

DEPARTMENT OF HEALTH AND HUMAN SERVICES**Public Health Service****42 CFR Part 50****Office of the Secretary****45 CFR Part 94**

RIN 0905-AE01

Objectivity in Research

AGENCY: Public Health Service and Office of the Secretary, HHS.

ACTION: Final rule.

SUMMARY: The Public Health Service (PHS) and the Office of the Secretary, HHS, are promulgating regulations establishing standards and procedures to be followed by institutions that apply for research funding from the PHS to ensure that the design, conduct, or reporting of research funded under PHS grants, cooperative agreements or contracts will not be biased by any conflicting financial interest of those investigators responsible for the research.

Under the rules, investigators are required to disclose to an official(s) designated by the institution a listing of Significant Financial Interests (and those of his/her spouse and dependent children) that would reasonably appear to be affected by the research proposed for funding by the PHS. The institutional official(s) will review those disclosures and determine whether any of the reported financial interests could directly and significantly affect the design, conduct, or reporting of the research and, if so, the institution must, prior to any expenditure of awarded funds, report the existence of such conflicting interests to the PHS Awarding Component and act to protect PHS-funded research from bias due to the conflict of interest.

EFFECTIVE DATE: October 1, 1995.

FOR FURTHER INFORMATION CONTACT: Dr. George J. Galasso, Associate Director for Extramural Affairs, National Institutes of Health, Building 1, Room 552, 9000 Rockville Pike, MSC 0154, Bethesda, MD 20892-0154. The telephone number is (301) 496-5356 (this is not a toll-free number).

SUPPLEMENTARY INFORMATION: On June 28, 1994 the Department of Health and Human Services (HHS) published proposed regulations (59 FR 33242) to ensure that PHS-funded research would not be compromised by financial interests of investigators that could be reasonably expected to bias the design, conduct or reporting of the research. In

addition to setting forth proposed rules requiring institutional procedures for the disclosure and management, reduction or elimination of Significant Financial Interests that would reasonably appear to be directly and significantly affected by the research funded by PHS, or proposed for funding, the Notice of Proposed Rulemaking (NPRM) raised several specific questions about alternatives for implementing the pertinent statutes and for ensuring that PHS-funded research is not compromised by any financial conflicts of interest.

The NPRM was published in the **Federal Register** at the same time the National Science Foundation (NSF) published its Investigator Financial Disclosure Policy and reflected coordination between the two agencies. Since that time, we have continued to work closely with the NSF to ensure that the NSF policy and our regulations do not impose disparate requirements upon the many institutions that receive funding from both agencies. Elsewhere in this separate part in this **Federal Register**, the NSF is issuing changes in its policy necessary to maintain consistency with this final rule, and the changes we have made to conform to the NSF policy are referenced in the discussion that follows. The agencies intend to continue their cooperation by working together to develop common guidance, including a set of questions and answers, to help institutions implement conflict of interest policies that comply with both HHS and NSF requirements.

During the 60 day comment period that ended on August 28, 1994, the PHS received 102 comments on the NPRM. Most of the comments were generally supportive of giving the applicant institutions primary responsibility for identifying and resolving financial conflicts of interest that could directly and significantly affect the PHS-funded research. The comments are summarized below under the headings: Changes in the NPRM; Comments Not Resulting in Any Changes; and Responses to Questions on Alternatives.

Changes in the NPRM

A summary of the changes made in the regulations as proposed on June 28, 1994, follows.

1. In the section titles, §§ 50.601, 50.602, 50.605 and several other sections,¹ references to "Significant Financial Interests" or "Significant

¹ Only the sections in 42 CFR part 50 are referenced. Similar changes have been made in the regulations at 45 CFR part 94 which will apply to contracts.

Financial Interests of the type described in § 50.605," have been changed to refer to a conflict of interest or conflicting financial interests. This change has been made in response to many of the comments. It was pointed out that this change will make the HHS regulations consistent with the NSF regulations and that the institutions can only manage the conflict, not the financial interests.

2. In response to several comments, the "Purpose" sections in the grants and the contracts regulations have been rewritten to make them more concise and parallel.

3. A reference to § 50.604(a) has been added to the "Applicability" section. As explained more fully in paragraph 6 below, this change and the change in § 50.604(a) clarify that the regulations apply to Investigators carrying out the PHS-funded research for subgrantees or contractors of the awardee institution.

4. In response to several comments, the definition of "Investigator," has been amended to delete the phrase "at the Institution."

5. The definition of "Significant Financial Interest" in § 50.603 has been changed in several respects. Clause (i) has been split so that ownership interests are now referenced in a new clause (ii). Some commenters felt that it was not clear whether the requirement that an institution be an applicant under the SBIR program modified both ownership interest and salary, royalties or other remuneration.

The exception for financial interests in business enterprises has been split to clarify that the per annum measurement applies only to salary, royalties or other payments not reasonably expected to exceed \$10,000 per annum. In addition, the dollar limits have been changed from \$5,000 to \$10,000 and the applicability of the alternative measures of \$10,000 in value or five percent ownership interest, has been clarified. These changes have been made in response to a large number of comments stating that the \$5,000 limit was too low. A majority of those comments indicated that \$10,000 would be an appropriate figure, particularly since the experience of state universities in California, and some other universities, is that interests up to this amount do not raise conflict of interest concerns.

The reference to determining the value of equity interests on the basis of public prices or other reasonable measures of fair market value was adapted from a similar provision in the proposed FDA rule on conflict of interest (59 FR 48708 *et seq.*, September 22, 1994).

6. Section 50.604(a) has been revised to clarify that the Institution must

maintain an appropriate written, enforced conflict of interest policy (this parallels NSF language) and that the Institution must make reasonable efforts to ensure compliance with the regulations by Investigators working for subgrantees and contractors, either by including those Investigators in the Institution's policy or by receiving appropriate assurances from their employers. This latter change was recommended in several comments and is consistent with current regulations and policies on the applicability of grant terms and conditions to subgrantees and contractors.

