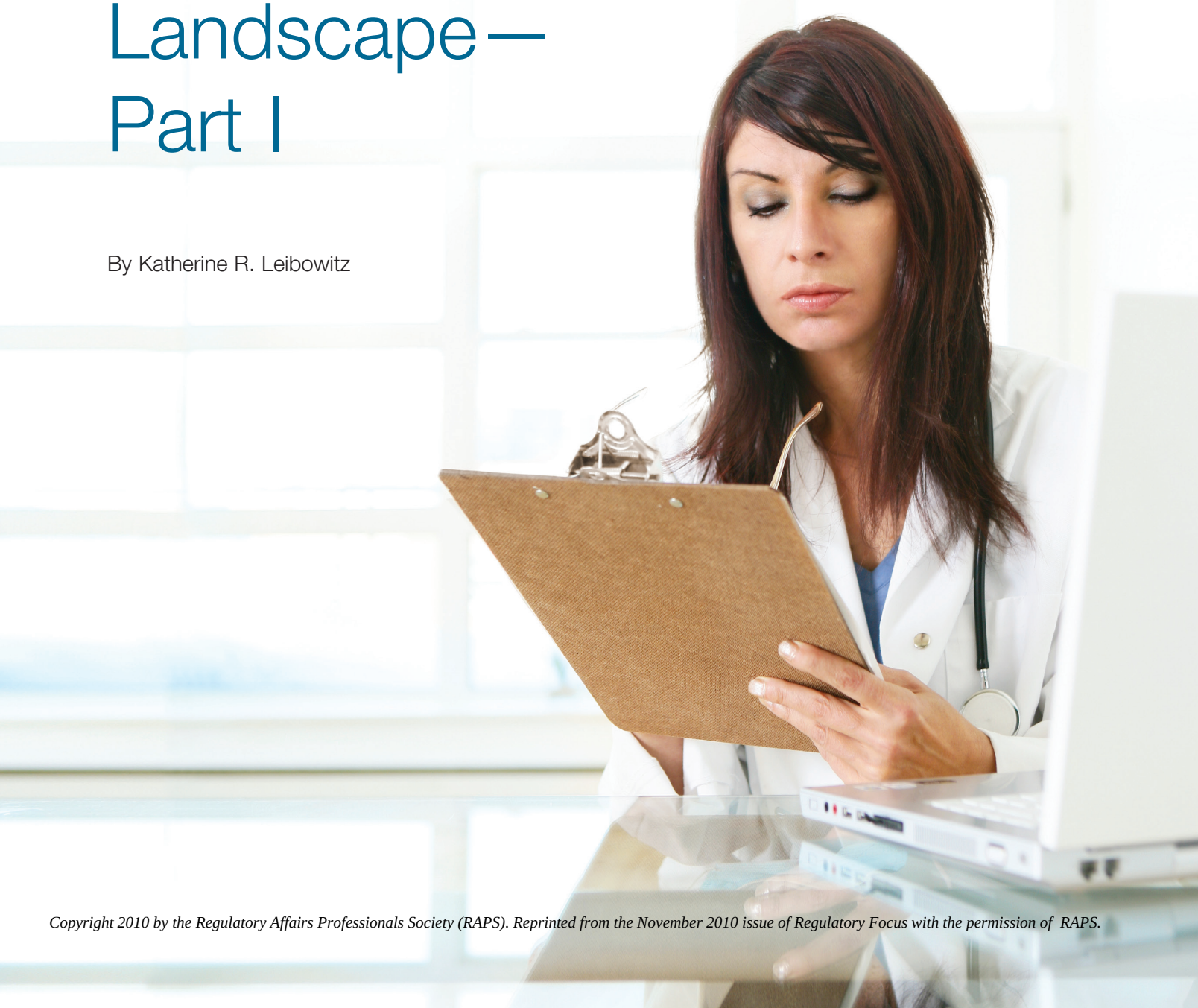
FDA's Financial Disclosure Regulations: Careful Compliance in a Changing Landscape—Part I

By Katherine R. Leibowitz



At first glance, compliance with US Food and Drug Administration (FDA) financial disclosure regulations set forth in 21 CFR Part 54 looks straightforward. The regulations are short, and the FDA guidance[1] clarifies a number of issues. However, when faced with a mountain of invoices, financial data and contracts documenting financial ties to investigators and their institutions, trial sponsors often must make judgments about whether to disclose particular financial arrangements to FDA.

