Guidance for Clinical Investigators, Industry, and FDA Staff

Financial Disclosure by Clinical Investigators

U.S. Department of Health and Human Services
Food and Drug Administration
Office of Good Clinical Practice
Center for Drug Evaluation and Research
Center for Biologics Evaluation and Research
Center for Devices and Radiological Health

February 2013

Contains Nonbinding Recommendations

Guidance for Clinical Investigators, Industry, and FDA Staff Financial Disclosure by Clinical Investigators

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This guidance represents the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

I. INTRODUCTION

This guidance is intended to assist clinical investigators, industry, and FDA staff in interpreting and complying with the regulations governing financial disclosure by clinical investigators, 21 CFR part 54. This document is a revision of the *Guidance for Industry: Financial Disclosure by Clinical Investigators* dated March 20, 2001. In order to address issues raised by the Office of the Inspector General (OIG), Department of Health and Human Services, in its report, OEI-05-07-00730, *The Food and Drug Administration's Oversight of Clinical Investigators' Financial Information*[2] as well as questions FDA has received from industry and the public, FDA issued a revised guidance in draft in May 2011 for public comment. Comments were received from 13 individuals and entities, which were considered in preparing this final guidance. FDA encourages applicants and sponsors to contact the agency for advice concerning specific circumstances regarding financial disclosures that may raise concerns as early in the product development process as possible.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in agency guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

The Financial Disclosure by Clinical Investigators regulation (21 CFR part 54) requires applicants who submit a marketing application for a drug, biological product or device to submit certain information concerning the compensation to, and financial interests and arrangements of, any clinical investigator conducting clinical studies covered by the regulation (see generally the

[1] This revised guidance was prepared by the Office of the Commissioner, with input from the Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER) and Center for Devices and Radiological Health (CDRH).

[2] The OIG's report is available at http://oig.hhs.gov/oei/reports/oei-05-07-00730.pdf.

purpose of the regulation at 21 CFR § 54.1). The regulation, which became effective on February 2, 1999, applies to clinical studies submitted in a marketing application, including a supplement or amendment to an original application, that the applicant or FDA relies on to establish that the product is effective, and any study in which a single investigator makes a significant contribution to the demonstration of safety (21 CFR §§ 54.2(e) and 54.3). The regulation requires applicants to certify the absence of certain financial interests and arrangements of clinical investigators that could affect the reliability of data submitted to FDA, or to disclose those financial interests and arrangements to the agency and identify steps taken to minimize the potential for bias (21 CFR § 54.4(a)). If the applicant does not include certification and/or disclosure, or does not certify that it was unable to obtain the information despite exercising due diligence, the agency may refuse to file the application (21 CFR § 54.4(c)).

III. FINANCIAL DISCLOSURE REQUIREMENTS

Under the applicable regulations,[3] an applicant is required to submit to FDA a list of all clinical investigators who conducted covered clinical studies and to identify those who are full-time or part-time employees of the sponsor of each covered study (21 CFR § 54.4). For each clinical investigator who was not a full-time or part-time employee of a sponsor of the clinical study, the applicant must provide either a certification, using FORM FDA 3454, that none of the financial interests or arrangements described in 21 CFR § 54.4(a)(3) (see Section III.B. below) exists, or completely and accurately disclose, using FORM FDA 3455, the nature of those interests and arrangements to the agency and describe any steps taken to minimize the potential for bias resulting from those interests and arrangements (21 CFR § 54.4(a)). If the applicant acts with due diligence to obtain the required information but is unable to do so, the applicant may certify that it acted with due diligence but was unable to obtain the information and include the reason the information could not be obtained (21 CFR § 54.4).

FDA generally expects that applicants will be able to provide this information. Under 21 CFR §§ 312.53(c), 812.20(b)(5) and 812.43(c), a sponsor is required to obtain clinical investigator financial information before allowing the clinical investigator to participate in a covered clinical study. Under 21 CFR § 54.4(b), each clinical investigator who is not a full-time or part-time employee of the sponsor of the covered clinical study is required to provide the sponsor with sufficient accurate financial information to allow for complete disclosure or certification and to update this information if any relevant changes occur during the study and for one year following its completion.

A. Definitions

Clinical Investigator – For purposes of part 54, "clinical investigator" means a "listed or identified investigator or subinvestigator who is directly involved in the treatment or evaluation of research subjects," including the spouse and each dependent child of the investigator or subinvestigator. (See 21 CFR § 54.2(d).) See Section IV.D, Clinical Investigator, for additional information. Clinical investigators are included in the definition even if they did not participate for the entire length of the study. If a clinical investigator did not participate in the entire study,

[3] 21 CFR parts 54, 312, 314, 320, 330, 601, 807, 812, 814, and 860

information collected should be for the period of time he or she participated in the study and for one year following the end of his or her participation.

Covered clinical study – The part 54 regulations define "covered clinical study" to mean "any study of a drug or device in humans submitted in a marketing application or reclassification petition subject to this part that the applicant or FDA relies on to establish that the product is effective (including studies that show equivalence to an effective product) or any study in which a single investigator makes a significant contribution to the demonstration of safety. This would, in general, 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." (See 21 CFR § 54.2(e).) This definition includes clinical studies submitted in support of new drug applications (NDAs) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), abbreviated new drug applications (ANDAs) under section 505(j) of the FD&C Act, premarket notification submissions under section 510(k) of the FD&C Act, reclassification petitions under section 513 of the FD&C Act, premarket approval applications (PMAs) under section 515 of the FD&C Act, and biologics licensing applications (BLAs) submitted under section 351 of the Public Health Services Act (PHS Act), as well as studies submitted in support of amendments or supplements to any such applications. (See 21 CFR §§ 54.3 and 54.4(a).) Covered clinical studies would generally not include expanded access under section 561 of the FD&C Act. If an applicant is unsure of whether a particular study is included in this definition, it may consult with FDA as to which clinical studies constitute "covered clinical studies" for purposes of complying with financial disclosure requirements. (21 CFR § 54.2(e).) See Section IV.G, Covered Clinical Study, for additional information.

Applicant – "Applicant" means the party who submits a marketing application to FDA for approval of a drug, device or biologic product or who submits a reclassification petition. The applicant is responsible for submitting the required certification and disclosure statements. (See 21 CFR § 54.2(g).) Note that for purposes of financial disclosure the term "applicant" includes "submitter" and the term "application" includes "510(k) submission." See Section IV.F, Applicant, for additional information.

Sponsor of the covered clinical study – For purposes of part 54, "sponsor of the covered clinical study" means "a party supporting a particular study at the time it was carried out." (See 21 CFR § 54.2(h).) A covered clinical study may have more than one sponsor for whom financial information will need to be collected. For example, if one party designed and conducted the covered clinical study, a second party provided funding, and a third party provided the test product, there would be three sponsors of the covered clinical study. However, if the third party in this example was reimbursed for the test product, it would not be considered a sponsor of the covered clinical study and the study would be considered to have two sponsors. Note also that the definition of "sponsor" for purposes of part 54 is different than the definition of "sponsor" for purposes of investigational new drug applications (INDs) and investigational device exemptions applications (IDEs) (see 21 CFR §§ 312.3(b) and 812.3(n)). See Section IV.E, Sponsor, for additional information.

B. Disclosable Financial Interests and Arrangements

The financial interests, arrangements, and payments that must be disclosed (see 21 CFR § 54.4(a)(3), referred to herein as "disclosable financial interests and arrangements") are described below.[4] Note that the dollar amounts that trigger reporting are the combined financial interests of the investigator, spouse, and dependent children.

1. Any compensation made to the investigator by any sponsor of the covered clinical study in which the value of compensation could be affected by study outcome.

2. A proprietary interest in the tested product including, but not limited to, a patent, trademark, copyright or licensing agreement.

3. Any equity interest in any sponsor of the covered clinical study, i.e., any ownership interest, stock options, or other financial interest whose value cannot be readily determined through reference to public prices. The requirement applies to interests held during the time the clinical investigator is carrying out the study and for one year following completion of the study.

4. Any equity interest in any sponsor of the covered study if the sponsor is a publicly held company and the interest exceeds $50,000 in value. The requirement applies to interests held during the time the clinical investigator is carrying out the study and for one year following completion of the study.

5. Significant payments of other sorts (SPOOS) are payments that have a cumulative monetary value of $25,000 or more and are made by any sponsor of a covered study to the investigator or the investigator's institution during the time the clinical investigator is carrying out the study and for one year following completion of the study. This would include payments that support activities of the investigator (e.g., a grant to the investigator or to the institution to fund the investigator's ongoing research or compensation in the form of equipment), exclusive of the costs of conducting the clinical study or other clinical studies, or to provide other reimbursements such as retainers for ongoing consultation or honoraria. See Section IV, Questions C.4, C.5, and C.6 for additional information on SPOOS.

