Financial Disclosure by Clinical Investigators
0910-0396
21 CFR Part 54
SUPPORTING STATEMENT

Terms of Clearance: This ICR was approved consistent with revised supporting statement.

A. JUSTIFICATION

1. Circumstances Making the Collection of Information Necessary

The Food and Drug Administration (FDA) has become increasingly aware of the existence of potentially problematic compensation arrangements between sponsors of FDA-regulated products and clinical investigators who conduct clinical studies of the sponsors products to determine whether they meet FDA marketing requirements. Examples include payment schemes whereby the value of the compensation to the clinical investigator in the form of generous grants to fund ongoing research, expensive laboratory equipment, retainers for ongoing consultation, and honoraria. The agency is also aware of proprietary and equity interests of some clinical investigators in the tested products, or in the sponsors of these products. Among the sources of the agency's information are published newspaper articles, congressional reports, a Government Accounting Office report, congressional inquiries, and public testimony and comments.

These arrangements clearly have the potential to bias the results of clinical studies that are critically important in establishing the safety and effectiveness of products that can impact on public health and well being. However, prior to this information collection, FDA has had no formal mechanism to learn of the existence of such arrangements and to obtain information on them--a situation identified by the Inspector General of the Department of Health and Human Services in a 1991 management advisory report as a potential material weakness under the Federal Managers Financial Integrity Act. FDA has concluded that there is a need for the agency to collect this information in order to strengthen its product reviewing process, to help assure safe and effective therapeutic products for public use, and to clarify for sponsors and investigators the arrangements the agency finds problematic. Clinical studies can be designed to minimize the occurrence of bias from arrangements that FDA has identified, and the agency affirms that it will work with sponsors on the design of studies to help preclude questions on data integrity from arising in the course of product review.

FDA is requesting approval of the information collection requiring the sponsors of any drug, biologic, or device marketing application to either certify to the absence of certain financial arrangements with clinical investigators or disclose the nature of those arrangements to FDA and the steps taken by the applicant or sponsor to minimize the potential for bias.

21 CFR 54.4(a) - Reporting by Sponsors of Product Marketing Applications; Certification (Form FDA 3454) or Disclosure (Form FDA 3455) (Reporting)
The sponsor of an application submitted under sections 505, 506, 510(k), 513, or 515 of the Federal Food Drug, and Cosmetic Act, or section 351 of the Public Health Service Act, that

relies in whole or in part on clinical studies, shall submit for each clinical investigator who participated in a covered clinical study either a certification as described in § 54.4(a)(1) and (a)(2), or a disclosure statement as described in § 54.4(a)(3).

The applicant covered by this section shall submit for all clinical investigators (as defined in § 54.2(d)) to whom the certification applies, a completed Form FDA 3454 attesting to the absence of financial interest and arrangements described in § 54.4(a)(3).

For any clinical investigator defined in § 54.2(d), for whom the applicant does not submit the certification described in § 54.4(a)(1) and (a)(2), the applicant shall submit a completed Form FDA 3455 disclosing completely and accurately the following: Any financial arrangements, any significant payments, any proprietary interest, any significant equity interest, and any steps taken to minimize the potential for a bias resulting from any of the disclosed arrangement, interest, or payments.

21 CFR 54.4(b) - Certification and Disclosure Requirements (Third-Party Disclosure)
Clinical investigators subject to investigational new drug application (IND) or investigational device exemption (IDE) regulations must provide the sponsor of the study with sufficient accurate information needed to allow subsequent disclosure or certification.

21 CFR 54.6 - Recordkeeping and Record Retention
A sponsor who has submitted a marketing application containing covered clinical studies shall keep on file certain information pertaining to the financial interests of clinical investigators.

2. Purpose and Use of the Information Collection

The information to be collected from sponsors of product marketing applications will be submitted to FDA as part of the marketing applications, using Form FDA 3454 and Form FDA 3455. For each clinical investigator who took part in a covered clinical study, the sponsor will either certify that the investigator has no financial interest or arrangement identified in § 54.4(a)(3), or will disclose identified interests and arrangements held by the clinical investigator and describe steps taken to minimize potential bias of such interests and arrangements on the clinical study results. Clinical investigators will provide sponsors with sufficient accurate information to enable the sponsor to submit certification and disclosure statements. Certification of a clinical investigator helps to assure FDA reviewers of the integrity of a clinical study. Disclosure of an identified interest or arrangement and steps taken to minimize potential bias is used by reviewers to evaluate whether the integrity of the study may be relied on. When identified interests or arrangements are disclosed, FDA responds in one of the following ways: If the clinical study in which the investigator participated was well designed and managed, FDA may accept the data without further question. If a clinical investigator's financial interests and arrangements raise serious questions about the integrity of the data and the study design does not include sufficient bias-minimizing steps to offset these questions, FDA initiates audits of the data by reviewers, requests further analyses of the data from the sponsor, requests that the sponsor conduct additional studies to confirm the potentially biased study, or refuses to treat data from the

