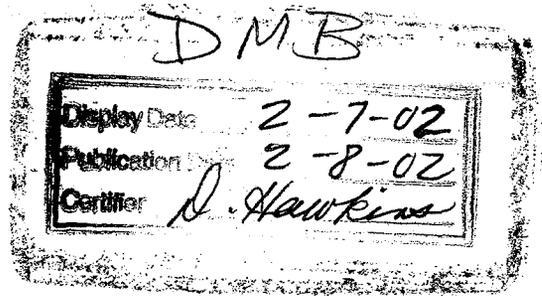


DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. 01 N-03081



**Agency Information Collection Activities; Submission for OMB Review; Comment Request; Financial Disclosure by Clinical Investigators**

**AGENCY:** Food and Drug Administration, HHS.

**ACTION:** Notice.

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**SUMMARY:** The Food and Drug Administration (FDA) is announcing that the proposed collection of information listed below has been submitted to the Office of Management and Budget (OMB) for review and clearance under the Paperwork Reduction Act of 1995.

**DATES:** Submit written comments on the collection of information by *[insert date 30 days after date of publication in the **Federal Register**]*.

**ADDRESSES:** Submit written comments on the collection of information to the Office of Information and Regulatory Affairs, OMB, New Executive Office Bldg., 725 17th St. NW., rm. 10235, Washington, DC 20503, Attn: Stuart Shapiro, Desk Officer for FDA.

**FOR FURTHER INFORMATION CONTACT:** Karen L. Nelson, Office of Information Resources Management (HFA-250), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-827-1482.

**SUPPLEMENTARY INFORMATION:** In compliance with 44 U.S.C. 3507, FDA has submitted the following proposed collection of information to OMB for review and clearance.

**Financial Disclosure by Clinical Investigators (OMB Control No. 0910-0396)**

Respondents are sponsors of marketing applications that contain clinical data from studies covered by the regulations. These sponsors represent pharmaceutical, biologic, and medical device

firms. The applicant will incur reporting costs in order to comply with the final rule. Applicants will be required to submit, for example, the complete list of clinical investigators for each covered study, not employed by the applicant and/or sponsor of the covered study, and 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. The clinical investigator will have to supply information regarding financial interests or payments held by the sponsor of the covered study. FDA has said that it has no preference as to how this information is collected from investigators and that sponsors/applicants have the flexibility to collect the information in the most efficient and least burdensome manner that will be effective.

FDA estimated that the total reporting costs of sponsors would be less than \$450,000 annually. Costs could also occur after a marketing application is submitted if FDA determines that the financial interests of an investigator raise significant questions about the integrity of the data.

FDA estimates the burden of this collection of information as follows:

TABLE 1.—ESTIMATED ANNUAL REPORTING BURDEN<sup>1</sup>

21 CFR Section	No. of Respondents	Annual Frequency per Response	Total Annual Responses	Hours per Response	Total Hours
54.4(a)(3)	1,000	5	5,000	1	5,000
54.4(a)(3)	46,000	1	46,000	20	9,200
54.4		1	46,000	.10	4,600
Total					11,600

<sup>1</sup> There are no capital costs or operating and maintenance costs associated with this collection of information.

In the **Federal Register** of July 25, 2001 (66 FR 38712 ), the agency requested comments on the proposed collections of information. Three comments were received. Two comments were not on the proposed information collection and will be addressed separately. The third comment had concerns whether the proposed collection of information is necessary for the proper performance of FDA's functions, including whether the information will have practical utility.

The comment states that member companies reported that in calendar year 2000, less than 1 percent of all investigators, subinvestigators and their spouses and dependent children reported any financial arrangement with the sponsor. According to the comment, large global companies

almost never pay investigators with proprietary interests in the product or give compensation that is affected by study outcome.

FDA's Center for Drug Evaluation and Research (CDER) surveyed the rate of disclosure of financial information according to numbers of applications. CDER reviewed 129 total applications, including 119 new drug applications (NDAs) and 10 abbreviated new drug applications. Out of the original 129 applications, 33 applications or 25 percent of the total number of applications included the disclosure form (FDA 3455), meaning that at least one investigator had a disclosable interest. Out of those reporting, 12 applications included disclosable equity interests in the sponsor, 18 applications reported significant payments of other sorts (SPOOS) and 3 included information about clinical investigations who held proprietary interests in the product under study. FDA did not break down submission of financial information according to individual investigators, but it is, as the comment states, clearly a small minority.

