evaluate the accumulating outcome data in some trials. A clinical trial DMC is a group of individuals with pertinent expertise that reviews on a regular basis accumulating data from an ongoing clinical trial. The DMC advises the sponsor regarding the

continuing safety of current trial subjects and those yet to be recruited to the trial, as well as the continuing validity and scientific merit of the trial.

The guidance document referenced in this document is intended to assist sponsors of clinical trials in determining when a DMC is needed for study monitoring, and how such committees should operate. The guidance addresses the roles, responsibilities, and operating procedures of DMCs, and describes certain reporting and recordkeeping responsibilities.

2. Purpose and Use of the Information Collection

The submission of the requested information provides the appropriate parties with essential information regarding the clinical trial upon which they may base their recommendations. The SOPs ensure that established written procedures are followed and proper recordkeeping is performed.

3. Use of Improved Information Technology and Burden Reduction

Manufacturers may use electronic data storage such as computer tapes and discs, microfiche, or microfilm in lieu of hard copy records for the purpose of maintaining records. Manufacturers may submit the applicable information to FDA electronically. There are no technical obstacles for electronic reporting of the applicable information to FDA. FDA continues to pursue methods of applying technology to reduce the burden to the respondents.

4. Efforts to Identify Duplication and Use of Similar Information

FDA is the only agency that requests this information. There is no similar information available from any other source.

5. Impact on Small Businesses or Other Small Entities

This collection of information applies to small as well as large facilities. Although FDA must apply the regulatory and statutory requirements to all enterprises, FDA does provide help to small businesses. The Center for Biologics Evaluation and Research (CBER), Office of Communications, Outreach and Development, Division of Manufacturer's Assistance and Training, the Center for Drug Evaluation and Research (CDER), Office of Communication, Division of Drug Information, and the Center for Devices and Radiological Health (CDRH), Division of Small Manufacturers, International and Consumer Assistance provide assistance to small businesses subject to FDA's regulatory requirements.

6. Consequences of Collecting the Information Less Frequently

Less frequent collection of information or other methods of reducing the frequency of information would not provide the information needed by FDA or the DMC to evaluate the submitted information. There are no technical or legal obstacles to reducing the burden.

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

There are no special circumstances for this collection of information.

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

In accordance with 5 CFR 1320.8(d), FDA published a 60 day notice for public comment in the FEDERAL REGISTER of December 22, 2011 (76 FR 79689). No comments were received.

9. Explanation of Any Payment or Gift to Respondents

No payment or gift was provided to respondents.

10. Assurance of Confidentiality Provided to Respondents

The confidentiality of information received by FDA is consistent with the Freedom of Information (FOI) Act and FDA's published regulations of "Public Information" under 21 CFR Part 20.

11. Justification for Sensitive Questions

Questions of a sensitive nature are not applicable to this collection of information.

12. Estimates of Annualized Burden Hours and Costs

The total annual estimated burden for the disclosure, reporting, and recordkeeping burdens under the guidance are 1,794.75 hours.

12a. Annualized Hour Burden Estimate

Table 1--Estimated Annual Reporting Burden					
Section of guidance/reporting activity	Number of Respondents	Number of Responses per Respondent	Total Annual Responses	Average Burden per Response	Total Hours
5. Sponsor reporting to FDA on DMC recommendations related to safety	37	1	37	0.50 (30 minutes)	18.5

Table 2--Estimated Annual Recordkeeping Burden

Recordkeeping Activity	Number of Record-keepers	Number of Records per Recordkeeper	Total Annual Records	Average Burden per Record-keeping	Total Hours
4.1. and 6.4 SOPs for DMCs	37	1	37	8	296
4.4.3.2. DMC meeting records	370	1	370	2	740
Total					1,036

Table 3--Estimated Annual Third-Party Disclosure Burden					
Section of Guidance/Reporting Activity	Number of Respondents	Number of Responses per Respondent	Total Annual Responses	Average Burden per Response	Total Hours
4.4.1.2. Sponsor notification to the DMC regarding waivers	1	1	1	.25 (15 minutes)	.25
4.4.3.2. DMC reports of meeting minutes to the sponsor	370	2	740	1	740
Total					740.25

Based on information from FDA review divisions, FDA estimates there are approximately 740 clinical trials with DMCs regulated by CBER, CDER, and CDRH. FDA estimates that the average length of a clinical trial is two years, resulting in an annual estimate of 370 clinical trials. Because FDA has no information on which to project a change in the use of DMCs, FDA estimates that the number of clinical trials with DMCs will not change significantly in the next few years. For purposes of this information collection, FDA estimates that each sponsor is responsible for approximately 10 trials, resulting in an estimated 37 sponsors that would be affected by the guidance annually.