study as pivotal or primary data upon which an agency action can be taken. Under currently applicable product review regulations, reviewers can and do request further analyses of data from a sponsor as appropriate, or request that a sponsor conduct additional studies to confirm the results of a questionable study.

3. Use of Improved Information Technology and Burden Reduction

Sponsors may electronically maintain and make available records in accordance with the requirements in § 54.6. FDA will also accept electronic submissions, such as are required under § 54.5(a) to the extent allowed by the agency's capability for automated data processing of marketing applications. FDA is working to improve this capability, with the goal of eventually accepting electronically all submissions related to product review.

4. Efforts to Identify Duplication and Use of Similar Information

In drafting the regulation, FDA consulted with the Public Health Service (PHS) and National Science Foundation (NSF), which have issued respectively a regulation and a policy statement on financial disclosure by scientific investigators. It should be noted that the PHS and NSF documents respond to principles that govern federally funded grants and contracts. Such funds are granted for all types of research, and these organizations must guard against bias in all types of research. In contrast, FDA must rely on clinical data in making safety and effectiveness determinations for regulated products, and FDA's primary interest is in clinical data. There is potential for the FDA and PHS regulations to overlap in a very small number of instances involving PHS-funded clinical research on FDA-regulated products. In the preamble to the proposed regulation, FDA asked for public comment on whether, in such instances, meeting the PHS requirement for disclosure should be considered to meet FDA's requirement. Based on comments received and further deliberation, FDA has concluded that FDA's reporting requirements meet different needs for the most part and the information submitted in the PHS and NSF formats does not overlap and is not adequate for product review purposes.

Because there is currently no other FDA mechanism for collecting the information that is required under the FDA regulation, there is no internal duplication.

5. Impact on Small Businesses or Other Small Entities

FDA has conducted a Regulatory Flexibility Analysis of this regulation and concludes that it will not have a significant impact on a substantial number of small businesses. This is the case because in developing the regulation FDA has kept in mind that, not only are the majority of firms that submit marketing applications to FDA of a size to be considered small businesses by the Small Business Administration, but also the firms most apt to be affected by the disclosure provisions of the regulation are small entities of two types: (1) firms whose owners are likely to have developed the tested product and who serve as clinical investigators and (2) small start-up firms that are not heavily capitalized and provide clinical investigators with equity interests as reimbursement. FDA has addressed the need to minimize burden in a number of ways. The regulation does not prohibit any financial interest, such as

compensation to investigators in the form of equity in the sponsors firm, nor is the agency proposing to require divestiture by the investigator of any financial interest, because such provisions could impact significantly on small entities and hinder their ability to bring innovative products to market. The reporting and recordkeeping burdens are the minimum necessary to achieve the goals of the proposed regulation.

Submission of the required information has been made as simple as possible for small entities. FDA has developed forms for certification and disclosure, and a sponsor may submit one form for all clinical investigators for whom certification is being made.

6. Consequences of Collecting the Information Less Frequently

The required information is to be submitted as part of a product marketing application, which amounts to a one-time collection. The concept of less frequent collection is not applicable.

Without the information that is required by this regulation, FDA lacks the means to evaluate whether clinical data submitted in support of the safety and effectiveness of a regulated product are vulnerable to a recognized source of potential bias, and to assure that the public health is not threatened with the consequences of biased data.

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

There is one special circumstance relating to the guidelines of 5 CFR 1320.5: The records required to be kept under § 54.6 would be retained by sponsors for 2 years after the date of approval of the application. As such, records will be generated at the outset of a clinical trial; it is conceivable that they would be kept by sponsors for more than 3 years. Two years after the date of approval of the application is the normal period of time for retention of all other information related to an application.

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 March 28, 2012 (77 FR 18826). No comments were received.

9. Explanation of Any Payment or Gift to Respondents

There will not be any payment or gift to respondents.