C. Agency Actions

The agency may refuse to file a marketing application that does not contain the financial information required by 21 CFR part 54 or a certification by the applicant that the applicant has

[4] These are the requirements for studies begun on or after the effective date of the part 54 regulations, February 2, 1999. For older studies, the disclosure requirements vary based on the study's status as of the effective date of the regulation. For studies that were completed prior to February 2, 1999, disclosure of financial interests and arrangements described in paragraphs 1 through 3 is required. For studies ongoing as of February 2, 1999, disclosure of financial interests and arrangements described in paragraphs 1 through 4 is required as well as payments as described in paragraph 5 that were made on or after February 2, 1999. (See *Federal Register*, volume 63, December 31, 1998, page 72172-3.)

acted with due diligence to obtain the information but was unable to do so stating a sufficient reason. (21 CFR § 54.4(c).)

If FDA determines that the financial interests or arrangements of any clinical investigator raise a serious question about the integrity of the data, FDA will take any action it deems necessary to ensure the reliability of the data (21 CFR § 54.5(c)) including:

1. Initiating agency audits of the data derived from the clinical investigator in question;

2. Requesting that the applicant submit further analyses of data, e.g., to evaluate the effect of the clinical investigator's data on the overall study outcome;

3. Requesting that the applicant conduct additional independent studies to confirm the results of the questioned study; and

4. Refusing to treat the covered clinical study as providing data that can be the basis for an agency action.

IV. QUESTIONS AND ANSWERS

A. GENERAL

A.1. Q: Why did FDA develop the financial disclosure regulations?

A: In June 1991, the Inspector General of the Department of Health and Human Services submitted a management advisory report[5] to FDA stating that FDA's failure to have a mechanism for collecting information on "financial conflicts of interest" of clinical investigators who study products that undergo FDA review could constitute a material weakness under the Federal Managers' Financial Integrity Act. As stated in the preamble to the final rule, although FDA determined that a material weakness did not exist, the agency did conclude that there was a need to address this issue through regulation.[6] During the rulemaking process, FDA also learned about potentially problematic financial interests and arrangements through published newspaper articles, Congressional inquiries, and public testimony and comments. Based on the information gathered, FDA determined that it was appropriate to require the submission of certain financial information with marketing applications that, in part, rely on clinical data.

[5] Office of the Inspector General (OIG), Department of Health and Human Services (DHHS), *Management Advisory Report – Financial Involvement of Clinical Investigators with Sponsors of Research Leading to Food and Drug Administration Marketing Approval*, June 1991, OI-HQ-91-003.

[6] The final rule was published in the *Federal Register*, Vol. 63, February 2, 1998, pages 5233-5254. The referenced statement appears on page 5235.

A.2. Q: What is the purpose of FDA's review of clinical investigator financial disclosure information and how can sponsors minimize bias?

A: FDA's review of clinical investigator financial disclosure information alerts FDA staff to financial interests and arrangements that could lead to bias in covered clinical studies. The financial disclosure process also provides FDA with information regarding whether and to what extent the sponsors have taken steps to minimize the risk of bias. An important means of minimizing the potential for bias resulting from such financial interests and arrangements is through proper study design (see 21 CFR § 54.5(b)). For example, using randomization and blinding helps to minimize the potential for bias in assigning subjects to receive the test article or placebo and in assessing study outcomes and analyzing results. Similarly, having someone with no financial interests or arrangements evaluate study endpoints, especially in an unblinded study, can help minimize potential bias in assessing therapy outcomes.

FDA staff consider the financial disclosure information and the methods the sponsor used to minimize bias during the review of marketing applications to assess the reliability of the clinical data (see 21 CFR § 54.1). Additionally, because sponsors of studies conducted under INDs and IDEs are required to collect financial information from clinical investigators prior to study initiation,[7] sponsors can work with FDA to minimize any potential bias. FDA strongly encourages sponsors of studies not conducted under an IND/IDE to collect financial information prior to study initiation for the same reasons.

B. FORMS AND INFORMATION TO BE SUBMITTED

B.1. Q: What financial disclosure information is to be included in a marketing application?

A: The application must contain a list of all clinical investigators who conducted each covered clinical study (21 CFR § 54.4). For purposes of this list, investigators and subinvestigators who meet the definition of "clinical investigator" in 21 CFR § 54.2(d) must be included. Note that the term clinical investigator includes the spouse and each dependent child of a clinical investigator (21 CFR § 54.2(d)). This list must also identify those clinical investigators who are full or part-time employees of the sponsor of the covered study (21 CFR § 54.4). If a spouse or dependent child is an employee of a sponsor, that clinical investigator should be identified as an employee for purposes of financial disclosure. For each clinical investigator who is not identified as an employee of the sponsor, <u>one</u> of the following must be submitted (21 CFR § 54.4(a)):

[7] 21 CFR §§ 312.53(c)(4), 812.20(b)(5), and 812.43(c)

1. FORM FDA 3455, Disclosure Statement,[8] for each clinical investigator who, or whose spouse or dependent child, had disclosable financial interests in and/or arrangements with any sponsor of the covered clinical study. The form should include an attachment with detailed information about those financial interests and arrangements (for example, the nature of the contingent payment or the equity holdings of the investigator, or the investigator's spouse or dependent child, that exceeded the threshold) and a description of the steps taken to minimize the potential for bias resulting from the disclosed financial interests and arrangements (21 CFR § 54.4(a)(3)). See Section IV.C for additional information;

2. FORM FDA 3454, Certification, for any clinical investigator who has no disclosable financial interests in or arrangements with any sponsor of the covered clinical study (21 CFR § 54.4(a)(1)); the applicant may append a list of investigator names to a single FORM FDA 3454 for those investigators with no disclosable financial interests or arrangements; or

3. If the applicant was unable to obtain some or all of the financial information needed to disclose or certify for a clinical investigator, the applicant must identify any disclosable financial interests or arrangements of which it is aware, certify that it acted with due diligence to obtain the information (listed as option 3 on FORM FDA 3454), and include an attachment identifying the reason why any missing information could not be obtained (21 CFR § 54.4). FDA expects that in the vast majority of cases, applicants will be able to provide a complete financial Certification or Disclosure Statement and that the need to certify that they acted with due diligence will be rare. See Question B.7 and Question F.2 for additional information on due diligence.

FDA encourages applicants to submit financial disclosure information in a format that will ensure all required information is included. For example, applicants should provide the total number of investigators in the study and a table indicating, for each clinical investigator listed who is not identified as an employee, whether they are providing a Certification (FORM FDA 3454), a Disclosure Statement (FORM FDA 3455) or certification that they acted with due diligence but were unable to obtain the information (option 3 on FORM FDA 3454). Applicants should also ensure that all required attachments, as identified above, are included. Applicants with questions about acceptable formats for submitting the financial disclosure information should contact the Center representatives identified in Question K.1.

[8] As an alternative to a separate FORM FDA 3455 for each clinical investigator with information to disclose, applicants may submit a single FORM FDA 3455, with attachments clearly identifying all clinical investigators with information to disclose and, for each investigator, identifying the study, the specific details of their financial interests and arrangements and the steps taken to minimize the potential for bias. Applicants with questions about alternative formats should contact the Center representatives identified in Question K.1.

B.2. Q: May an applicant rely upon the policies and procedures of the clinical investigator's institution for disclosure, review and management of financial conflicts of interest of their employees (including spouse and dependent children)?

A: Each applicant is responsible for disclosing or certifying as required by 21 CFR part 54. Compliance with institutional policies or procedures by an investigator is not a substitute for compliance with part 54.

Although a clinical investigator's institution may take steps to manage a clinical investigator's financial interests and arrangements, in order to minimize study bias, FDA must make its own evaluation of the clinical investigator's financial interests and arrangements (21 CFR § 54.5). When a clinical investigator has disclosable financial interests and arrangements, the disclosure statement submitted to FDA is required to include a description of any steps taken to minimize the potential for bias resulting from any of the disclosed financial interests and arrangements (21 CFR 54.4(a)(3)(v)). A description of the steps taken by the institution to minimize bias should be included with the disclosure statement, if pertinent. See Section IV, Question D.7 for additional information.

B.3. Q: Where in a marketing application for a drug or a biological product should an applicant include the certification or disclosure forms and attachments?

A: Applicants using the format described in FORM FDA 356h (Application to Market a New Drug, Biologic, or an Antibiotic Drug for Human Use) should include the clinical investigator list and financial certification and/or disclosure forms and attachments as part of item 19 (Financial Information) of the application.[9] Applicants using the Common Technical Document (CTD) format should include this information in Module 1.3.4.[10]

B.4. Q: Where should the information be included in a device marketing application?

A: Applicants should submit the clinical investigator list and financial certification/disclosure forms and attachments according to the format outlined in the appropriate submission guidance.[11]

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[9] Application to Market a New Drug, Biologic, or an Antibiotic Drug for Human Use, available at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM082348.pdf.

[10] The eCTD Backbone Files Specification for Module 1, available at http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163552.pdf.

[11] For premarket notification submissions, see "Guidance for Industry and FDA Staff: Format for Traditional and Abbreviated 510(k)s," available at www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm084365.htm.
For premarket approval applications, see "Guidance for Industry and FDA Staff: Premarket Approval Application Filing Review," available at http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm089430.htm.