FDA agrees with the comment that it would be very unlikely for a company to compensate investigators differentially, depending on study outcome or to include investigators who hold proprietary interests in the product under study, and we did not expect to encounter many such financial arrangements. Providing assurance that such financial interests do not exist, however, imposes almost no collection burden on companies because they can certify that investigators hold none of these types of financial interest without asking the investigators.

These financial interests represent an unusual occurrence, but other interests also deserve attention. FDA has found that it is not unusual for investigators to have received significant payment of other sorts and to hold equity interest in the sponsor exceeding \$50,000. Collecting this information is clearly more difficult. For both of these cases, however, FDA has amended the final rule (21 CFR 54.2(b) and (f)) in order to help reduce the collection burden and has lifted the retroactive requirement on studies completed before February 2, 1999, on SPOOS and equity interests in publicly held companies, thereby relieving the sponsor from contracting the investigators retroactively. With regard to SPOOS, FDA has asked for information on payments

made on or after February 2, 1999, and for equity interests in publicly held companies whose value exceeds \$50,000 in value, FDA has asked only for those financial holdings relating to ongoing studies after February 2, 1999.

Another concern was the accuracy of FDA's estimate of the burden of the proposed collection of information, including the validity, methodology, and assumptions used.

Some companies report that it takes approximately 15 workweeks to collect, compile, and verify the information about financial relationships for a single phase 3 study involving 50 sites. According to the comment, these figures translate into an average low of approximately 3 and a high of 26 workweeks to collect, compile, and verify the information. Also, according to the comment, an additional, but a smaller amount of staff time is necessary to compile and verify information for phase 2 and phase 1 studies; the comment concluded that FDA's estimates of 1 to 4 hours to complete a response is unrealistic.

FDA held extensive discussions with the drug, device, and biotechnology companies as well as discussion with the academic medicine community and individual investigators, including numerous public meetings. Six extensions were permitted for public comment. Based on this input, FDA estimates the effort needed for the data collection requirement would not be unduly burdensome. FDA expected that the data collection would become easier as mechanisms to collect it routinely under the investigational new drug (IND) became established. A factor that may have complicated collection of this information is the multiple drug company acquisition and mergers that have taken place in recent years. In addition, subsequent to the issuance of the rule, FDA learned that many companies had no organized records of total monies distributed to investigators (e.g., SPOOS).

Companies, therefore, have to ask the investigators about SPOOS or develop new tracking systems for such payments. Because no organized tracking systems existed in many companies, large companies through the public comment process and during meetings asked FDA whether it would be acceptable for a company to use a questionnaire to collect information on SPOOS

from an investigator. FDA said it had no preference as to how the information is collected and that sponsor/applicants may collect the information in the most efficient and least burdensome manner that is still effective. Although FDA did make a good faith estimate of the data collection burden based on extensive discussions with the affected communities, FDA will revise its burden estimate upward to reflect the fact that companies could not easily access some of the information, particularly relating to SPOOS payments. FDA noted that industry queries to investigators about SPOOS payments may be made in the initial letter that inquires about equity interests held by clinical investigators and that both could also be updated through the same inquiry.

In the comment, concerns were raised on the issue of ways to enhance the quality, utility, and clarity of the information to be collected. The comment has said some companies collect, compile, and report investigator financial interest information for all studies, whether or not they are covered by the rule. They have asked that we clarify the definition of covered study and ensure that reviewers apply a consistent definition of what studies are covered. They have asked that FDA exclude all large, multicenter studies in which no single investigator contributes more than 20 percent of the data. The comment also said that companies report difficulties locating investigators who have already left the study prior to completion and also during the 1-year period following completion of the study. The comment asked that FDA define what constitutes due diligence in attempting to locate those investigators. The comment also recommended that FDA clarify and **limit** the definition of investigator and subinvestigator because some companies are interpreting the definition very broadly.