10. Assurance of Confidentiality Provided to Respondents

FDA has made no guarantee of confidentiality to sponsors or clinical investigators, but will keep disclosed information private to the fullest extent allowed by law. Information provided to, or obtained by, FDA is subject to release under the Freedom of Information Act (5 U.S.C. 552) and the implementing regulations contained in 21 CFR Parts 20 and 21.

11. Justification for Sensitive Questions

The information collection does not include questions that are of a sensitive nature, such as, sexual behavior and attitudes, religious beliefs, and other matters that are commonly considered private.

12. Estimates of Annualized Burden Hours and Costs

12a. Annualized Hour Burden Estimate

Respondents to this collection are sponsors of marketing applications that contain clinical data from studies covered by the regulations. These sponsors represent pharmaceutical, biologic, and medical device firms. Respondents are also clinical investigators who provide financial information to the sponsors of marketing applications. Applicants already submit in a marketing application a complete list of clinical investigators for each covered study (BLAs, 21 CFR part 601, are covered under OMB control number 0910-0338; PMAs, 21 CFR part 814, are covered under OMB control number 0910-0231; 510(k)s, 21 CFR part 807 subpart E, are covered under OMB control number 0910-0120; NDAs and ANDAs, 21 CFR part 314, are covered under OMB control number 0910-0001).

Table 1.--Estimated Number of Applications, Clinical Trials, and Investigators Subject to the Regulation by Type of Application[1]

Application Type	Total Number of Applications	Number of Applications Affected	Number of Trials	Number of Investigators
Drugs:				
New drug application (NDA), new molecular entity (NME)	35	35	3 to 10	3 to 100
NDA nonNME	100	100	1 to 3	10 to 30
NDA efficacy supplement	100	100	1 to 3	10 to 30
Abbreviated new drug application (ANDA)	400	240	1.1	2
ANDA supplement	2500	120	1	2
Rx switch	20	10	2	4
Biologics:				
Biologics license application (BLA)	25	25	3 to 10	3 to 100
BLA efficacy supplement	10	10	1 to 3	3 to 100
Medical Devices:				
Premarket approval (PMA)	40	40	1 to 3	10 to 20
PMA supplement	12	12	1 to 3	3 to 10
Reclassification devices	19	10	1	3 to 10
510(k)	3900	200	1	3 to 10

[1] Source: Agency estimates

Reporting Burden:

For clinical investigators not employed by the applicant and/or the sponsor of the covered study, the applicant must either certify to the absence of certain financial arrangements with clinical investigators or disclose those arrangements to FDA. FDA estimates that almost all

applicants submit a certification statement under § 54.4(a)(1) and (a)(2). Preparation of the statement using Form FDA 3454 should require no more than 1 hour per study. The number of respondents is based on the estimated number of affected applications (see table 1 above).

When certification is not possible and disclosure is made using form FDA 3455, the applicant must describe, under § 54.4(a)(3), the financial arrangements or interests and the steps that were taken to minimize the potential for bias in the affected study. As the applicant would be fully aware of those arrangements and the steps taken to address them, describing them will be straightforward. The agency estimates that it will take about 5 hours to prepare this narrative. Based on our experience with this collection, FDA estimates that approximately 10 percent of the respondents with affected applications will submit disclosure statements.

Table 2.--Estimated Annual Reporting Burden

21 CFR Section	No. of Respondents	No. of Responses per Respondent	Total Annual Responses	Average Burden per Response	Total Hours
Certification--54.4(a)(1) and (a)(2)--Form FDA 3454	902	1	902	1	902
Disclosure--54.4(a)(3)--Form FDA 3455	90	1	90	5	450
Total					1,352

Recordkeeping Burden:

The sponsors of covered studies are required to maintain complete records of compensation agreements with any compensation paid to nonemployee clinical investigators, including information showing any financial interests held by the clinical investigator, for a time period of 2 years after the date of approval of the applications. This time is consistent with the current recordkeeping requirements for other information related to marketing applications for human drugs, biologics, and medical devices. Under § 54.6, sponsors of covered studies must maintain many records with regard to clinical investigators, including protocol agreements and investigator resumes or curriculum vitae. FDA estimates that it takes an average of 15 minutes for each recordkeeper to add this record to clinical investigators' file.