The FDA financial disclosure regulations are designed to help uncover potential investigator bias that may arise due to financial ties between the investigator and the trial sponsor. For example, if a trial sponsor compensates an investigator with company stock or royalties based upon product sales, the investigator may be motivated to influence the outcome of the trial to increase the value of his compensation. Although the regulations do not ban certain financial arrangements that might bias the investigator, they require the sponsor to disclose these arrangements. FDA uses the disclosed information in its assessment of the reliability of the trial data.[2]

In today's world, the consequences of failing to properly disclose investigator financial interests in the sponsor can go beyond the unwanted—but known—penalties such as an FDA audit or rejection of the study data. Federal and state governments, trade associations, manufacturers, academia and medical journals are among those weighing in on physician ties to industry. This attention to transparency of financial conflicts of interest is not specifically connected to enforcement of the financial disclosure regulations. However, at least partly in response to this pressure, FDA has begun increasing its attention to financial disclosure. Given the magnitude and variety of transparency concerns raised by a range of entities, a prudent company will recognize the likelihood of stricter FDA scrutiny of its financial disclosures and therefore will follow a conservative approach.

This article, which will be published in two parts, provides legal and practical guidance for sponsors as they navigate the world of financial disclosure under the FDA regulations. This first installment sets forth the general requirements of the FDA financial disclosure regulations and actions FDA may take. It also discusses the challenges many sponsors face in interpreting the regulatory requirements relating to "significant payments of other sorts,"[3] or SPOOS. The second article in this series will delve further into SPOOS and will then move onto the three other types of financial arrangements covered by the regulations. It will also acknowledge the seachange currently underway both within and outside FDA regarding financial conflicts of interest, and conclude with proactive steps companies can take to help stay under the radar.

FDA Financial Disclosure Regulations

General Requirements

Applicants that submit clinical data from covered clinical studies to FDA as part of a marketing application for a device, drug or biologic must comply with financial disclosure regulations in 21 CFR Part 54. These regulations cover studies upon which the applicant or FDA relies to establish the product's effectiveness and any study where a single investigator makes a significant contribution to demonstrating the safety of the product.[4] FDA supplemented the regulations with guidance in 2001.[5]

Specifically, the financial disclosure regulations require any applicant submitting a marketing application that contains clinical data to either certify the absence of certain financial interests of clinical investigators; or disclose those financial interests and explain any steps taken by the applicant to minimize the potential for bias.[6] The regulations contain a due diligence exemption for applicants that, despite the exercise of due diligence, have been unable to obtain the information.[7]

The regulations require disclosure of four types of financial arrangements with the investigator:

Compensation Affected by the Outcome of Clinical Studies

This disclosure covers compensation whose value could increase if the study results are favorable. Examples include stock, stock options and other equity interests in the sponsor. Also included are royalties from product sales and other compensation tied to sales of the product being studied.[8]

Proprietary Interest in the Tested Product

This category includes patents, trademarks, copyrights and licensing agreements.[9]

Significant Equity Interest in the Sponsor of a Covered Study

The regulations address private and public company interests separately. For privately held companies, this category means any ownership interest, stock, stock options or other financial interest on the part of the investigator. For public companies, this covers any equity interest that exceeds $50,000 in value, as well as any equity interest whose value cannot readily determined through public pricing.[10]

Significant Payments of Other Sorts (SPOOS)

SPOOS covers payments of more than $25,000 by the sponsor to the investigator and/or the investigator's institution to support the activities of the investigator, excluding payments for clinical studies. Examples include grants, honoraria, consulting fees and compensation in the form of equipment.[11]

Additional Nuances

For purposes of the regulation, the term "investigator" means the clinical investigator,

the investigator's spouse and/or dependent children.[12] The time period covered by the regulations is the study period and one year following completion of the study. The investigators and the sponsor must update the financial disclosure information if any relevant changes occur during the covered time period.[13]

The financial disclosure regulations require the "applicant" to submit the financial disclosure information to FDA. The applicant is the party that submits a marketing application to FDA for approval, and is typically the trial sponsor.[14] For ease of reference, this article assumes that the applicant is the trial sponsor.