B.5. Q: How should the financial information be submitted?

A: The financial information is required to be submitted using FORMS FDA 3454 and/or 3455 (21 CFR § 54.4(a)), which are available on the Web at the following Internet address: http://www.fda.gov/AboutFDA/ReportsManualsForms/Forms/default.htm (Forms are listed in numerical order).

B.6. Q: Who, specifically, is responsible for signing the financial certification/disclosure forms?

A: The forms are to be signed and dated by the chief financial officer or other responsible corporate official or representative of the applicant. FDA recommends that the "other responsible corporate official or representative" be a senior official who has the authority to ensure the information is collected and reported accurately. Depending on company structure, such an individual could be the person in charge of regulatory or clinical affairs.

B.7. Q: What does FDA mean by the term "due diligence"?

A: "Due diligence" is a measure of activity expected from a reasonable and prudent person under a particular circumstance, in this case, collecting information about financial interests or arrangements. FDA expects that applicants will typically be able to obtain the required information because investigators are required to provide financial disclosure information to sponsors before participating in a clinical study. (21 CFR §§ 54.4, 312.53(c), 812.43(c) and 812.20(b)(5).) In the rare circumstance where applicants are unable to obtain required financial information, applicants must certify that they acted with due diligence and explain why the information was not obtainable (21 CFR § 54.4).

If all of the information required to make a complete certification or disclosure is not available from a sponsor, applicants should make appropriate efforts to obtain the information by other means. That may mean contacting an individual investigator or subinvestigator directly. If an investigator's whereabouts are unknown, for example because the investigator left a study prior to its completion or prior to one year following completion of the study, FDA recommends that sponsors and/or applicants try to locate the clinical investigator. Sponsors and applicants should exercise reasonable judgment regarding the appropriate amount of effort to expend when attempting to contact investigators, which may include consideration of the role of the investigator in the study and the importance of the investigator's data contribution.

In most cases, FDA suggests that more than one attempt at contacting an investigator would be appropriate and that more than one method of contact be attempted. FDA also recommends that each attempt to contact the investigator be documented, for example, by maintaining copies of e-mails and letters and documenting telephone calls and conversation by written memoranda. FDA also suggests that sponsors and applicants consider using a method of contacting investigators that allows verification of receipt, such as certified mail or reliable courier service that provides notice of recipient's receipt

of a letter. When such methods are used, copies of the delivery notice or undeliverable notice should be maintained.

If an investigator is no longer at the institution where the study was conducted, FDA recommends that the sponsor or applicant make a reasonable attempt to locate the investigator, for example, by requesting contact information from the institution where the study was conducted or the institution with which the investigator was affiliated, contacting professional associations the investigator may have been affiliated with, and/or conducting Internet searches.

If a clinical investigator cannot be located or information for some other reason cannot be obtained from the investigator, the sponsor should have access to certain disclosable financial information and arrangements, for example, payments made specifically to the investigator or information related to product sales that may generate royalties due to the investigator. On request from an applicant, sponsors should check their records for such information and, subject to any privacy laws (noting that other countries' laws may differ from United States law), the sponsor should then provide disclosable information to the applicant. In addition, and as necessary, efforts should be made to obtain disclosable financial information from other reasonably available, reliable, public sources of information. For example, information on proprietary interests in the test product, such as patents and trademarks, should be available from publicly available sources.[12] Another possible source of information is the clinical investigator's institution, which may have collected financial information and, if consistent with their policies, may release this information to the applicant upon request. Appropriate certifications, disclosures, and/or explanations should be provided to FDA on the basis of information obtained. See Question F.2 for additional information.

An applicant must exercise due diligence whether a covered study is conducted at foreign or domestic sites. The agency expects that a reasonable and prudent applicant will take affirmative steps at the first opportunity to see that the financial information required for a complete certification or disclosure under part 54 is collected and maintained. This is not only to ensure that the applicant will be able to make a complete submission but also to ensure that the study sponsor will take steps to protect the study against possible bias. See Questions E.3, E.5, and F.3 for additional information.

B.8. Q: Is clinical investigator financial disclosure information required in IND or IDE applications?

A: No, IND/IDE sponsors are not required to submit information regarding clinical investigator financial interests or arrangements in IND or IDE applications. They are, however, required to collect this information before a clinical investigator participates in a clinical study (see 21 CFR §§ 312.53(c)(4), 812.20(b)(5), and 812.43(c)(5)), and

[12] Such sources include the Patent and Trademark Office website and, once available, the federal reporting website proposed by the Centers for Medicare & Medicaid Services as required by Section 6002 of the Patient Protection and Affordable Care Act. See the final rule, "Transparency Reports and Reporting of Physician Ownership or Investment Interests," *Federal Register*, Vol. 78, February 8, 2013, page 9458.

clinical investigators are required to disclose financial information to sponsors (see 21 CFR §§ 312.64(d) and 812.110(d)). The information need not be submitted to FDA until a marketing application is submitted containing the results of the covered clinical study (21 CFR § 54.4).

Study sponsors are encouraged to consult with FDA prior to and during clinical studies about the management of specific situations involving potential bias on the part of a clinical investigator. During these consultations, FDA staff should focus on the protection of research subjects and the minimization of bias from all potential sources.

C. FINANCIAL INTERESTS AND ARRANGEMENTS SUBJECT TO DISCLOSURE

C.1. Q: What information about a financial interest or arrangement should be disclosed to the agency? For example, if an investigator owns more than $50,000 of stock in a publicly held company, can the applicant just disclose that there is an interest that exceeds the $50,000 threshold or is it necessary to disclose in written detail the interest or arrangement in question?

A: The applicant must make a complete and accurate disclosure (21 CFR § 54.4(a)(3)). The specific details of the financial interest or arrangement, including its size and nature, should be disclosed as should any steps taken to minimize the potential for study bias resulting from the interest or arrangement. In describing financial interests, for example, the applicant might list: stock valued at $77,000, speaking fees of $7,500, consulting fees of $22,000, and a grant of $125,000 and include a discussion of the specific steps taken to minimize potential bias. Sponsors should request that clinical investigators provide sufficient detail about their financial disclosure information to allow the appropriate disclosures to be made.

C.2. Q: Should a clinical investigator report all fluctuations above and below the $50,000 level during the course of the investigation and one year after completion of the study?

A: In light of the potential volatility of stock prices, FDA recognizes that the dollar value of an investigator's equity holding in a sponsoring company is likely to fluctuate during the course of a study. Clinical investigators should report an equity interest when the investigator becomes aware that the holding has exceeded the threshold and the investigator should use judgment in updating and reporting on fluctuations in equity interests exceeding $50,000. FDA does not expect the investigator to report when an equity interest fluctuates below that threshold. See Question E.4 for additional information.

C.3. Q: Are equity interests in mutual funds and 401(k)s reportable?

A: FDA expects that equity interests held in publicly traded mutual funds will not be reportable in the vast majority of cases. If, however, an investigator would have control

over buying or selling stocks in a mutual fund, equity interests held in such publicly traded mutual funds would be reportable.

If an investigator holds an equity interest in a sponsor over $50,000 in a 401(k) or equivalent account, and has control over whether to buy or sell the interest, the equity interest is reportable.

C.4. Q: How do significant payments of other sorts (SPOOS) relate to the variety of payments the sponsor might make to an individual or institution for various activities?

A: The term "significant payments of other sorts" was intended to capture substantial payments or other support that has a value of more than $25,000 provided to an investigator or institution that could create a sense of obligation to the sponsor.

These payments do not include payments for the cost of conducting the clinical study of the product under consideration or clinical studies of other products, under a contractual arrangement, but do include other payments made directly to the investigator or to an institution for direct support of the investigator.

“Significant payments of other sorts” would include, for example, payments, retainers and honoraria from a sponsor to a clinical investigator for activities such as participating on committees, providing consultation, or serving as a preceptor (21 CFR § 54.2(f)). Grants to fund ongoing research, including laboratory activities and equipment, and compensation in the form of actual equipment for the laboratory/clinic would also be considered significant payments of other sorts. This means that if an investigator were given equipment or money to purchase equipment for use in the laboratory/clinic but not in relation to the conduct of the clinical study, payment would be considered a significant payment of other sorts (21 CFR § 54.4(a)(3)(ii)). If, however, the investigator were provided with computer software or money to buy software needed for use in the clinical study, that payment would not need to be reported.

Payments made to the institution that are not made on behalf of the investigator and are not specifically targeted towards the investigator generally would not need to be reported. Under certain circumstances, however, a grant made to an institution would be considered targeted towards the investigator (and therefore considered reportable); for example, if the grant is worded in such a way that only the investigator could fulfill it.

Finally, payments that meet the criteria for significant payments of other sorts that are made to other researchers at the institution, who are not part of the covered study, do not need to be reported.

C.5. Q: Are payments made to investigators to cover travel expenses (such as transportation, lodgings and meal expenses) reportable as significant payments of other sorts (SPOOS)?