In response to the concerns above, a covered clinical study means any study of drug, biologic, or device in humans submitted in a marketing application or reclassification petition that the applicant or FDA relies on to establish efficacy of a product or any study where a single investigator makes a significant contribution to the demonstration of safety. This, in general, does not include phase 1 tolerance studies or pharmacokinetic studies, most clinical pharmacology studies (unless they are critical to an efficacy determination), large open safety studies conducted at multiple sites,

treatment protocols and parallel track protocols. FDA continues to strongly encourage companies to consult with FDA early on about which clinical studies constitute “covered clinical studies” for purposes of complying with these requirements. Regarding comments about ensuring that reviewers apply a consistent definition of covered study, FDA has provided clarification through the guidance process. In addition, FDA has extensively discussed these requirements with review staff in training sessions; FDA will also issue Manuals of Practices and Procedures (MaPPs) to CDER staff to help further ensure consistent interpretation of the financial disclosure requirements by FDA staff.

Large scale, multicenter efficacy studies with many investigators are considered covered clinical studies within the meaning of the final rule. (See 21 CFR 54.4(c)). Data from an investigator having only a small percentage (<20 percent) of the total subject population (in a study with large numbers of investigators and multiple sites) could still affect the overall study results. FDA has, therefore, declined to exclude all large, multicenter studies in which no single investigator contributes less than 20 percent of the data.

The comment also mentioned difficulty in locating clinical investigators who leave the study or clinical trial site prior to completion of the study or completion of the 1-year followup period and asked for clear parameters in defining the term due diligence to search out these investigators. With regard to the definition of due diligence, FDA has suggested through guidance that sponsors and applicants should use reasonable judgment in deciding how much effort should be expended to collect this information. This suggestion was made in an effort to provide flexibility to sponsors and applicants and encourage them to use their best judgment while complying with the requirements.

However, based on the comment, FDA is now providing more specific advice on due diligence in seeking information from investigators who have left the study prior to its completion, or 1 year following completion of the study period. FDA recommends that sponsors and applicants try to locate the investigator through at least two telephone calls and include written memoranda

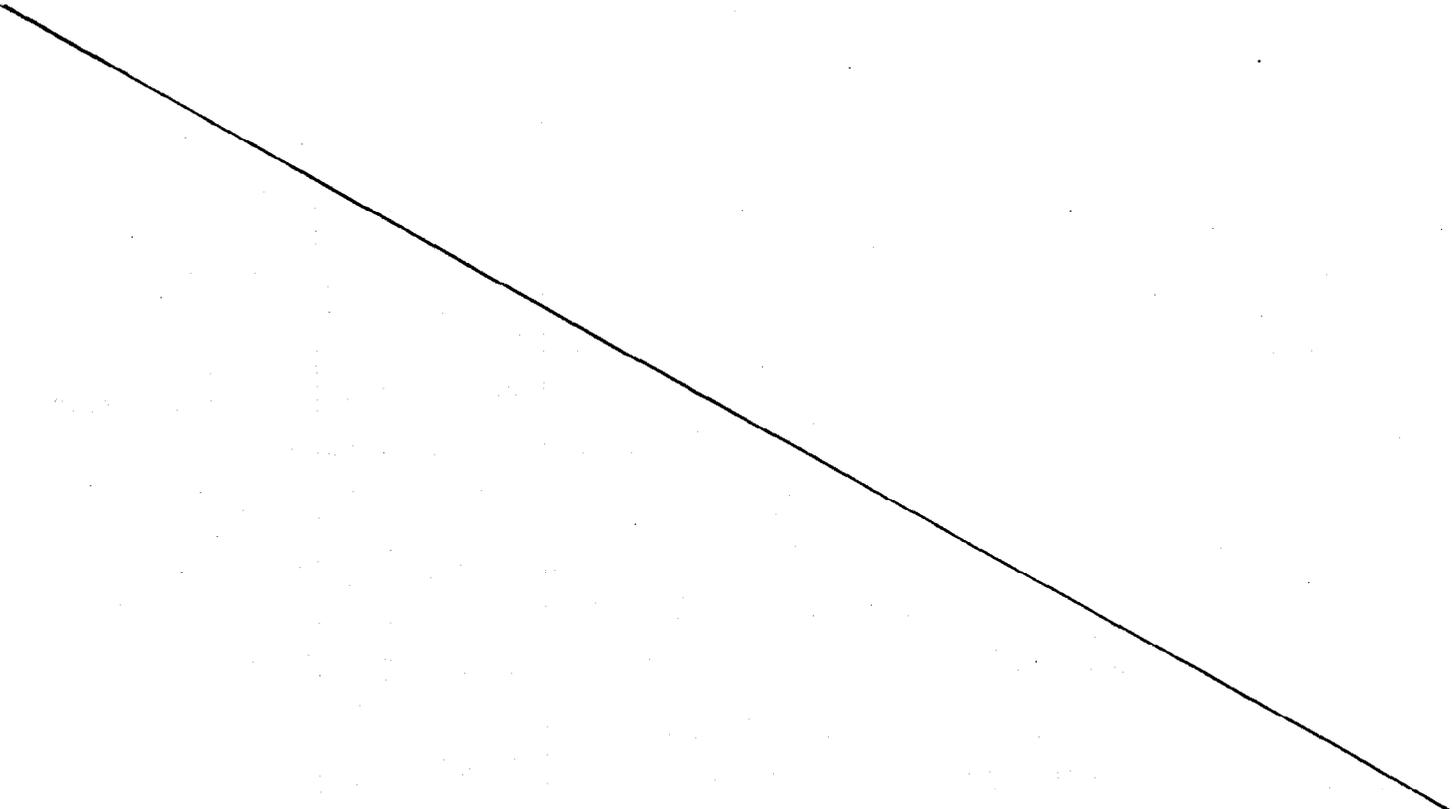
of telecons. In addition, they should **followup** in writing and send no fewer than two certified letters in an effort to locate lost investigators. For all clinical trials begun after February 2, 1999, which is the effective date of the regulation, information should be collected from clinical investigators prior to study start, which should prevent the difficulty in collecting the information retrospectively.