7. In response to many comments, paragraph (a)(3) (redesignated as paragraph (c)) of § 50.604 has been changed from requiring the institution to "ensure" that investigators have disclosed all Significant Financial Interest to simply "require" disclosures by each investigator. In addition, in response to several comments and for uniformity with the NSF guidelines, this paragraph has been revised to require disclosure, by the time an application is submitted to PHS, of those Significant Financial Interests attributable to the Investigator that would reasonably appear to be affected by the research, including interests in entities whose financial interests would reasonably appear to be affected by the research. This change eliminates the need to cross-reference the description of a conflict of interest in § 50.605(a). Also, the changes in this section and in §§ 50.604(c) and 50.605(a) will result in a slightly broader disclosure by the Investigator than under the NPRM. The institutional official(s) will review the disclosures and determine which disclosed interests could directly and significantly affect the design, conduct or reporting of the research, necessitating the management, reduction or elimination of the conflict of interest. In addition, in response to a significant number of comments, the reference to "pendency" of the award has been changed to "period" of the award.

Paragraph (a)(5) of § 50.604 (redesignated as paragraph (e)) has been changed to delete the requirement that records be identifiable to each award, and to refer to the applicable retention requirements in the HHS grants administration regulations. The former change has been made for conformity with the NSF policy, and the latter change clarifies that the recordkeeping requirements of these regulations are intended to be consistent with the HHS grants administration regulations. The change in paragraph (f) of § 50.604 (formerly paragraph (a)(6)) has also been

made for conformity with the NSF policy.

8. In response to many comments, § 50.604(a)(7)(ii), now redesignated as (g)(2), has been revised to reduce the burden on institutions and ensure that the application does not have to state whether a conflict of interest has been found. Rather, the provision now requires the applicant to certify that action will be taken, prior to the institution's expenditure of any funds under the award, to report to the PHS awarding component the existence of a conflicting interest and assure that the interest has been managed, reduced or eliminated in accordance with the regulations. The commentors felt that review of an application would be biased if the application indicated there was a conflict of interest and that, in any case, it would not be feasible for an institution to review the disclosed financial interests and determine whether a conflict of interest was present in the limited time available prior to submission of the application.

In addition, the previous § 50.604(a)(8)(i) has been incorporated into § 50.604(g)(2) with minor changes. Many commentors felt that the 60 day period for management of a conflict of interest found after the award should be doubled. However, the 60 day period does not seem unreasonable, since we have clarified that it is measured from the time the institution identifies the conflict of interest and that only interim action is required by the end of the 60 day period. As stated in the NPRM, section 493A of the PHS Act imposes a continuing obligation on awardees to identify conflicts of interest in clinical research projects and report their management, reduction or elimination. This and other statutory requirements for clinical research have been applied to all PHS-funded research in order to avoid confusion and provide for uniform PHS reporting requirements. We would not expect this reporting requirement to be burdensome, as only a few conflicts of interest are likely to be identified after the award.

Section 50.604(a)(8)(ii) has been incorporated into § 50.606(b), because the review of records referenced in the former section is directly related to the inquiry into actions regarding conflicts of interest addressed in the latter section. Section 50.604(a)(8)(iii) has been deleted as duplicative of the statement in the definition of "Significant Financial Interest" (§ 50.603), that salary, royalties or other remuneration from the institution is not considered a Significant Financial Interest. Under current regulations and policies governing applications for PHS

research grants, if the applicant receives non-PHS grant support for the same project to be supported by the PHS award, the grant must be listed in the "Other Support" section of the application for PHS support.

9. Section 50.605(a) has been revised to clarify that the institutional official(s) must identify and manage, reduce or eliminate any conflicts of interest. Consistent with the language in the NSF guidelines, this provision states that a conflict of interest exists when the designated official(s) reasonably determines that a Significant Financial Interest could directly and significantly affect the design, conduct, or reporting of the PHS-funded research. As noted above in the discussion of the changes to § 50.604(c), Investigators must disclose those Significant Financial Interests that would reasonably appear to be affected by the research and the institutional official must decide which of those interests are conflicting under the standard prescribed in § 50.605(a). This change is intended to more clearly define and limit the types of financial interests that must be managed, reduced or eliminated because they are considered to be conflicting interests.

In response to a few comments, the clause introducing the examples of methods for managing, reducing or eliminating conflicts has been clarified by adding after "include," the phrase "but are not limited to."

10. In § 50.606, the first sentence has been deleted because it essentially duplicated the provision in proposed § 50.604(a)(6). In the next sentence, the term "employee" has been changed to the defined term "Investigator" and, in response to a comment, the phrase "or to be taken" has been added at the end of the sentence. In addition, paragraph (b) has been rewritten to incorporate § 50.604(b), because the two provisions were somewhat duplicative.

11. Many commentors were concerned about what they considered to be a significant underestimation of the annual reporting and recordkeeping burden. In response, burdens have been further reduced by raising the dollar threshold for financial interests that are considered Significant Financial Interests subject to the regulations, and by amending § 50.604(g)(2) to require the reporting of a conflict of interest and its management, reduction or elimination only after an award has been made (but before any expenditure of funds). In addition, the estimated annual reporting and record keeping burden has been recalculated in light of these changes and the public comments.

12. Many commentors urged uniformity with the NSF guidelines, but

indicated the pursuit of that end should not interfere with necessary changes to the NPRM. As noted above, many of the changes result in greater uniformity between these regulations and the NSF guidelines. The few remaining differences between these regulations and the NSF guidelines are based upon requirements in section 493A of the PHS Act, 42 U.S.C. 289b-1, and differences between the grant programs and experiences under those programs.

The effective date for these regulations, October 1, 1995, is the same as the effective date for the NSF guidelines. Although some commentors felt that a longer lead time would be necessary to enable institutions to prepare for implementation of the regulations, we believe the time period provided is ample, particularly because institutions have had since June 28, 1994, to prepare for implementation of the similar provisions of the NSF guidelines and because many institutions already have conflict of interest procedures.