A: Generally, reasonable payments made to investigators to cover reimbursable expenses such as transportation, lodgings and meals do not fall within the definition of SPOOS and, therefore, would not need to be reported. Payment for other expenses that are generally considered outside of normal reimbursable expenditures and not expenses necessary to conduct the study would be considered SPOOS. Such payments would include, for example, entertainment costs, travel costs associated with transporting and/or providing lodgings and meals for family members, and other payments that exceed reasonable expectations (for example, if an investigator was flown to a resort location for an extra week of vacation). These types of expenses are reportable and should be tracked as SPOOS. FDA understands that such payments may be limited or prohibited by industry ethical codes.[13] To the extent such payments are made, they would be SPOOS.

C.6. Q: Is the dollar amount that triggers reporting of significant payments of other sorts (SPOOS) cumulative over the course of the study or is it based on the amount received on an annual basis?

A: The $25,000 threshold amount for reporting SPOOS is based on the cumulative amount of SPOOS received by the clinical investigator (including payments made to the spouse and dependent children) over the course of the study and for one year following completion of the study.

C.7. Q: Does FDA have expectations about how the financial information should be collected? Will FDA consider it acceptable practice for a company to use a questionnaire to collect financial information from investigators rather than constructing an internal system to collect and report this information?

A: FDA regulations do not prescribe a particular method for collecting financial information from investigators. Sponsors/applicants have the flexibility to collect the information in the most efficient and least burdensome manner that will allow for complete and accurate certifications and disclosures. They may use questionnaires completed by the clinical investigators and/or information already available to the sponsor, as appropriate. FDA does not require sponsors to establish elaborate systems to collect and track financial information.

If sponsors intend to use a questionnaire to collect financial information from investigators, FDA recommends that they develop forms suited to that purpose. FORM FDA 3455 was designed for applicants to use to report financial information they collected from clinical investigators to FDA. It does not include the background

[13] Examples of industry ethical codes would be the "Principles on Conduct of Clinical Trials and Communication of Clinical Trials Results" from the Pharmaceutical Research and Manufacturers of America (PhRMA) and the "Code of Ethics on Interactions with Health Care Professionals" from the Advanced Medical Technology Association (AdvaMed).

information needed for clinical investigators to be aware of the financial information to be provided. For example, there is no statement that the reporting requirements apply to the spouse and dependent children as well as to the investigator; no information as to the dollar amounts triggering reporting of equity interests or SPOOS; and no statement that the investigator must report the details of the financial interests and arrangements, not just a statement, for example, of equity interest greater than $50,000. In addition, when there is more than one sponsor for financial disclosure purposes, the investigator should be apprised that the dollar amounts triggering reporting apply separately to each sponsor. This type of explanatory information should be provided to the clinical investigators to ensure that the financial disclosure information collected is as accurate and complete as possible. Please see the Appendix for considerations for collecting financial disclosure information from clinical investigators.

C.8. Q: The regulation requires that investigators provide information on financial interests and arrangements during the course of the study and for one year after completion of the study (see 21 CFR § 54.4(b)). What does "during the course of the study" mean? What does "completion of the study" mean?

A: "During the course of the study" refers to the time from the date the clinical investigator entered into an agreement with the sponsor to conduct the study until the completion of the study. For the purposes of financial disclosure under part 54, completion of the study means that all study subjects have been enrolled and follow-up of primary endpoint data on all subjects has been completed in accordance with the clinical protocol. Many studies have more than one phase (e.g., a study could have a short-term endpoint and a longer term follow-up phase). "Completion of the study" here refers to the part of the study that is being submitted in the application. If there were a subsequent application based on longer term data, completion of the study would be defined using completion of follow-up for the longer term data. An applicant is not required to submit updated financial information to FDA after submission of the application, but applicants must retain complete records (21 CFR § 54.6). Where there is more than one study site, the sponsor may consider completion of the study to occur when the last study site is complete, or may consider each study site individually as it is completed.

C.9. Q: What if the sponsor changes during the course of the study or within one year of completion of the study, for example, through purchase or merger?

A: Agency regulations require that an IND/IDE sponsor collect financial information from all clinical investigators and that clinical investigators promptly update this information if any relevant changes occur during the course of the investigation and for one year following completion of the study (21 CFR §§ 54.4, 312.53(c)(4), 312.64(d), 812.43(c)(5) and 812.110(d)). Therefore, if the study sponsor changes during the course of the study, the clinical investigators will need to update their financial disclosure information relevant to the new sponsor. The new sponsor is responsible for collecting this information, and to ensure that the new sponsor has complete financial disclosure information, the new sponsor should seek this information from the original sponsor, and the agency encourages the original sponsor to share their records with the new sponsor.

With respect to covered clinical studies conducted outside the United States not pursuant to an IND or IDE (such as studies submitted pursuant to § 312.120 or § 814.15), the agency expects applicants to take affirmative action, at the earliest opportunity, to see that this information is collected and available to make a complete disclosure and/or certification under part 54.

D. CLINICAL INVESTIGATOR

D.1. Q: Who is included in the definition of "clinical investigator"?

A: Under part 54, "clinical investigator means only a listed or identified investigator or subinvestigator who is directly involved in the treatment or evaluation of research subjects" (21 CFR § 54.2(d)). This definition is intended to identify the individuals for whom reporting under this regulation is required. Generally, these individuals are considered to be the investigators and subinvestigators taking responsibility for the study at a given study site. The definition also includes the spouse and each dependent child of such an investigator or subinvestigator.

It should be noted that hospital staff, including nurses, residents, fellows, and office staff who provide ancillary or intermittent care but who do not make direct and significant contribution to the data are not meant to be included under the definition of clinical investigator. Additionally, individuals who only collect specimens or perform routine tests (such as blood pressure, EKG, x-ray) are not meant to be included under the definition of clinical investigator for purposes of financial disclosure.

D.2. Q: How does the definition of "clinical investigator" in the financial disclosure regulation (21 CFR part 54) relate to the definition in the IND regulations (21 CFR part 312)?

A: For drugs and biological products, an investigator under 21 CFR part 312 is defined as "an individual who actually conducts a clinical investigation (i.e., under whose immediate direction the drug is administered or dispensed to a subject). In the event an investigation is conducted by a team of individuals, the investigator is the responsible leader of the team. 'Subinvestigator' includes any other individual member of that team." (21 CFR § 312.3(b).)

For purposes of the financial disclosure regulation, a clinical investigator is an investigator or subinvestigator who is directly involved in the treatment or evaluation of research subjects (21 CFR § 54.2(d)). Therefore, the term clinical investigator in this context would generally include anyone who fits any of the following criteria: signs the FORM FDA 1572 (Statement of Investigator), is identified as an investigator in initial submissions or protocol amendments under an IND, or is identified as an investigator in the marketing application. This could include individuals identified as subinvestigators

on a FORM FDA 1572.[14] For studies not conducted under an IND, the sponsor will need to identify the investigators and subinvestigators they consider covered by the regulation and provide FORMS FDA 3454 and/or 3455 as appropriate. FDA expects that there will be at least one such person at each clinical site. If other individuals are responsible for a study at a site, those persons should also be included as clinical investigators.

D.3. Q: How does the definition of "clinical investigator" in the financial disclosure regulation (21 CFR part 54) relate to the definition in the medical device regulations (21 CFR part 812)?

A: For medical devices, investigator is defined under 21 CFR part 812 as an individual under whose immediate direction the subject is treated and the investigational device is administered, including follow-up evaluations and treatments. Where an investigation is conducted by a team of individuals, the investigator is the responsible leader of the team. (21 CFR § 812.3(i).)

In general, investigators and subinvestigators sign "investigator agreements" in accordance with 21 CFR § 812.43(c), and it is these individuals whose financial interests and arrangements should be reported as they would fall under the definition at 21 CFR § 54.2(d). For studies not conducted under an FDA-approved IDE (that is, a non-significant risk IDE or an exempt study), the sponsor would need to identify the investigators and subinvestigators they consider covered by the regulation and provide FORMS FDA 3454 and/or 3455, as appropriate. We expect that there will be at least one such person at each clinical site.

D.4. Q: Is it necessary to collect financial information on spouses and dependent children of clinical investigators?

A: Yes. The definition of clinical investigator in 21 CFR part 54 includes the spouse and dependent children of the investigators and subinvestigators who are required to report. Therefore, the financial interests and arrangements of the spouse and each dependent child of each investigator and subinvestigator are to be included in the disclosure (21 CFR § 54.2(d)). The dollar amount that triggers reporting is the total of the financial interests of the investigator, spouse, and dependent children (21 CFR § 54.2(d)). If a spouse or dependent child is an employee of the sponsor, the clinical investigator should be identified as an employee of the sponsor and no further disclosure is required. (See 21 CFR § 54.4.)

D.5. Q: Who is considered a "dependent child"?