Based on information provided to FDA by sponsors that have typically used DMCs for the kinds of studies for which this guidance recommends them, FDA estimates that the majority of sponsors have already prepared SOPs for DMCs, and only a minimum amount of time would be necessary to revise or update them for use for other clinical studies. FDA receives very few requests for waivers regarding expedited reporting of certain serious events; therefore, FDA has estimated one respondent per year to account for the rare instance a request may be made. Based

on FDA's experience with clinical trials using DCMs, FDA estimates that the sponsor on average would issue two interim reports per clinical trial to the DCM. FDA estimates that the DMCs would hold two meetings per year per clinical trial resulting in the issuance of two DMC reports of the meeting minutes to the sponsor. One set of both of the meeting records should be maintained per clinical trial.

The "Average Burden per Response" and "Average Burden per Recordkeeping" are based on FDA's experience with comparable recordkeeping and reporting provisions applicable to FDA regulated industry. The "Average Burden per Response" includes the time the respondent would spend reviewing, gathering, and preparing the information to be submitted to the DMC, FDA, or the sponsor. The "Average Burden per Recordkeeping" includes the time to record, gather, and maintain the information.

The information collection provisions in the guidance for 21 CFR 312.30, 312.32, 312.38, 312.55, and 312.56 have been approved under OMB control number 0910-0014; 21 CFR 314.50 has been approved under OMB control number 0910-0001; and 21 CFR 812.35 and 812.150 have been approved under OMB control number 0910-0078.

12b. Annualized Cost Burden Estimate

The estimated annual cost to Respondents is $143,647.00.

Activity	Total Burden Hours	Hourly Wage Rate	Total Respondent Cost
Reporting	18.50	$52.00	$962.00
Recordkeeping	296	$52.00	$15,392.00
Recordkeeping	740	$86.00	$63,640.00
Disclosure	.25	$52.00	$13.00
Disclosure	740	$86.00	$63,640.00
Total			$143,647.00

The cost is based on a regulatory affairs specialist ($52/hr) who would be responsible for preparing and submitting the appropriate information to FDA or the DMC, and maintaining the SOPs; and the DMC Chair ($86/hr) who would be responsible for issuing a report to the sponsor, and maintaining the records. The salary estimate includes benefits but no overhead costs.

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

There are no capital costs or operating and maintenance costs associated with this collection of information.

14. Annualized Cost to the Federal Government

The estimated annualized cost to the Federal Government is $29,748. The estimate includes the average numbers of hours by FDA to review the safety-related recommendations. The estimated cost is based on an average grade scale of a GS-14 ($67/hour) reviewer. The salary estimate includes benefits but no overhead costs.

Activity	Number of Responses	Hours per Response	Cost per Hour	Total Cost
Review	37	12	$67.00	$29,748.00

15. Explanation for Program Changes or Adjustments

There are no program changes or adjustments in total burden hours from the previous submission. In a side-by-side comparison of the supporting statement burden tables from the 2009 submission and 2012 submission all the burden hours are the same. However, the burden in the 2009 submission was entered into ICRAS as an average in one IC. The total burden was correct but the total number of responses was averaged by the system which resulted in an incorrect total. The burden in the 2012 submission has been broken down by activity and entered into ICRAS as such. The numbers entered in the 2012 submission reflect the true numbers, not an average. Thus, in the system, the number of responses appears to have increased from the 2009 submission

16. Plans for Tabulation and Publication and Project Time Schedule

There are no tabulated results to publish for this information collection.

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

FDA is not seeking approval to exempt the display of the expiration date of the OMB approval.

18. Exceptions to Certification for Paperwork Reduction Act Submissions

N/A.