Comments Not Resulting in Any Changes

1. Title

Two commentors felt that the title of the regulations should be changed to focus upon investigator financial disclosure or conflict of interest. These are not inappropriate titles, but we have chosen to focus the title upon the desired outcome of the review of investigator financial disclosures, that is, objectivity in the design, conduct and reporting of the research.

2. Section 50.602 Applicability

Several commentors recommended that the regulations be limited to clinical research. As explained in the preamble to the NPRM, experience indicates that financial conflicts of interest can arise in all types of research. It is expected that the risk of a conflict of interest will be higher in clinical research than in other types of research, but we have concluded that the latter risk is sufficiently likely that pertinent financial interests should be disclosed and reviewed.

In response to a specific request for comments on the NSF exemption from its conflict of interest policy for grantees employing fifty persons or less, it was generally agreed by those responding that PHS-funded investigators working for small entities may be just as subject to conflicts of interest as investigators working at large institutions. This view is consistent with the PHS experience referred to in the preamble of the NPRM. The NSF experience has

differed, apparently because of the differences between the research funding that is provided to small entities by HHS and NSF.

3. Section 50.603 Definitions

Investigator. There were diverse comments on the definition of the term, "Investigator." Although one commentor supported the approach of the NPRM of leaving it to the institutions to determine who are persons "responsible for the design, conduct, or reporting" of the PHS funded research, others felt that the definition should offer more guidance on who would fall within that category. It was recommended that the term be limited to Principal Investigators, Co-Principal Investigators, and faculty collaborators and that students and technical staff be excluded. It was also recommended that administrators be excluded by limiting the definition to the "scientific design" of the research. The definition of Investigator has not been changed, except for deleting the phrase "at the institution," as explained above. The degree to which individuals are responsible for the design, conduct, or reporting of the PHS-funded research will vary. In some circumstances students, technical personnel and administrators may not be "responsible," but in other circumstances, they may be, in that they are given responsibility for a task that could have a significant effect on the design, conduct or reporting of the research. Based on their knowledge of the specific circumstances, we believe the institutions are in the best position to determine who is responsible for the design, conduct or reporting of the research to such a degree that his/her financial interests should be reviewed.

Significant Financial Interest. As noted above, the public comments led to several changes in this definition. There were a number of other detailed comments that were not adopted, primarily because they would have: Complicated the definition and its application (e.g., have different threshold levels for publicly traded equity interests and those not so traded, differentiate between large and small companies, and adopt criteria for determining reasonably anticipated future value); led to a long, cumbersome list of additional exclusions (e.g., exclude copyright that is not licensable, mutual funds, pensions, and reimbursement for expenses); or were based upon a misunderstanding of the definition and its effect (some apparently did not understand that any remuneration an investigator receives from the applicant institution was

excluded). Some commentors questioned the exclusion of ownership interests in SBIR applicants. No change has been made in response to that comment because we believe such ownership interests are apparent to PHS funding agencies based on the application. Furthermore, the exclusion does not prohibit institutions from adopting more rigorous standards, if they wish to do so.

The definition of Significant Financial Interest alone does not delineate what the investigator must disclose or what the institution must manage, reduce or eliminate. The Investigator must consider all Significant Financial Interests, but need disclose only those that would reasonably appear to be affected by the research proposed for funding by the PHS, including the Investigator's financial interest in entities whose interests would be affected. Following this disclosure, the institutional official must determine, on the basis of the regulatory standard, whether there are conflicting interests that need to be managed, reduced, or eliminated. We think it is appropriate to have a relatively broad range of financial interests considered by the Investigator in making his/her determination of those that must be disclosed. In this manner, broad consideration of possibly conflicting interests is assured with minimal burdens, since only a limited number of interests need to be disclosed and an even smaller number will need to be managed, reduced or eliminated.

There were a number of comments recommending different thresholds than those that were adopted, including a threshold adjusted for inflation. The threshold amounts adopted were recommended in many comments and seem to represent a reasonable balance between the need to consider a broad range of financial interests and the burdens imposed upon the investigators and the institutions.

4. Section 50.604

Many commented that the requirement for updating financial disclosures (in § 50.604(c) of these regulations) needed to be clarified. The provision, which has not been changed, except for a minor word change, states that financial disclosures must be updated during the period of the award, either on an annual basis or as new reportable Significant Financial Interests are obtained. We believe this language is reasonably clear in conveying that the institutions have the option of adopting either of two methods for investigators to report changes in financial interests during the

period of the PHS award: reporting on an annual basis any changes in the previously reported financial interests; or requiring investigators to update disclosures as new reportable Significant Financial Interests are obtained. An annual reporting requirement would serve as a reminder for investigators to review their prior disclosures, but it might be burdensome if in fact there are no changes and it could result in delayed reporting as compared to the alternative. This burden would be eliminated by the other reporting alternative, but there would be no annual reminder to investigators to review and update their disclosures. The weighing of these factors and the decision are left to the institutions. The reference to "new reportable Significant Financial Interests" is intended to include financial interests that become reportable due to an increase in value that meets the reporting threshold, as well as the acquisition of new interests that are reportable. Of course, both types of interests are subject to disclosure by the investigator only if they meet the criteria in § 50.604(c).

It was recommended that the requirement in § 50.604(g)(2) for the reporting to the PHS Awarding Component of the existence of a conflicting interest be changed to conform with the NSF approach that requires such reporting only "if the institution finds that it is unable to satisfactorily manage an actual or potential conflict of interest." As stated in the NPRM, section 493A of the Public Health Service Act requires that institutions report conflicting interests for clinical research projects. To avoid disparate requirements for clinical and nonclinical research, the regulations apply this reporting requirement to all PHS-funded research.

5. Section 50.606

One commentor felt that the notification required in paragraph (a) should go to HHS, rather than to the PHS Awarding Component. Because PHS Awarding Components are responsible for the award and have delegated authority, it is appropriate for those components to receive notifications and to act on them. On the other hand, paragraph (b) refers to HHS inquiries into institutional procedures and actions because such audit type activities may be conducted by HHS components other than the awarding agencies. As is made clear in the definitions, the term HHS encompasses all components of the Department, including the PHS Awarding Components.