A: For purposes of clinical investigator financial disclosure under part 54, a dependent child is the investigator's child (whether by blood or adoption), stepchild or foster child who is unmarried, and for whom the investigator provides more than one-half of the

[14] For guidance on who should be listed as an investigator or subinvestigator on Form FDA 1572, please see FDA's Information Sheet Guidance, "Frequently Asked Questions – Statement of Investigator (Form FDA 1572)" available at http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM214282.pdf.

child's support. This would include a child who, at any time during the course of the study and for one year following completion of the study, is under the age of 19, under the age of 24 if a full-time student, or who is permanently and totally disabled. Such a child would generally have the same principal residence as the investigator.

D.6. Q: What obligations does the clinical investigator have under the financial disclosure regulations?

A: Clinical investigators are to provide sponsors sufficient accurate financial information to allow the applicant to submit complete and accurate certification or disclosure statements (see 21 CFR §§ 54.4, 312.53(c)(4), 312.64(d), 812.43(c)(5) and 812.110(d)). Clinical investigators must provide this information to sponsors and also promptly update the information if any relevant changes occur during the course of the investigation and for one year following the completion of the study (see 21 CFR §§ 54.4(b), 312.53(c)(4), 312.64(d), 812.43(c)(5) and 812.110(d)). See also Question C.2.

D.7. Q: May a clinical investigator rely on the information he/she provided to comply with his/her institution's policies and procedures pertaining to financial conflicts of interest to comply with the investigator obligations for financial disclosure under FDA's regulations?

A: The financial information a clinical investigator provides to his/her institution is based on the institution's requirements, which may not be sufficient to meet FDA's regulations. FDA's regulations require the clinical investigator to provide sufficient and accurate financial information to the sponsor to allow the sponsor to submit complete and accurate certification or disclosure statements under FDA's clinical investigator financial disclosure regulations (21 CFR § 54.4(b)). However, if an investigator determines that the financial information he/she provided to his/her institution adequately fulfills the disclosure requirements in FDA's regulations, a clinical investigator could provide the same information to the sponsor. The clinical investigator would still need to commit to promptly updating the financial information if any relevant changes occur during the course of the study and for one year following completion of the study (21 CFR § 54.4(b)).

E. SPONSOR

E.1. Q: How does the definition of "sponsor" in the financial disclosure regulation (21 CFR part 54) relate to the definition in the IND/IDE regulations (21 CFR parts 312 and 812)?

A: In 21 CFR part 54, the term "sponsor of the covered clinical study" means "the party supporting a particular study at the time it was carried out" (21 CFR § 54.2(h)). FDA interprets "support" to include those who provide material support, for example, monetary support or the test product under study. (See Question E.9 for further explanation of "material support.") This differs from the meaning of "sponsor" in other FDA regulations (such as 21 CFR parts 312 and 812), where the sponsor may be the

person who initiates or takes responsibility for a clinical investigation (21 CFR §§ 312.3(b) and 812.3(n)). While the definition of sponsor under part 54 usually would include the sponsor of an IND/IDE (as defined in 21 CFR parts 312 and 812), it also includes any other individuals who provide material support for the study. Therefore, a covered clinical study may have more than one sponsor for financial disclosure purposes. When there is more than one sponsor, FDA interprets the regulation to mean that the dollar amounts triggering reporting apply separately to each sponsor.

E.2. Q: What obligations do IND and IDE sponsors have regarding information collection prior to study start?

A: The IND and IDE regulations provide that, before permitting an investigator to begin participation in an investigation, the IND/IDE sponsor (that is, the sponsor as defined in 21 CFR parts 312 and 812) must obtain sufficient and accurate financial information that will allow an applicant to submit complete and accurate certification or disclosure statements as required under 21 CFR part 54 (21 CFR §§ 312.53 and 812.43). In order to fulfill these requirements and ensure complete disclosure, the IND/IDE sponsor should identify all "sponsors of the covered clinical study" (as defined in 21 CFR § 54.2(h)) for investigators because the identity of all parties providing support may not be known to investigators.

The sponsor is also required to obtain the investigator's commitment to promptly update this information if any relevant changes occur during the course of the investigation and for one year following the completion of the study (21 CFR §§ 312.53 and 812.43). By collecting the information prior to the study start, the sponsor will be aware of any potential problems, can consult with the agency early on, and can take steps to minimize any possibility for bias.

E.3. Q: Why is the IND/IDE sponsor responsible for obtaining financial information from investigators?

A: Although reporting to the FDA is the responsibility of the applicant, the IND/IDE sponsor is required to collect the financial information before permitting an investigator to participate in a clinical study (21 CFR §§ 312.53, 812.20(b)(5), and 812.43). The purpose of this requirement is twofold:

1. to alert the IND/IDE sponsor of the study of any potentially problematic financial interests or arrangements as early in the product development process as possible in order to minimize the potential for study bias, and

2. to facilitate the accurate collection of financial information that may not be submitted until several years later.

The IND/IDE sponsor, who is in contact with the investigator, is best placed to inquire as to the financial interests and arrangements of investigators, and this obligation applies to any IND/IDE sponsor (e.g., commercial, government, or contract research organization

(CRO)). The IND/IDE sponsor is required to maintain complete and accurate records showing any financial interest in, or arrangement with, a sponsor of the covered study, as described in 21 CFR § 54.4(a)(3)(i-iv) (21 CFR §§ 312.57(b) and 812.140(b)(3)). The IND/IDE sponsor is also best situated to ensure that required financial information is collected and made available to the applicant company, so that the information can be included in the marketing application. (Refer to 21 CFR §§ 54.4, 312.53, 312.57(b), 812.43, and 812.140(b)(3).)

IND/IDE sponsors conducting covered clinical studies outside the United States should note that the part 54 regulations do not distinguish between foreign and domestic sites. See Question F.3 for additional information.

E.4. Q: Is the IND/IDE sponsor responsible for obtaining 1-year follow-up financial information from clinical investigators?

A: As noted in response to Question E.2 above, the IND/IDE sponsor is required to obtain financial information from clinical investigators before permitting the investigators to begin participation in an investigation and to obtain the investigator's commitment to promptly update this information if any relevant changes occur during the course of the study and for one year following the completion of the study (21 CFR §§ 312.52 and 812.43). The regulations do not specifically require the IND/IDE sponsor to obtain information from clinical investigators one year following completion of the study. The regulations, however, do require IND/IDE sponsors to maintain complete and accurate records concerning all financial interests and arrangements of clinical investigators subject to part 54 (see 21 CFR §§ 312.57(b) and 812.140(b)(3)) and to secure investigator compliance with the regulations (see 21 CFR §§ 312.56(b) and 812.46(a)). Therefore, an IND/IDE sponsor should take steps to ensure clinical investigator compliance, such as reminding the clinical investigators of the requirement to promptly update their financial information when any relevant changes occur during the study and for one year following completion.

E.5. Q: What if the IND/IDE sponsor is not the party who will be submitting a marketing application?

A: In many cases, the IND/IDE sponsor, the part 54 sponsor, and the applicant will be the same party. However, there may be times when they are not. For example, consider the case when an academic institution serves as the IND/IDE sponsor and a drug company serves as the part 54 sponsor by providing funding or the investigational drug for the study. When a marketing application is submitted, the drug company is likely to be the applicant. If, however, the drug company was sold to another company, the applicant may be neither the IND/IDE sponsor nor a part 54 sponsor.

It should be noted, however, that even if the IND/IDE sponsor will not be submitting the marketing application, the IND/IDE sponsor is still responsible for collecting financial information from the clinical investigators. The responsibility for reporting financial information to FDA falls upon the applicant; that is, part 54 requires the applicant to

submit financial information when the marketing application is submitted to FDA (21 CFR § 54.4(a)).

As stated above and in Question E.3, an IND/IDE sponsor is responsible for collecting financial information from both foreign and domestic clinical investigators. If a sponsor did not collect this information, for example, because the sponsor conducted a foreign study that was not conducted under an IND/IDE and was not originally intended for submission to the FDA, the applicant is expected to contact the sponsor and/or clinical investigators to retrospectively obtain the financial disclosure information. See Questions F.2 and F.3 for additional information.

E.6. Q: If a contract research organization (CRO) is conducting a covered clinical study on behalf of another company, should the CRO collect the financial information from investigators? Is it necessary to collect financial information from investigators who have financial interests in or arrangements with CROs?

A: If a CRO meets the definition of an IND/IDE sponsor or has contracted to collect financial information from clinical investigators on behalf of a sponsor, the CRO must collect financial information on clinical investigators' interests in any sponsors of the covered clinical study. See 21 CFR § 312.52. To satisfy the requirements in part 54, if the CRO provides material support for a covered study, financial information on clinical investigators' financial interests in and arrangements with the CRO is to be collected. If another entity provided material support for the study, and the CRO was responsible for collecting the information, then the CRO also would collect financial information relative to that entity.

E.7. Q: Suppose a public or academic institution conducts a covered clinical study without any support from a commercial sponsor, but the study is later used by an applicant to support its marketing application. In that case, who is the "sponsor" of the study and what information should the applicant submit?