Timing and Format

The regulations require the sponsor to collect the financial disclosure information from each investigator prior to permitting the investigator to participate in the study.[15] Typically, sponsors provide each investigator with a questionnaire. The sponsor does not submit the completed investigator questionnaire to FDA, but instead uses FDA Form 3454 and, if applicable, FDA Form 3455 to make the required certification and/or disclosures.

The sponsor reports the financial disclosure information to FDA as part of its marketing application. While the regulations require the investigator to update financial disclosure information during the course of the study and for one year following completion, the sponsor does not submit the updated information to FDA. Rather, the sponsor retains the updated information in its files.[16]

Agency Actions

FDA will evaluate the disclosed financial information to determine the impact of the investigator's financial interests on the reliability of the study data. The regulations state that FDA may consider both the size and nature of the disclosed interest, and steps taken to minimize investigator bias.

In assessing potential bias, FDA will take into account the study design and purpose. The regulations list the following as steps that may adequately protect against any bias created by a disclosable financial interest: study designs that use multiple investigators (most of whom lack disclosable financial interests) and blinding objective endpoints or measurement of endpoints by someone other than the interested investigator.[17] According to FDA, randomized assignment to treatment is another common way to minimize bias.[18]

If FDA determines that the investigator's financial interests raise a serious question about the study data integrity, the agency can take any action it deems necessary to ensure the reliability of the study data, including:

- auditing the data from the study in question
- requesting the applicant to submit further analyses of the data, such as to evaluate the effect of the financially interested investigator's data on the overall outcome of the study
- requesting the applicant to conduct additional independent studies to confirm the results of the questioned study
- refusing to treat the study as providing data that can be the basis for an agency action[19]

Common Financial Disclosure Questions Raised by Sponsors

Identifying, Tracking and Reporting SPOOS

For a number of reasons, the most challenging financial disclosure reporting category is often SPOOS.[20] On the administrative side, the sponsor must track a complex web of payments and other ties with all investigators and their institutions over the course of the study and for one year thereafter. Further, because SPOOS does not include payments for conducting clinical studies, the sponsor must look into the precise nature of each payment to see if it falls into the SPOOS category.

Large sponsors may have multiple divisions with separate accounting systems not configured to track SPOOS. To further complicate matters, payments may come not only from the sponsor's clinical or research department, but also from sales and marketing departments or elsewhere. These sponsors must pull records from various systems and eliminate overlapping data. Payments by related companies such as parent and sister corporations may also need to be reviewed. Sponsors often find that their accounting systems do not provide sufficient detail about the payment and may need to delve further into the records or even the underlying contracts, some of which may not be readily available.

On the payee side, the sponsor must track payments not only to the clinical investigators, but also to the investigator's spouse and dependent children and the investigator's institution. Perhaps the most time-consuming review involves identifying and tracking SPOOS made to the investigator's institution.

An investigator can have ties to multiple institutions, such as a university, hospital, medical practice and/or a research foundation affiliated with the investigator's practice. Further, if the investigator recently changed institutions, the sponsor needs to check previous institutions that received payments during the study and for one year following completion.

All of these potential SPOOS payments need to be tracked during the reporting period, although sponsors must disclose them to FDA only if, when combined, they exceed the $25,000 regulatory threshold.