A number of commentors objected to the requirement for submission of records to the HHS, fearing that the confidentiality of such records could not be assured. 45 CFR 74.53 already gives the HHS a right of access to all records pertinent to grants, which would include the records relating to financial conflicts of interest of investigators carrying out the PHS-funded research. It is expected that the PHS funding agencies will not often require the submission of records or retain copies from audits at the institution, but when that occurs the records will be maintained confidentially. In addition, although a few commentors objected to the reference to suspension of funding pending the resolution of a conflicting interest determined by the PHS awarding agency as biasing the objectivity of the research, that provision has been retained and a reference to the regulatory authority for the suspension has been added. Such suspension action would be necessary to protect Federal funds only in unusual situations, but we believe awardees subject to the regulations should be notified of the potential for such action.

Responses to Questions on Alternatives

The NPRM requested specific comments on the following issues: (1) Whether the regulations should address institutional conflicts of interest, as well as individual conflicting interests and, if so, how; (2) what types of financial interests should be disclosed; (3) whether the disclosed financial interests should include financial interests in products that would compete with the product or potential product of the PHS-funded research; (4) whether an employee's equity or other nonsalary financial interests in an applicant institution should be excluded from the definition of Significant Financial Interest; and (5) whether there should be an exemption for all compensation other than that tied to the outcome of the research. Most of the commentors addressed at least some of these issues. Those comments are summarized below.

Institutional Conflicts

Those addressing this issue were nearly unanimous in concluding that the regulations should not address the institutional conflict of interest issue because of the need to carefully consider that issue through a separate process. We agree with that conclusion. The comments on the alternatives for addressing institutional conflicts of interest will be considered separately from this rulemaking.

Competing Products

Over 30 commentors opposed any requirement for disclosing financial interests in entities or products that would compete with the PHS-funded research. Twelve commentors supported investigator disclosure of such competing entities or products, but some felt that the disclosure should be limited to those financial interests in competitors or competing products known to the investigator. As revised, the regulation would not specifically require the disclosure of such interests, but, depending upon the circumstances, those interests might come within the definition of the financial interests that must be disclosed. In clinical research, it is probable that a financial interest in a product that competes with the product being evaluated could reasonably appear to be affected by the PHS-funded research. Such a relationship is much less probable where the PHS funding is for basic research.

Types of Financial Interests Disclosed

Most of the comments on this issue are summarized above in the discussion of comments on the definition of Significant Financial Interests and on the financial interest that must be disclosed. The financial interests to be disclosed must be known to the investigator and determined by him/her to be a financial interest that would reasonably appear to be affected by the PHS-funded research or to be a financial interest in an entity whose financial interest would reasonably appear to be affected by the research. This criterion would, in most cases, require that the financial disclosure be relevant to biomedical research or health care, as was recommended by one commentor, but the disclosure would not necessarily be limited to those fields, because other types of financial interests could reasonably appear to be affected by the PHS-funded research.

Exclusion of Financial Interests

There were few specific comments on the questions relating to the exclusion from the definition of Significant Financial Interest of equity interests in, or compensation from, the applicant institution. The general comments on the definition emphasized the need for limiting disclosures to financial interests related to the research proposed for PHS funding. We are retaining the exclusion for all remuneration paid to an investigator by an applicant institution and the exclusion of any ownership interest in the applicant institution if it is an

applicant under the SBIR or STTR program. We have not expanded the exclusion for ownership interests to encompass all institutions, because we believe there may be situations in which an ownership interest in a for-profit applicant could be in conflict with the investigator's responsibility for the conduct of the PHS-funded research and that ownership interest should be subject to appropriate institutional review. Experience under the regulations may prove this reasoning to be incorrect. If so, we will consider appropriate amendments to the regulations.

Regulatory Impact

The Department has concluded that this rule is not economically significant under Executive Order 12866 and that it thus does not require the development of a comprehensive benefit-cost analysis. While we agree with comments received that the initial estimate of implementation costs was low, none of these comments indicated that the costs would exceed \$100 million annually; in addition, changes made in the final regulations will reduce implementation costs. Commentors did not provide any evidence that the rule will hamper desirable research or otherwise have an adverse effect on the conduct of research under PHS-funded grants or on the consequent technological progress that is so important to the Nation's economy.

Executive Order 12866 requires that the Office of Management and Budget (OMB) review all regulations that may create a serious inconsistency with or otherwise interfere with an action taken or planned by another Federal agency. This rule was thus reviewed by OMB and coordinated with the policy of the NSF on this subject (see the notice of technical changes in NSF policy published elsewhere in this separate part of this **Federal Register**).

The Department prepares a regulatory flexibility analysis, in accordance with the Regulatory Flexibility Act of 1980 (5 U.S.C. chapter 6), if a rule is expected to have a significant impact on a substantial number of small entities. Although we have not followed the NSF approach of exempting entities with 50 or fewer employees, we have concluded that the regulation will not have a significant impact on small entities. Any such effect is mitigated by the provisions of the regulations and the fact that the regulations impose obligations primarily on those receiving grants that can be used, in part (amounts for indirect costs), to offset the costs of compliance with the regulatory

requirements. The regulations do not apply to SBIR and STTR Phase I applications. These programs are for small businesses and the Phase I grants are for limited amounts. Phase II grants are for larger amounts and thus more funds would be available for meeting the costs of compliance. Furthermore, we have changed the regulations to reduce burdens and costs of compliance for all entities subject to the regulations by eliminating more financial interests from consideration and by reducing burdens upon institutions through changes in the certification requirements. Institutions do not have to take action to identify, report and manage conflicting interests until after being notified by the PHS Awarding Agency of its decision to award funds.

For the same reasons, this rule will not create an unfunded mandate on State-owned institutions and thus would not trigger the requirements of Executive Order 12875 on "Enhancing the Intergovernmental Partnership." The proposed rule has been changed to significantly reduce burdens on institutions and, as noted above, institutions will be able to use amounts awarded for indirect costs to meet the costs of implementing the regulations.