A: In this case, the part 54 sponsor of the study is the public or academic institution. Because such institutions are often not commercial entities, there may not be relevant equity interests to report. However, if the clinical investigator is not a full-time or part-time employee of the public or academic institution, the clinical investigator would need to report any relevant interests under 21 CFR § 54.4, such as any proprietary interest in the tested product, including but not limited to a patent, trademark, copyright or licensing agreement, and reportable financial arrangements with the institution, such as compensation affected by the outcome of studies or significant payments of other sorts. The clinical investigator's financial interests in and arrangements with the applicant would not need to be reported because the company was not a sponsor of the covered clinical study.

If, however, the applicant provided material support for the study (for example, by providing the study product for free), then it would be considered a sponsor for financial disclosure purposes. The academic institution conducting the study would need to collect

information regarding the clinical investigators' financial interests and arrangements with the company.

E.8. Q: If a subsidiary of a larger parent company is conducting a covered clinical study, are the financial interests and arrangements of the clinical investigators with only the subsidiary reported? Or, are the financial interests of the investigators in the parent company to be reported also?

A: If the subsidiary company meets the definition of a sponsor of the covered study as defined in 21 CFR part 54, the IND/IDE sponsor is required to collect clinical investigators' financial information related to the subsidiary company. If the parent company is a 21 CFR part 54 sponsor of the study, the IND/IDE sponsor also must collect financial information related to the parent company. If there are multiple companies providing material support for a covered study, the IND/IDE sponsor is responsible for collecting financial information from clinical investigators related to all companies providing that support (21 CFR §§ 54.4, 312.53 and 812.43). The company that will submit the marketing application is ultimately responsible for submitting to the agency the disclosable financial interests and arrangements of clinical investigators with respect to all the covered study's sponsors, as defined in 21 CFR part 54, at the time the marketing application is submitted (21 CFR § 54.4).

E.9. Q: What is considered "material support" when identifying sponsors of the covered study?

A: Parties that provide "material support" are considered sponsors of the covered clinical study. This would include providing direct funding or other monetary support such as through a grant, or providing services or materials. If a party receives reimbursement for the services and/or materials it is providing, then that party generally would not be considered a sponsor. For example, a CRO paid by a sponsor to perform services would not be considered a sponsor of the covered clinical study. Materials could include the product under study as well as other products and/or equipment that are needed for the conduct of the study, such as ancillary medication and equipment used in testing required by the protocol.

F. APPLICANT

F.1. Q: Do applicant companies need to collect information for a year after completion of the study? Who is responsible for collecting/providing this information?

A: The investigator must promptly provide updated financial information to the sponsor whenever any relevant changes occur during the course of the investigation and for a one-year period following completion of the study (21 CFR §§ 54.4(b), 312.64(d) and 812.110(d)). In addition, sponsors should record SPOOS that are paid to the investigator or the investigator's institution to support activities of the investigator that have a cumulative monetary value of more than $25,000, exclusive of the costs of conducting the covered clinical studies, both during the study and for one year following completion

of the study (21 CFR §§ 54.2(f) and 54.4(a)(3)(ii)). FDA specified the one-year time frame because anticipation of payments or expectation of employment may be as influential as payments already received. Applicants need only report these financial interests and arrangements when the marketing application is submitted, but sponsors and applicants are responsible for keeping updated financial information from the investigators in company files (21 CFR §§ 54.6, 312.57 and 812.140).

F.2. Q: Suppose an applicant has obtained the results of a clinical study conducted by another sponsor and that sponsor certifies it has no financial disclosure information in its files. Is the applicant obligated to use due diligence in attempting to contact the clinical investigators directly to obtain the information? Is the applicant obligated to provide any certification as to proprietary interests? Is the sponsor obligated to provide the applicant with a statement as to outcome payments?

A: The applicant is required to provide financial disclosure information in a marketing application or certify that it acted with due diligence to obtain necessary information but was unable to do so and state the reason (21 CFR § 54.4). (See Question B.7 for a further explanation of "due diligence.") The sponsor should collect financial disclosure information from the clinical investigators, and, regardless of whether it collected all necessary financial information, should have information on any outcome payments (that is, payment that is dependent on the outcome of the study) and/or SPOOS made to the investigators. The applicant should request this information from the sponsor. The applicant should also make reasonable efforts to contact the clinical investigators to obtain disclosable financial information. Information on proprietary interests, such as patents and trademarks, should also be available to the applicant from publicly available sources.

F.3. Q: Do applicants need to provide information on investigators who participate in foreign studies?

A: The applicant has the same financial disclosure obligations (21 CFR part 54) with respect to studies conducted at foreign and domestic sites. An applicant must include a certification or disclosure of information for each investigator participating in a foreign covered study, or, to the extent the applicant is unable to obtain sufficient information to certify or disclose, it must certify that it acted with due diligence but was unable to obtain the information and state the reason why (21 CFR § 54.4).

Sponsors of foreign covered studies should obtain financial disclosure information from clinical investigators prior to study initiation and provide this information to applicants.[15]

The agency believes that a prudent applicant would take affirmative action at its earliest opportunity to collect financial information relating to a foreign covered study or to ensure that the information is collected by the study sponsor. Where possible, the agency strongly encourages the applicant to arrange for the collection of financial information

[15] If a foreign study is conducted pursuant to an IND or IDE, the sponsor has a legal obligation to comply with applicable rules, including the requirement to collect and maintain financial disclosure information.

prior to study initiation – to ensure that the information is preserved so that a complete submission can be made and to take any steps necessary to minimize potential bias. Where this is not possible, for example, because an applicant is submitting a foreign covered study sponsored by another entity and the applicant did not oversee, support, or direct the study, the applicant should take appropriate steps to obtain financial information from the study sponsor, investigators, or other reasonably available sources. See Question F.2.

G. COVERED CLINICAL STUDY

G.1. Q: Disclosure of financial interests and arrangements is required only for covered clinical studies, specifically, those studies relied upon to provide support for the effectiveness of a product or in which a single investigator makes a significant contribution to the demonstration of safety (21 CFR §§ 54.2(e) and 54.3). An IND sponsor, acting much earlier, must inquire into investigator financial interests and arrangements before the ultimate role of a study in the application is determined (21 CFR § 312.53). How will the IND sponsor determine which studies will ultimately require certification/disclosure statements?

A: The IND sponsor will need to consider the potential role of a particular study based on study size, design, and other considerations. Almost any controlled effectiveness study could, depending on outcome, become part of a marketing application, but other studies might be critical too, such as a pharmacodynamic study in a population subset or a bioequivalence study supporting a new dosage form. So, for many studies, it would be prudent to collect the information in the event that the study will ultimately require certification and disclosure statements.

G.2. Q: Do the reporting requirements apply to studies that include large numbers of investigators and multiple sites? Will the agency consider a waiver mechanism to exempt applicants from collecting information from clinical investigators conducting these kinds of studies?

A: Large multi-center efficacy studies with many investigators are considered covered clinical studies within the meaning of the regulation (21 CFR § 54.2(e)). Data from investigators having only a small percentage of the total subject population (in a study with large numbers of investigators and multiple sites) could still affect the overall study results depending on the impact of their results on the overall study results. Or, if a sponsor submitted data from a large, multi-center, double-blind study that included several thousand subjects, a single clinical investigator at a large site could be responsible for a significant number of study subjects. In either case, if the investigator fabricated data or otherwise affected the integrity of the data, the results could have been influenced.

By contrast, large open safety studies and treatment protocols that have large numbers of investigators would generally not be considered covered clinical studies. As discussed in the preamble to the final rule,[16] in these large open safety studies and treatment protocols,

[16] See *Federal Register*, volume 63, February 2, 1998, page 5239.

the large number of investigators generally means that no single investigator has a major impact on the data. In addition, important adverse events will generally be apparent because they lead to cessation of therapy and submission of the case report form. Although it is possible that a financial interest could be important in these studies, it is relatively unlikely.

The regulations[17] allow a sponsor to seek a waiver of certain requirements, including financial disclosure requirements. FDA believes it is highly unlikely, however, that a waiver would be justified for studies begun after February 2, 1999, the effective date of the regulation, because the sponsor should already have begun collecting the information on an ongoing basis. FDA will evaluate any request for waiver on a case-by-case basis.

G.3. Q: The definition of a covered clinical study includes "any study in which a single investigator makes a significant contribution to the demonstration of safety." What does this mean?

A: Examples of commonly conducted studies in which a single investigator makes a significant contribution to the demonstration of safety would be studies that are designed to address a particular safety concern. For example, an endoscopy study to evaluate a product's effect on the stomach lining or a study in a subset of patients with a particular pre-existing condition or disease, such as significant cardiovascular risk factors or a history of poor (adverse) response to other treatments. Such studies could have a single investigator, or could involve more than one clinical investigator. If each investigator makes a significant contribution to the study and, therefore, to a demonstration of safety, such studies would be considered covered clinical studies and subject to financial disclosure.