Regarding the comment requesting additional clarification on the definition of clinical investigator. FDA would like to reiterate once again the definition of clinical investigator and subinvestigator. The definition of clinical investigator in 21 CFR part 54 is intended to identify the individuals who should be considered investigators for purposes of reporting under the rule, generally, the people taking responsibility for the study at a given study site. (For purposes of this rule, the term investigator also includes the spouse and each dependent child of the investigator and subinvestigator). For drugs and **biologics**, clinical investigator means the individual(s) who actually conduct(s) and take(s) responsibility for an investigation, i.e., under whose immediate direction the drug or biologic is administered to a subject or who is directly involved in the evaluation of research subjects. Where an investigation is directed by more than one person at a site, there may be more than one investigator who must report. These definitions could, in some cases, leave uncertainty about whether a particular individual was an investigator for purposes of the rule. The agency has, therefore, recommended specific criteria that should be considered for determining who fits the definition of clinical investigator for purposes of the financial disclosure rules. Investigators are persons who fit *any of these* criteria: Have *signed* the Form FDA 1572, are identified as an investigator in initial submissions or protocol amendments under an IND, or are identified as an investigator in the **NDA/biologic** license application (BLA).

The comment raised concerns over ways to minimize the burden of the collection of information on the respondents, including through the use of automated collection techniques when appropriate, and other forms of information technology.

The comment stated that it is not so much the initial startup costs to develop tracking mechanisms but the ongoing costs of collecting, compiling, verifying and maintaining the information that are high. In the comment, a request was made that FDA limit the scope of people for whom sponsors are required to collect financial information. In addition, the comment recommended streamlining the data collection process by allowing sponsors to use e-mail to communicate with potential investigators; allowing investigators to fax completed forms to the sponsor, rather than requiring that sponsors retain forms with original signatures; and allowing sponsors to collect information at or near the start of each investigator's participation in the trial rather than prior to initiation of the study.

FDA has addressed in detail the definition of clinical investigator earlier in this response and believes it has provided appropriate clarification. The suggested ways of streamlining the data collection process are acceptable. It is permissible to communicate through e-mail or fax machines with investigators. E-mails should be printed and all hard copies of correspondence should be maintained in company files. Finally, as has been stated earlier, information must be collected prior to study start in order to alert the IND/investigational device exemption (IDE) sponsor of the study to any potentially problematic financial interest as early in the drug development process



as possible in order to minimize the potential for study bias and to facilitate accurate collection of data that may be submitted many years later.

Dated: 2-1-02  
February 1, 2002.



Margaret M. Dotzel,  
Associate Commissioner for Policy.

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