Paperwork Reduction Act

The final rules contain information collection requirements that are subject to review by OMB under the Paperwork Reduction Act of 1980. The title, description, and respondent description applicable to the information collection are shown below with an estimate of the annual reporting and recordkeeping burden. These estimates have been revised in light of the comments on the proposed rules and the changes in the regulations. Consistent with the comments and a thorough consideration of the potential burdens imposed by the reporting, recordkeeping and disclosure requirements of the regulations, the statement of the burden has been reduced from that stated in the NPRM, based upon changes in the regulations that will significantly reduce the burdens on institutions and upon more accurate estimates of the burdens imposed by specific requirements.

The mean hours per response for initial reports of conflicts of interest have been significantly increased to account for the review by the institution of all the financial disclosures relating to an award. Although not more than 200 reports of conflicts of interest are expected, the institutions will need to review all financial disclosures associated with PHS funding awards to determine whether or not any conflicts of interest exist. Thus, the total burden

of 16,000 hours is based on estimates that it will take, on the average, four-fifths of an hour to review each of the 20,000 financial disclosures associated with PHS funding awards. If the number of disclosures is reduced because of the increase in the amount of the threshold for significance, the burden may be an overestimate.

The burden for subsequent reports of conflicts (made during the twelve month period after the initial report) is significantly less, because we do not expect many additional reportable conflicts and there will be only a limited number of disclosures to review.

We have significantly reduced the respondent number for reporting that failure of an investigator to comply with the institution's conflict of interest policy has biased the design, conduct or reporting of the research (§ 50.606(a)). We have estimated there will be no more than five such instances and we think that is a generous estimate.

For recordkeeping, we have listed the number of files expected to be necessary, rather than the number of institutions, because it will result in a more accurate estimation. The 20,000 figure is based upon 35,000 awards annually, reduced to account for those investigators who will not have any disclosures (no files are required to be established) and those investigators with more than one award. We have estimated it will take four hours, on the average, for the establishment and maintenance of each file. Although we believe this to be a very generous estimate, we note that it will include the time of both administrative and clerical personnel.

The burden figures for informing each investigator of the institution's policy are based upon 2,000 recipient institutions and 20 hours for the performance of this function. This time burden could be reduced even further if institutions choose to inform investigators through a notice in the grant application procedures. This method of notification would be acceptable because the regulations do not specify the method of notification.

The financial disclosures burden estimate (§ 50.604(c)) is based upon an investigator figure of 35,000 with an average response time of one hour. We believe experience may show that the number of disclosures will be significantly less because of the increases in the reporting threshold. Note that we have not attempted to calculate the overall hours spent by the institution to establish the necessary administrative mechanisms to comply with the regulations. The estimates are for burdens imposed by disclosure,

reporting and recordkeeping requirements, not all activities of an institution that may result from the regulations.

Title: Responsibility of Applicants for Promoting Objectivity in Research for which Public Health Service (PHS) Funding is Sought.

Description: The regulations would require each applicant/offeree Institution to establish procedures to identify and manage, reduce, or eliminate any conflicting financial interest of an Investigator involved in the design, conduct or reporting of the

research for which PHS funding is sought.

Description of Respondents: Public and private non-profit institutions, small business, and other for-profit organizations and investigators working for such institutions, businesses and organizations.

ESTIMATED ANNUAL REPORTING AND RECORDKEEPING BURDEN

Applicable section of regulation 42 CFR	Applicable section of regulation 45 CFR	Total number of respondents	Mean hours per response	Total hours 42 CFR	Total hours 45 CFR	Total hours
Reporting:						
50.604(g)(2) (initial report of conflict of interest)	94.4(g)(2)	200	80.0	14,000	2,000	16,000
50.604(g)(2) (subsequent reports of conflict of interest).	94.4(g)(2)	30	2.0	54	6	60
50.606(a)	94.6(a)	5	10.0	40	10	50
Total						16,110
Recordkeeping:						
50.604(e)	94.4(e)	20,000	4	72,000	8,000	80,000
Total						80,000
Disclosure:						
50.604(a)	94.4(a)	2,000	20.0	36,000	4,000	40,000
50.604(c)	94.4(c)	35,000	1	31,600	3,400	35,500
Total						75,000
Total Burden						171,110

In accordance with the requirements of the Paperwork Reduction Act of 1980, the Department of Health and Human Services has submitted the information collection requirements cited above to OMB for review and approval. Organizations and individuals desiring to submit comments on the information collection requirements and the estimated burden should direct such comments to the information address cited above and to: NIH/PHS Desk Officer, Office of Information and Regulatory Affairs, OMB, New Executive Office Building, room 10235, 725 17th Street NW., Washington, DC 20503.

Catalogue of Federal Domestic Assistance

The rule will affect all extramural research, research and development, and research and development support funded by the Public Health Service. Questions about the rule should be directed to Dr. George J. Galasso, Associated Director for Extramural Affairs, National Institutes of Health, Building 1, Room 552, 9000 Rockville Pike, MSC 0154, Bethesda, MD 20892-0154. The telephone number is (301) 496-5356 (this is not a toll-free number).

List of Subjects

42 CFR Part 50

Grant programs—health; Conflict of interest; Medical research; Behavioral, biological, biochemical, psychological and psychiatric research.

45 CFR Part 94

Government procurement.

Dated: March 13, 1995.

Philip R. Lee,

Assistant Secretary for Health.

Approved: May 17, 1995.

Donna E. Shalala,

Secretary.

Accordingly, 42 CFR part 50 and 45 CFR subtitle A are amended as set forth below:

1. Subpart F is added to 42 CFR part 50 to read as follows:

Subpart F—Responsibility of Applicants for Promoting Objectivity in Research for Which PHS Funding Is Sought

Sec.

- 50.601 Purpose.
- 50.602 Applicability.
- 50.603 Definitions.
- 50.604 Institutional responsibility regarding conflicting interests of investigators.
- 50.605 Management of conflicting interests.
- 50.606 Remedies.
- 50.607 Other HHS regulations that apply.