Studies that generally would not be covered studies are large open safety studies (where a large number of clinical investigators enroll subjects) that are designed to look at adverse events in general and do not focus on specific safety concerns.

G.4. Q: Can a literature report be considered a covered clinical study?

A: Yes, a literature report could be considered a covered clinical study if it is being relied upon by the applicant or FDA to establish that the product is effective (including showing equivalence to an effective product) or where a single investigator makes a significant contribution to the demonstration of safety.[18] When an applicant relies on a literature report in this manner, clinical investigator financial disclosure is required. The author(s) and clinical investigators in the study should be contacted for this information to allow the applicant to submit the certification and/or disclosure forms or, if the applicant is unable to obtain the information, certification that the applicant acted with due diligence to obtain the information. Because the financial interests and arrangements

[17] See 21 CFR §§ 312.10, 812.10, 314.90 and 814.20.

[18] Applicants should be aware that additional information may be needed in order for the agency to be able to use published literature reports in support of a marketing application. For example, details about study methodology, the actual products studied, specifics about the patient population, patient accounting, etc. may be needed.

to be reported are those relating to the sponsor(s) of the covered clinical study and the product under study, the clinical investigators would not be required to report their financial interests in and arrangements with the applicant unless the applicant was a sponsor of the covered study.

G.5. Q: Does the regulation include abbreviated new drug applications (ANDAs)? Does the regulation include 510(k)s that include clinical data? What about biosimilars?

A: The regulation requires an applicant whose submission relies in part on clinical data to disclose certain financial interest and arrangements. A "covered clinical study" means any study of a drug (including a biological product) or device in humans submitted in a marketing application or reclassification petition that the applicant or FDA relies on to establish that the product is effective (including studies that show equivalence to an effective product), or any study in which a single investigator makes a significant contribution to the demonstration of safety. This would, in general, 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 expanded access protocols. (21 CFR §§ 54.2 and 54.3.) ANDAs are subject to 21 CFR part 54 (21 CFR § 314.94(a)(13)), as are 510(k)s (21 CFR § 807.87(i)). In addition, applications for biological products, including applications submitted under 351(k) of the Public Health Services Act, are also subject to the regulation.

G.6. Q: Does the regulation apply to studies in support of labeling changes?

A: The regulation applies to studies submitted in a supplement when those studies meet the definition of a covered clinical study. The definition includes studies to support safety labeling changes where individual investigators make a significant contribution to the safety information. Studies to support the effectiveness of a new claimed indication are also included. (21 CFR §§ 54.2 and 54.3.)

G.7. Q: Do actual use and labeling comprehension studies conducted to support a request to switch a drug product from prescription to over-the-counter (OTC) status fit the definition of covered clinical study?

A: Applicants who file supplements requesting that FDA approve a switch of a prescription drug to OTC status or who file a new drug application for OTC use often conduct actual use and labeling comprehension studies. These may be intended to demonstrate that the product is safe and effective when used without the supervision of a licensed practitioner; in other cases, they may test labeling comprehension or other aspects of treatment by consumers. Actual use studies performed to support these applications are considered covered clinical studies if they are used to demonstrate effectiveness in the OTC setting or if they represent a safety study where any investigator makes a significant contribution (21 CFR §§ 54.2 and 54.3). Labeling comprehension studies would not be considered covered studies.

G.8. Q: Are clinical investigators of in vitro diagnostics (IVDs) covered under this regulation?

A: Yes. Applicants who submit marketing applications for IVDs that include covered clinical studies must provide the appropriate financial certification or disclosure information (21 CFR § 54.3). Although IVD studies may only involve specimens, under 21 CFR § 812.3(p), "subject" is defined as a "human who participates in an investigation, either as an individual on whom or on whose specimen an investigational device is used or as a control." Under 21 CFR § 812.3(h), an "investigation" is defined as a clinical investigation or research involving one or more subjects to determine the safety or effectiveness of a device." Thus, if an investigation of an IVD is used to support a marketing application and it meets the definition of a covered clinical study, it would be subject to this regulation (21 CFR § 54.3).

H. FDA REVIEW

H.1. Q: Under what circumstances relating to financial disclosure would FDA refuse to file an application?

A: FDA may refuse to file any marketing application supported by covered clinical studies that does not contain, for each clinical investigator who is not an employee of the sponsor, a certification that no financial interest or arrangement specified in 54.4(a)(3) exists, a disclosure statement identifying the specified financial interests or arrangements and the steps taken to minimize bias, or a certification that the applicant has acted with due diligence to obtain the required information but was unable to do so and stating the reason (21 CFR § 54.4(c)). In general, if, during the filing review, an FDA reviewer identifies missing information, an attempt will be made to contact the applicant to obtain the missing information; however, applicants should take reasonable steps to ensure that applications are complete upon submission. Applicants are encouraged to discuss their concerns on particular matters about financial information with FDA.

H.2. Q: Who will review a disclosure of the specified financial interests and arrangements when such information is submitted in a marketing application?

A: FDA review staff, which may include project managers, consumer safety officers, medical officers, and/or others with regulatory or scientific expertise or supervisory authority, will evaluate financial disclosure information.

H.3. Q: What will FDA reviewers consider when evaluating the financial disclosure information?

A: FDA reviewers will evaluate the information disclosed about each covered clinical study in an application to determine the impact of any disclosed financial interests or arrangements on the reliability of the data. See 21 CFR § 54.5(a). FDA may consider many factors in making its evaluation (21 CFR §§ 54.5(a) and (b)).

Part 54 does not categorically prohibit financial interests or arrangements, but it does require applicants to submit a list of clinical investigators who are full-time and part-time employees of the sponsor and to disclose or certify with respect to other investigators so that FDA can assess the possibility of bias. The type of financial interest or arrangement disclosed is important because some financial interests and arrangements are of greater concern than others when assessing the reliability of the data. For example, outcome payments (that is, payment that is dependent on the outcome of the study) elicit the highest concerns, followed by proprietary interests in the test article (such as patents, royalties, etc.). With respect to equity interests and/or SPOOS, the amount and nature of the equity interests and payments may be considered.

When a clinical investigator has disclosable financial interests or arrangements, the FDA reviewer will carefully consider the steps taken by the sponsor to minimize bias[19] as described in the attachment to the FORM FDA 3455. These steps may include study design, use of multiple clinical investigators and study sites, and replication of study results. The agency also gives careful scrutiny to data from clinical investigators who are full-time or part-time employees of the sponsor, because of the possibility of significant financial interests in the outcome of studies. (Hereafter, we refer to these investigator types jointly as "disclosing investigators.") Investigators for whom the applicant is not able to disclose or certify, despite exercising due diligence, will be considered on a case by case basis.

The FDA reviewer may consider elements of the study design, including the method of randomization, the level of blinding (double-blind, single-blind), the presence or absence of a control group, whether placebo or active, the nature of the primary and secondary endpoints (objective, subjective), the method of endpoint assessment, the method of evaluation (including whether someone other than the disclosing investigator measured the endpoints), and whether many investigators, most of whom were not disclosing investigators, participated in the study. The FDA reviewer may also consider the total number of investigators and subjects in the study, the number and percentage of subjects enrolled by the disclosing investigator, information obtained from on-site inspections, and the data (including adverse events) of the disclosing investigator compared to other investigators in the study. The reviewer may look at a re-analysis of the data performed either by the applicant or FDA that excludes the disclosing investigator's results, other relevant types of reanalysis, and/or whether the results were replicated over multiple studies.

The reviewer will make a judgment as to whether the financial interests or arrangements disclosed may have affected the interpretation of study results or otherwise require further action. For example, if a disclosing investigator was a participant in a covered clinical study that (1) had randomized assignment of patients to treatment, (2) had a clearly objective endpoint (such as survival) or an endpoint assessed by a blinded observer other than the clinical investigator, (3) had multiple study sites (so that each investigator enrolled a small fraction of the total number of subjects), and (4) had results generally similar to the results of other investigators, then provided there were no other

[19] See Question A.2 for a discussion of methods to minimize bias.

material, countervailing considerations, the reviewer might determine that a financial interest, employment relationship, or lack of certification or disclosure does not raise serious questions about the integrity of the covered study that require further action. On the other hand, if the results of the disclosing investigator are clearly more favorable than results of the other investigators or centers and the disclosing investigator's results could have influenced outcome, the reviewer would generally need to consider further action. (21 CFR § 54.5(c).)

FDA reviewers should consult with their management as needed to determine appropriate actions.

H.4. Q: What actions may FDA take when a clinical investigator is the employee of a sponsor or has disclosable financial interests or arrangements?

A: If FDA determines that an investigator's financial interests raise a serious question about the integrity of the data, FDA will take any action it deems necessary to ensure the reliability of the data (21 CFR § 54.5(c)). Please see Section III.C of this guidance for actions that may be taken.

H.5. Q: How is the review to be documented?

A: Each FDA Center provides review templates or checklists for their review staff to use that include a section on financial disclosure issues.