Table 3.--Estimated Annual Recordkeeping Burden

21 CFR Section	No of Recordkeepers	No. of Records per Recordkeeper	Total Annual Records	Average Burden per Recordkeeping	Total Hours
Recordkeeping--54.6	902	1	902	0.25	226

Third-Party Disclosure Burden:

Under §54.4(b), clinical investigators must provide sponsors of the covered studies with sufficient accurate information to make the required disclosure or certification. Because much of the information required can be obtained from the applicant's own records, the costs incurred by the clinical investigator will be minimal. Clinical investigators are required to do one of two things: (1) Provide a statement that they, their spouse, and their dependent children did not have a significant equity interest as defined in § 54.2(b) in the sponsor of the

covered study, or (2) disclose any such interest. Clinical investigators are accustomed to supplying such information in even greater detail when applying for research grants. Most people know the financial holdings of their immediate family, and records of such interests are generally accessible because they are needed for preparing tax records. FDA estimates that the time required for this task may range from 5 to 15 minutes; we used the mean, 10 minutes, for the average burden per disclosure. We determined the number of respondents by multiplying the number of affected applications by the mean of the estimated number of investigators (see table 1 above).

Table 4.--Estimated Annual Third-Party Disclosure Burden

21 CFR Section	No. of Respondents	No. of Disclosures per Respondent	Total Annual Disclosures	Average Burden per Disclosure	Total Hours
54.4(b)--Clinical Investigators	10,554	1	10,554	0.17	1,794

12b. Annualized Cost Burden Estimate*

Reporting (certification and disclosure): FDA estimates that virtually all of the 902 sponsors submitting marketing applications that contain clinical data will be able to certify for one or more investigators, and the names of all investigators for whom the sponsor is certifying may be attached to one certification form. The agency estimates that preparation of the certification form will take at most 1 hour, of which 80% is clerical time ($13.72/hr.) and 20% management time ($48.39/hr.) plus 30% for overhead, providing a weighted wage rate of $26.86/hr. The agency bases this estimate on sampling of time taken in preparation of other portions of marketing applications. The total estimated time spent by sponsors of marketing applications on certification in a given year is estimated to be 902 hours.

The agency estimates that preparation of the disclosure form, which includes identifying the interest or arrangement held by the investigator and describing steps taken to minimize bias of study results, will take 5 hours, of which 90% is management time ($48.39/hr.) and 10% clerical time ($13.72/hr.) plus 30% overhead, providing a weighted wage rate of $58.66/hr. The total estimated time spent by sponsors of marketing applications on disclosure in a given year is estimated to be 450 hours.

Recordkeeping: As stated, recordkeeping requires minimal time because a sponsor can incorporate financial disclosure information into the sponsors existing system for maintaining investigator information. It is estimated that an average of 15 minutes is needed for inclusion of this information in an application record. In calculating the cost of recordkeeping, the same weighted wage rate is used as for certification: $26.86/hr.

Third-party disclosure: Clinical investigators report to sponsors, in whose studies they participate, sufficient, accurate information to enable the sponsor to complete certification and disclosure forms. Most clinical investigators will have no disclosable information to report to the sponsor, and for these investigators reporting will amount to checking a box or writing the equivalent of disclosable financial arrangements. Even if an investigator holds disclosable interests or arrangements, most of this information will already be known by the

sponsor, i.e., a financial arrangement between the sponsor and the clinical investigator whereby the value of the compensation to the investigator could be influenced by the outcome of the study; any significant payments of other sorts to the clinical investigator by the sponsor; any proprietary interest in the tested product held by the clinical investigator; and, if the sponsor is not a publicly held corporation, any significant equity interest in the sponsor that is held by the investigator. The investigator will need only provide the sponsor with information concerning a significant equity interest in the sponsor, providing the sponsor is publicly held. Because the investigator will have such information readily available for tax purposes, FDA estimates that only minimal time will be spent by the investigator in providing this information to the sponsor. FDA believes the average time spent by a clinical investigator in providing a sponsor with the required financial information will be 10 minutes (0.17 hours). Approximately 10,554 clinical investigators participate in covered clinical studies in a given year. Thus, a total of 1,794 burden hours is estimated for reporting by clinical investigators to sponsors in a given year. Cost of this burden is calculated using a physicians mean hourly wage of $88.78.