Authority: 42 U.S.C. 216, 289b-1, 299c-3.

Subpart F—Responsibility of Applicants for Promoting Objectivity in Research for Which PHS Funding Is Sought

§ 50.601 Purpose.

This subpart promotes objectivity in research by establishing standards to ensure there is no reasonable expectation that the design, conduct, or reporting of research funded under PHS grants or cooperative agreements will be biased by any conflicting financial interest of an Investigator.

§ 50.602 Applicability.

This subpart is applicable to each Institution that applies for PHS grants or cooperative agreements for research and, through the implementation of this subpart by each Institution, to each Investigator participating in such research (see § 50.604(a)); provided, that this subpart does not apply to SBIR Program Phase I applications. In those few cases where an individual, rather than an institution, is an applicant for PHS grants or cooperative agreements for research, PHS Awarding Components will make case-by-case determinations on the steps to be taken to ensure that the design, conduct, and reporting of the research will not be biased by any conflicting financial interest of the individual.

§ 50.603 Definitions.

As used in this subpart:

HHS means the United States Department of Health and Human Services, and any components of the Department to which the authority involved may be delegated.

Institution means any domestic or foreign, public or private, entity or organization (excluding a Federal agency).

Investigator means the principal investigator and any other person who is responsible for the design, conduct, or reporting of research funded by PHS, or proposed for such funding. For purposes of the requirements of this subpart relating to financial interests, "Investigator" includes the Investigator's spouse and dependent children.

PHS means the Public Health Service, an operating division of the U.S. Department of Health and Human Services, and any components of the PHS to which the authority involved may be delegated.

PHS Awarding Component means the organizational unit of the PHS that funds the research that is subject to this subpart.

Public Health Service Act or *PHS Act* means the statute codified at 42 U.S.C. 201 *et seq.*

Research means a systematic investigation designed to develop or contribute to generalizable knowledge relating broadly to public health, including behavioral and social-sciences research. The term encompasses basic and applied research and product development. As used in this subpart, the term includes any such activity for which research funding is available from a PHS Awarding Component through a grant or cooperative agreement, whether authorized under the PHS Act or other statutory authority.

Significant Financial Interest means anything of monetary value, including but not limited to, salary or other payments for services (e.g., consulting fees or honoraria); equity interests (e.g., stocks, stock options or other ownership interests); and intellectual property rights (e.g., patents, copyrights and royalties from such rights). The term does not include:

- (1) Salary, royalties, or other remuneration from the applicant institution;
- (2) Any ownership interests in the institution, if the institution is an applicant under the SBIR Program;
- (3) Income from seminars, lectures, or teaching engagements sponsored by public or nonprofit entities;

(4) Income from service on advisory committees or review panels for public or nonprofit entities;

(5) An equity interest that when aggregated for the Investigator and the Investigator's spouse and dependent children, meets both of the following tests: Does not exceed \$10,000 in value as determined through reference to public prices or other reasonable measures of fair market value, and does not represent more than a five percent ownership interest in any single entity; or

(6) Salary, royalties or other payments that when aggregated for the Investigator and the Investigator's spouse and dependent children over the next twelve months, are not expected to exceed \$10,000.

Small Business Innovation Research (SBIR) Program means the extramural research program for small business that is established by the Awarding Components of the Public Health Service and certain other Federal agencies under Pub. L. 97-219, the Small Business Innovation Development Act, as amended. For purposes of this subpart, the term SBIR Program includes the Small Business Technology Transfer (STTR) Program, which was established by Pub. L. 102-564.

§ 50.604 Institutional responsibility regarding conflicting interests of investigators.

Each Institution must:

(a) Maintain an appropriate written, enforced policy on conflict of interest that complies with this subpart and inform each Investigator of that policy, the Investigator's reporting responsibilities, and of these regulations. If the Institution carries out the PHS-funded research through subgrantees, contractors, or collaborators, the Institution must take reasonable steps to ensure that Investigators working for such entities comply with this subpart, either by requiring those Investigators to comply with the Institution's policy or by requiring the entities to provide assurances to the Institution that will enable the Institution to comply with this subpart.

(b) Designate an institutional official(s) to solicit and review financial disclosure statements from each Investigator who is planning to participate in PHS-funded research.

(c)(1) Require that by the time an application is submitted to PHS each Investigator who is planning to participate in the PHS-funded research has submitted to the designated official(s) a listing of his/her known Significant Financial Interests (and

those of his/her spouse and dependent children):

(i) That would reasonably appear to be affected by the research for which PHS funding is sought; and

(ii) In entities whose financial interests would reasonably appear to be affected by the research.

(2) All financial disclosures must be updated during the period of the award, either on an annual basis or as new reportable Significant Financial Interests are obtained.

(d) Provide guidelines consistent with this subpart for the designated official(s) to identify conflicting interests and take such actions as necessary to ensure that such conflicting interests will be managed, reduced, or eliminated.

(e) Maintain records of all financial disclosures and all actions taken by the Institution with respect to each conflicting interest for at least three years from the date of submission of the final expenditures report or, where applicable, from other dates specified in 45 CFR 74.53(b) for different situations.

(f) Establish adequate enforcement mechanisms and provide for sanctions where appropriate.

(g) Certify, in each application for the funding to which this subpart applies, that:

(1) There is an effect at that Institution a written and enforced administrative process to identify and manage, reduce or eliminate conflicting interests with respect to all research projects for which funding is sought from the PHS,

(2) Prior to the Institution's expenditure of any funds under the award, the Institution will report to the PHS Awarding Component the existence of a conflicting interest (but not the nature of the interest or other details) found by the institution and assure that the interest has been managed, reduced or eliminated in accordance with this subpart; and, for any interest that the Institution identifies as conflicting subsequent to the Institution's initial report under the award, the report will be made and the conflicting interest managed, reduced, or eliminated, at least on an interim basis, within sixty days of that identification;

(3) The Institution agrees to make information available, upon request, to the HHS regarding all conflicting interests identified by the Institution and how those interests have been managed, reduced, or eliminated to protect the research from bias; and

(4) The Institution will otherwise comply with this subpart.