In general, the review should document that a list of clinical investigators for each covered clinical study was provided, and that, as applicable, there was either certification or documentation of disclosable financial interests and arrangements for each investigator on the list who is not an employee of the sponsor[20] (21 CFR § 54.4).

When a disclosure of financial interests and arrangements is included (FORM FDA 3455), reviewers should ensure that the details of the disclosable financial interests and arrangements are attached to the forms along with a description of the steps the sponsor has taken to minimize the potential bias of clinical study results by any of the disclosed interests or arrangements (21 CFR § 54.4(a)(3)). The reviewer will address the question of whether these interests and arrangements raise questions about the integrity of the data and describe any actions taken to minimize bias. The reviewer will also describe any actions taken by the agency to address any questions raised by a disclosable financial interest or provide an explanation for why no action was indicated (21 CFR § 54.5). This documentation should be included in the appropriate section of the review template.

When a sponsor certifies that he/she acted with due diligence to obtain information regarding the clinical investigator's financial interests and arrangements but was unable to obtain it, reviewers should ensure that an explanation of the reason why the information could not be obtained and the efforts made to obtain the information is

[20] If the spouse or dependent child of an investigator is an employee of the sponsor, the investigator should be identified as an employee and further financial disclosure under this provision is not required.

attached to the FORM FDA 3454 (21 CFR § 54.4). See Question B.7 for a discussion of due diligence.

H.6. Q: Under what circumstances will FDA publicly discuss financial interests and arrangements disclosed to the agency?

A: As discussed in the preamble to the 1998 final rule,[21] FDA's policy is that certain types of financial information requested under the rule, notably clinical investigators' equity interests, will be protected from public disclosure unless circumstances relating to the public interest clearly outweigh the clinical investigator's identified privacy interest. FDA cited the example of a financial interest or arrangement so affecting the reliability of a study as to warrant its public disclosure during evaluation of the study by an advisory panel. FDA expects that only rarely would an investigator's privacy interest be outweighed by the public interest and thus warrant disclosure of the details of financial interest or arrangement. The agency will carefully evaluate each circumstance on a case-by-case basis.

FDA recognizes, however, that there is increased interest in the financial arrangements between clinical investigators and sponsors of the clinical trials in which the investigators participate. For this reason, FDA intends to provide information about the number of clinical investigators with disclosable financial interests or arrangements in the new product reviews FDA posts for an approval decision. This information would not identify clinical investigators by name but likely would include information such as the number of clinical investigators in the study and the number of investigators, if any, with disclosable financial interests or arrangements.[22]

I. RECORDKEEPING

I.1. Q: What are the recordkeeping requirements for financial disclosure information?

A: The recordkeeping requirements for applicants are described in 21 CFR § 54.6. Applicants must retain certain information on clinical investigators' financial interests and arrangements (21 CFR § 54.6(a)) and permit FDA employees to have access to the information and to copy the records at reasonable times (21 CFR § 54.6(b)(2)). Records are to be maintained for two years after the date of approval of the application (21 CFR § 54.6(b)(1)).

Additionally, IND and IDE sponsors are required to maintain complete and accurate records of financial disclosure information as part of the records for the investigation (21

[21] *Federal Register*, February 2, 1998, 63 *FR* 5233

[22] FDA also recognizes that subjects participating in a clinical trial may be interested in the financial interests/arrangements of the clinical investigator at the site where the subject is considering participation. The Department of Health and Human Services Guidance Document, "Financial Relationships and Interests in Research Involving Human Subjects: Guidance for Human Subject Protection," which is applicable to FDA regulated research, recommends that consideration be given to providing potential subjects with information about the financial interests and arrangements of the parties involved in the research. This guidance is available at http://www.hhs.gov/ohrp/policy/fguid.pdf.

CFR §§ 312.57(b) and 812.140(b)(3)) and to retain the records pursuant to the required retention periods identified in the IND and IDE regulations (21 CFR §§ 312.57(c) and 812.140(d)).

I.2. Q: What kind of documentation is necessary for applicants to keep in case questions about certification and/or disclosure arise?

A: To the extent that applicants have relied on investigators as the source of information about potentially disclosable financial interests and arrangements, the underlying documentation (e.g., copies of executed questionnaires returned by investigators, correspondence on the subject of financial disclosure, mail receipts, etc.) should be retained. Likewise, to the extent that applicants who did not sponsor a covered clinical study rely on information furnished by the sponsor, the underlying documentation, including all relevant correspondence with and reports from the sponsor, should be retained. To the extent that applicants rely upon information available internally, all appropriate financial documentation regarding the financial interests or arrangements in question should be retained. For example, in the case of significant payments of other sorts, applicants should keep documentation including, but not limited to, records of electronic financial transactions, certified mail delivery receipts, etc. (21 CFR §§ 54.6(a), 312.57(b) and 812.140(b)(3).)

If storage space is a concern, sponsors and applicants may use electronic storage. For example, required records may be scanned as certified copies [23] of the original and stored electronically, as long as the records remain accessible for inspection and copying by FDA (see Question J.1). If electronic records are used, you should consult guidance on electronic storage of clinical trial records under part 11, "Computerized Systems Used in Clinical Investigations,"[24] for further information about maintaining scanned documents.

J. FDA INSPECTIONS

J.1. Q: Will financial disclosure information be reviewed during a bioresearch monitoring program (BIMO) inspection of the sponsor?

A: During a sponsor inspection, it is FDA's policy to review financial disclosure information that clinical investigators provide to the sponsor, although FDA may request access to these records at other reasonable times. FDA has the authority to access and copy documents supporting an applicant's certification or disclosure statement submitted to the agency in a marketing application (21 CFR § 54.6(b)(2)). FDA's regulations require sponsors to establish and maintain records of data obtained during investigational

[23] FDA's guidance on "Computerized Systems Used in Clinical Investigations" defines "certified copy" as a copy of original information that has been verified, as indicated by dated signature, as an exact copy having all the same attributes and information as the original.

[24] This guidance may be accessed at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070266.pdf.

studies of drugs, biological products, and devices that will enable the agency to evaluate a product's safety and effectiveness.[25]

J.2. Q: Will financial disclosure be part of a BIMO inspection of a clinical site?

A: It is FDA's policy that FDA investigators should ask the clinical investigator if he/she submitted information to the sponsor prior to initiation of the study and updated that information, as needed, for up to one year after completion of the study at the site.

J.3. Q: Are there any instructions for FDA's inspectional staff with respect to reviewing records pertaining to financial disclosure?

A: FDA has provided instructions in the Compliance Program Guidance Manual (CPGM) chapters on clinical investigator inspections[26] and sponsor inspections.[27]

K. CONTACTS

K.1. Q: Who may be contacted in each FDA Center to answer questions regarding this regulation?

A: The following entities may be contacted: Division of Drug Information in the Center for Drug Evaluation and Research, phone 888-463-6332 or 301-796-3400, Division of Small Manufacturers, International and Consumer Assistance in the Center for Devices and Radiological Health, phone 800-638-2041 or 301-796-7100, and the Office of Communication, Outreach and Development in the Center for Biologics Evaluation and Research, phone 800-835-4709 or 301-827-1800.

[25] 21 CFR §§ 54.6, 312.57, 312.58, 812.140 and 812.145.
[26] http://www.fda.gov/ICECI/EnforcementActions/BioresearchMonitoring/ucm133562.htm
[27] http://www.fda.gov/ICECI/EnforcementActions/BioresearchMonitoring/ucm133777.htm

APPENDIX

Considerations for Collecting Financial Disclosure Information from Clinical Investigators

Suggested items to provide to clinical investigators to assist them in complying with financial disclosure reporting requirements:

1) Identify the sponsor(s) of the covered clinical study. **See Section IV.E.**

2) Identify whose financial interests and arrangements need to be reported (e.g., clinical investigators, their spouses and dependent children). **See Section IV.D.**

3) Identify the financial interests and arrangements that must be disclosed in detail. **See Section III.B and Question C.1.**

   NOTE: The threshold amounts apply separately for each sponsor (**see Question E.1**) but are cumulative for the investigator and his/her spouse and dependent children (**see Section III.B**).

   a) Employment by any sponsor. **See Section III and Questions B.1 and D.4.**

   b) Any compensation by any sponsor in which the value of compensation is affected by study outcome. **See Section III.B.1.**

   c) Any proprietary interest in the tested product. **See Section III.B.2.**

   d) Any equity interest in any sponsor of the covered clinical study whose value cannot be readily determined through reference to public prices. **See Section III.B.3.**

   e) Any equity interest in any sponsor of the covered clinical study if that sponsor is a publicly held company and the interest exceeds $50,000. **See Section III.B.4 and Questions C.2 and C.3.**

   f) Significant payments of other sorts (SPOOS) that have a cumulative monetary value of $25,000 or more made to the investigator or the investigator's institution. **See Section III.B.5 and Questions C.4, C.5 and C.6.**

4) Remind investigators of obligation to promptly update their financial disclosure information when relevant changes occur during the study and for one year following study completion. **See Questions C.2 and D.6.**