Annualized Cost Burden Estimate

	Hours	Hourly Wage Rate	Cost
Sponsors' costs:			
Certification	902	$26.86	$24,228
Disclosure	450	$58.66	$26,397
Recordkeeping	226	$26.86	$6,070
Sponsors' total costs:			$56,695
Clinical Investigators' costs:			
Third-party disclosure	1,794	$88.78	$159,271
Total costs to sponsors and investigators:			$215,966

* Wage rate calculations are based on: Bureau of Labor and Statistics May 2011 data (**http://www.bls.gov/oes/current/naics4_561100.htm#00-0000**) for "Office Clerks, General" (occupation code 43-9061); "Managers, All Others" (occupation code 11-9199); and "Physicians and Surgeons, All Other" (occupation code 29-1069).

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

There are no additional information collection costs to respondents and recordkeepers beyond those estimated in the previous item. This is because the information will be collected and submitted as part of preparation of a marketing application, and sponsors already have in place processes and equipment for collecting and maintaining information from clinical investigators who study FDA-regulated products. Investigators who participate in clinical studies of regulated products provide sponsors of the studies with a variety of information and are thus accustomed to this activity.

14. Annualized Cost to the Federal Government

Because FDA already has in place equipment and processes for handling information contained in product marketing applications, the information collected under this regulation will generate new costs to the agency in only two areas:

(1) Additional review of applications to assure that the required information has been submitted and all clinical investigators participating in covered studies are accounted for. Agency staff estimates that this review could take from 15 to 20 minutes for an application in which all clinical investigators are certified to upwards of 5 hours for an application that includes disclosure for an investigator. For planning purposes, an average of 2 hours is estimated for this review. The initial review and assessment of applications would be conducted by a Consumer Safety Officer at an average hourly rate of $55.46 (hourly wage rate of a GS-13, step 10 employee; OPM Salary Table 2012-DCB, **http://www.opm.gov/oca/12tables/html/dcb_h.asp**).

(2) Agency data audit of a covered clinical study. If a clinical investigators financial interests and arrangements raise serious questions about the integrity of the data, and the study design does not include sufficient bias-minimizing steps to offset these questions, one course of action FDA can take is to request a data audit by agency bioresearch monitoring staff. FDA estimates that 10 percent of sponsors of marketing applications will submit disclosures for clinical investigators in a given year. The agency estimates that only a very few would contain financial interests and arrangements that raise questions about the integrity of the data that are sufficiently serious, and study design sufficiently questionable, to trigger a data audit. For planning purposes, the agency has set this figure at one-half of one percent of submitted applications, or 5 applications. A data audit may cover a wide range of time, based on the size and complexity of a study and the number of investigators participating, but 40 hours is a realistic average time for such an audit. The cost per hour is the hourly wage rate of $55.46 for a Consumer Safety Officer who would conduct the review.

Estimated Annual Costs to FDA

	Hours per Review	Average Hourly Rate	No. of Applications	Cost
Additional review	2	$55.46	1,000	$110,920
Data audit	40	$55.46	5	$11,092
Total				$122,012

15. Explanation for Program Changes or Adjustments

After a review under the PRA, the burden to clinical investigators has been changed from reporting to third-party. FDA feels that regarding this portion of the burden as a third-party disclosure is more appropriate because clinical investigators disclose financial information to the sponsors of drug, biologic, or device marketing applications, i.e., third-parties, rather than directly to FDA.

The number of respondents has decreased from 1,000 to 902 for Certification, from 100 to 90 for Disclosure, and from 1,000 to 902 for Recordkeeping due to a decrease in the estimated number of affected applications. Upon review of our analysis, we made the following adjustments for improved accuracy and consistency: We recalculated the number of Clinical Investigators (now listed as third-party disclosure burden), which resulted in a decrease from 46,000 to 10,554, and we adjusted the estimated burdens per response, recordkeeping, and disclosure. For clarity, we also provided additional detail in paragraph 12 regarding the

burden calculations. The sum of these adjustments has resulted in a 15,378-hour decrease of the total hour burden. No program changes were made. In prior approvals we believe FDA over-estimated the burden by multiplying by the number of trials. We are correcting an inaccuracy in table 1 by changing "Clinical Investigations" to "Clinical Investigators", and no longer multiplying by the number of trials, since they are independent of the number of investigators. The collection is not changing, we are simply refining the estimate for accuracy.

16. Plans for Tabulation and Publication and Project Time Schedule

Results of this information collection will not be published.

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

The agency is not seeking exemption from displaying the expiration date of OMB approval of the information collection.

18. Exceptions to Certification for Paperwork Reduction Act Submissions

There are no exceptions to the certification.