§ 50.605 Management of conflicting interests.

(a) The designated official(s) must: Review all financial disclosures; and determine whether a conflict of interest exists and, if so, determine what actions should be taken by the institution to manage, reduce or eliminate such conflict of interest. A conflict of interest exists when the designated official(s) reasonably determines that a Significant Financial Interest could directly and significantly affect the design, conduct, or reporting of the PHS-funded research. Examples of conditions or restrictions that might be imposed to manage conflicts of interest include, but are not limited to:

- (1) Public disclosure of significant financial interests;
- (2) Monitoring of research by independent reviewers;
- (3) Modification of the research plan;
- (4) Disqualification from participation in all or a portion of the research funded by the PHS;
- (5) Divestiture of significant financial interests; or
- (6) Severance of relationships that create actual or potential conflicts.

(b) In addition to the types of conflicting financial interests described in this paragraph that must be managed, reduced, or eliminated, an Institution may require the management of other conflicting financial interests, as the Institution deems appropriate.

§ 50.606 Remedies.

(a) If the failure of an Investigator to comply with the conflict of interest policy of the Institution has biased the design, conduct, or reporting of the PHS-funded research, the Institution must promptly notify the PHS Awarding Component of the corrective action taken or to be taken. The PHS Awarding Component will consider the situation and, as necessary, take appropriate action, or refer the matter to the Institution for further action, which may include directions to the Institution on how to maintain appropriate objectivity in the funded project.

(b) The HHS may at any time inquire into the Institutional procedures and actions regarding conflicting financial interests in PHS-funded research, including a requirement for submission of, or review on site, all records pertinent to compliance with this subpart. To the extent permitted by law, HHS will maintain the confidentiality of all records of financial interests. On the basis of its review of records and/or other information that may be available, the PHS Awarding Component may decide that a particular conflict of interest will bias the objectivity of the

PHS-funded research to such an extent that further corrective action is needed or that the Institution has not managed, reduced, or eliminated the conflict of interest in accordance with this subpart. The PHS Awarding Component may determine that suspension of funding under 45 CFR 74.62 is necessary until the matter is resolved.

(c) In any case in which the HHS determines that a PHS-funded project of clinical research whose purpose is to evaluate the safety or effectiveness of a drug, medical device, or treatment has been designed, conducted, or reported by an Investigator with a conflicting interest that was not disclosed or managed as required by this subpart, the Institution must require the Investigator(s) involved to disclose the conflicting interest in each public presentation of the results of the research.

§ 50.607 Other HHS regulations that apply.

Several other regulations and policies apply to this subpart.

They include, but are not necessarily limited to:

- 42 CFR Part 50, Subpart D—Public Health Service grant appeals procedure
- 45 CFR Part 16—Procedures of the Departmental Grant Appeals Board
- 45 CFR Part 74—Uniform Administrative Requirements for Awards and Subawards to Institutions of Higher Education, Hospitals, Other Non-Profit Organizations, and Commercial Organizations; and Certain Grants and Agreements with States, Local Governments and Indian Tribal Governments
- 45 CFR Part 76—Government-wide debarment and suspension (non-procurement)
- 45 CFR Part 79—Program Fraud Civil Remedies
- 45 CFR Part 92—Uniform Administrative Requirements for Grants and Cooperative Agreements to State and Local Governments

2. A new part 94 is added to 45 CFR, subtitle A, to read as follows:

PART 94—RESPONSIBLE PROSPECTIVE CONTRACTORS

Sec.

- 94.1 Purpose.
- 94.2 Applicability.
- 94.3 Definitions.
- 94.4 Institutional Responsibility Regarding Conflicting Interests of Investigators.
- 94.5 Management of Conflicting Interests.
- 94.6 Remedies.

Authority: 42 U.S.C. 216, 289b-1, 299c-3.

§ 94.1 Purpose.

This part promotes objectivity in research by establishing standards to ensure there is no reasonable expectation that the design, conduct, or reporting of research to be performed

under PHS contracts will be biased by any conflicting financial interest of an Investigator.

§ 94.2 Applicability.

This part is applicable to each Institution that seeks PHS funding for research and, through the implementation of this part, to each Investigator who participates in such research (see § 94.4(a)); provided that this part does not apply to SBIR Program Phase I applications.

§ 94.3 Definitions.

As used in this part:

Contractor means an entity that provides property or services for the direct benefit or use of the Federal Government.

HHS means the United States Department of Health and Human Services, and any components of the Department to which the authority involved may be delegated.

Institution means any public or private entity or organization (excluding a Federal agency)

(1) That submits a proposal for a research contract whether in response to a solicitation from the PHS or otherwise, or

(2) That assumes the legal obligation to carry out the research required under the contract.

Investigator means the principal investigator and any other person who is responsible for the design, conduct, or reporting of a research project funded by PHS, or proposed for such funding. For purposes of the requirements of this part relating to financial interests, "Investigator" includes the Investigator's spouse and dependent children.

PHS means the Public Health Service, an operating division of the U.S. Department of Health and Human Services, and any components of the PHS to which the authority involved may be delegated.

Public Health Service Act or *PHS Act* mean the statute codified at 42 U.S.C. 201 *et seq.*

PHS Awarding Component means an organizational unit of the PHS that funds research that is subject to this part.

Research means a systematic investigation designed to develop or contribute to generalizable knowledge relating broadly to public health, including behavioral and social-sciences research. The term encompasses basic and applied research and product development. As used in this part, the term includes any such activity for which funding is available from a PHS Awarding Component, whether

authorized under the PHS Act or other statutory authority.

Significant Financial Interest means anything of monetary value, including but not limited to, salary or other payments for services (e.g., consulting fees or honoraria); equity interests (e.g., stocks, stock options or other ownership interests); and intellectual property rights (e.g., patents copyrights and royalties from such rights). The term does not include:

- (1) Salary, royalties, or other remuneration from the applicant institution;
- (2) Any ownership interests in the institution, if the institution is an applicant under the SBIR program;
- (3) Income from seminars, lectures, or teaching engagements sponsored by public or nonprofit entities;
- (4) Income from service on advisory committees or review panels for public or nonprofit entities;
- (5) An equity interest that when aggregated for the Investigator and the Investigator's spouse and dependent children, meets both of the following tests: Does not exceed \$10,000 in value as determined through reference to public prices or other reasonable measures of fair market value, and does not represent more than a five percent ownership interest in any single entity; or
- (6) Salary, royalties or other payments that when aggregated for the investigator and the investigator's spouse and dependent children over the next twelve months, are not reasonably expected to exceed \$10,000.

Small Business Innovation Research (SBIR) Program means the extramural research program for small business that is established by the awarding components of the Public Health Service and certain other Federal agencies under Public Law 97-219, the Small Business Innovation Development Act, as amended. For purposes of this part, the term SBIR Program includes the Small Business Technology Transfer (STTR) Program, which was established by Public Law 102-564.

§ 94.4 Institutional responsibility regarding conflicting interests of investigators.

Each Institution must:

- (a) Maintain an appropriate written, enforced policy on conflict of interest that complies with this part and inform each Investigator of that policy, the Investigator's reporting responsibilities, and of these regulations. If the Institution carries out the PHS-funded research through subcontractors, or collaborators, the Institution must take reasonable steps to ensure that Investigators working for such entities

comply with this part, either by requiring those Investigators to comply with the Institution's policy or by requiring the entities to provide assurances to the Institution that will enable the Institution to comply with this part.

(b) Designate an institutional official(s) to solicit and review financial disclosure statements from each Investigator who is planning to participate in PHS-funded research.

(c)(1) Require that by the time an application is submitted to PHS, each Investigator who is planning to participate in the PHS-funded research has submitted to the designated official(s) a listing of his/her known Significant Financial Interests (and those of his/her spouse and dependent children):

- (i) that would reasonably appear to be affected by the research for which PHS funding is sought; and
- (ii) in entities whose financial interests would reasonably appear to be affected by the research.

(2) All financial disclosures must be updated during the period of the award, either on an annual basis or as new reportable Significant Financial Interests are obtained.

(d) Provide guidelines consistent with this part for the designated official(s) to identify conflicting interests and take such actions as necessary to ensure that such conflicting interests will be managed, reduced, or eliminated.

(e) Maintain records of all financial disclosures and all actions taken by the Institution with respect to each conflicting interest for three years after final payment or, where applicable, for the other time periods specified in 48 CFR part 4, subpart 4.7.

(f) Establish adequate enforcement mechanisms and provide for sanctions where appropriate.

(g) Certify, in each contract proposal, that:

(1) there is in effect at that Institution a written and enforced administrative process to identify and manage, reduce or eliminate conflicting interests with respect to all research projects for which funding is sought from the PHS;

(2) prior to the Institution's expenditure of any funds under the award, the Institution will report to the PHS Awarding Component the existence of any conflicting interest (but not the nature of the interest or other details) found by the Institution and assure that the interest has been managed, reduced or eliminated in accordance with this part; and, for any interest that the Institution identifies as conflicting subsequent to the Institution's initial report under the

award, the report will be made and the conflicting interest managed, reduced, or eliminated, at least on an interim basis, within sixty days of that identification.

(3) the Institution agrees to make information available, upon request, to the HHS regarding all conflicting interests identified by the Institution and how those interests have been managed, reduced, or eliminated to protect the research from bias; and

(4) the Institution will otherwise comply with this part.

§ 94.5 Management of conflicting interests.

(a) The designated official(s) must: Review all financial disclosures; and determine whether a conflict of interest exists, and is so, what actions should be taken by the institution to manage, reduce, or eliminate such conflict of interest. A conflict of interest exists when the designated official(s) reasonably determines that a Significant Financial Interest could directly and significantly affect the design, conduct, or reporting of the PHS-funded research. Examples of conditions or restrictions that might be imposed to manage conflicts of interest include, but are not limited to:

- (1) Public disclosure of significant financial interests;
- (2) Monitoring of the research by independent reviewers;
- (3) Modification of the research plan;
- (4) Disqualification from participation in all or a portion of the research funded by the PHS;
- (5) Divestiture of significant financial interests, or;
- (6) Severance of relationships that create actual or potential conflicts.

(b) In addition to the types of conflicting financial interests described in this paragraph that must be managed, reduced, or eliminated, an Institution may require the management of other conflicting financial interests, as the Institution deems appropriate.

§ 94.6 Remedies.

(a) If the failure of an Investigator to comply with the conflict of interest policy of the Institution has biased the design, conduct, or reporting of the PHS-funded research, the Institution must promptly notify the PHS Awarding Component of the corrective action taken or to be taken. The PHS Awarding Component will consider the situation and, as necessary, take appropriate action or refer the matter to the institution for further action, which may include directions to the Institution on how to maintain appropriate objectivity in the funded project.

(b) The HHS may at any time inquire into the Institutional procedures and actions regarding conflicting financial interests in PHS-funded research, including a review of all records pertinent to compliance with this part. HHS may require submission of the records or review them on site. To the extent permitted by law HHS will maintain the confidentiality of all records of financial interests. On the basis of its review of records and/or other information that may be available,

the PHS Awarding Component may decide that a particular conflict of interest will bias the objectivity of the PHS-funded research to such an extent that further corrective action is needed or that the Institution has not managed, reduced, or eliminated the conflict of interest in accordance with this part. The issuance of a Stop Work Order by the Contracting Officer may be necessary until the matter is resolved.

(c) In any case in which the HHS determines that a PHS-funded project of

clinical research whose purpose is to evaluate the safety or effectiveness of a drug, medical device, or treatment has been designed, conducted, or reported by an Investigator with a conflicting interest that was not disclosed or managed as required by this part, the Institution must require disclosure of the conflicting interest in each public presentation of the results of the research.

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