One common question is whether sponsors should track consulting payments made to investigators before the trial. Under the regulations, the SPOOS clock starts ticking when the study commences. But the regulations and guidance do not specify what constitutes "commencement"

of the study. Does the study start when the sponsor submits the investigational device exemption (IDE) or investigational new drug (IND) application to FDA? When FDA first grants conditional approval of the IDE? Upon final approval? What if the investigators assist in the development of the protocol or other activities prior to the sponsor's submission of the IDE or IND? To determine how far back to look, the sponsors may consider the size of the payment(s), how long before the trial the payments were made, when the payments stopped, the duration of the payments, whether the payments will continue into the trial period, and whether the inclusion of pre-trial payments would push the investigator over the $25,000 threshold for SPOOS.

SPOOS to the Investigator

This section addresses SPOOS paid directly to the investigators.[21]

Consulting and Advisory Board Services

Consulting fees are one of the most common forms of payment to investigators that the sponsor must track as SPOOS. Companies developing investigational products and the trial protocols often enter into consulting agreements with physicians who have experience in the relevant field. For medical devices, physicians may assist with designing and developing the devices and instrumentation, mechanical testing, drafting protocols or other preclinical activities. They may also serve on a company's medical advisory board or scientific advisory board for a variety of products under development.

The physicians who served as consultants or advisory board members often develop specialized knowledge of the company's investigational product. When the company reaches the clinical trials stage, it may retain these physicians for services such as refining the instrumentation for the device, preparing training manuals or training other physicians in the use of the device. It is natural for the company to want these physicians to serve as trial investigators. However, in the spirit of the FDA financial disclosure regulations, a consulting arrangement may make an investigator feel beholden to the sponsor and, therefore, more likely to produce favorable trial results than non-interested investigators.

A company can take steps before it reaches the clinical trials stage to minimize its future financial disclosure obligations for consultants and advisory board members. For example, when setting up advisory boards, a company could exclude thought leaders that it may later want to tap as trial investigators. While many companies find it unavoidable to use consultants as investigators, a prudent approach is to structure consulting agreements to terminate well before the clinical trials commence. The company also will carefully consider the ramifications of compensating consultants with equity in the firm or an interest in

the tested product and will keep SPOOS payments well below the $25,000 threshold.

Honoraria, Medical Meetings and Travel

The financial disclosure regulations require sponsors to track all honoraria paid to the investigator as SPOOS.[22] Payments for speaking engagements typically need to be tracked even if they occur indirectly, such as through sponsor support of an industry conference.

Sponsors often purchase tickets for investigators to attend industry conferences, and may cover their transportation, lodging and meal expenses. Sponsors must track conference tickets and program fees as SPOOS.

In contrast, travel expense reimbursement does not constitute SPOOS if the expenses are reasonable. The term "reasonable" is not defined by the regulations. The guidance gives the following example as an unreasonable travel expense: an investigator being "flown to a resort location for an extra week of vacation."[23] In addition, the guidance states that transportation, lodging and meal expenses for the investigator's family members "are considered unnecessary and should be tracked as SPOOS."[24]

SPOOS to the Investigator's Institution

The regulations require the sponsor to track as SPOOS all payments to the investigator's institution that support the investigator's activities.[25] Payments to the investigator's institution can be difficult to track for a number of reasons.

A company's accounting system may indicate that a payment went to a specific institutional department, but the department may be comprised of doctors with various specialties. For example, a sponsor of a knee study may make a payment to a university's orthopedics department that employs spine, hip, knee, shoulder and neck doctors. To see if the payment may have supported the activities of the investigator, the sponsor will need to review additional records. This second layer of review may show that the payment supported clinical studies, in which case the sponsor does not need to track the payment. The payment may have supported spine research, which presumably would not have involved a

knee study investigator. If the payment supported knee-related preclinical research, the sponsor will need to delve further to see if the payment supported the activities of the investigator.

Whether a payment can be considered as supporting the activities of the investigator often requires a judgment call. Although the regulations define SPOOS to the investigator's institution as payments to the institution "to support activities of the investigator,"[26] the meaning of this phrase is unclear. The guidance states that the payment to the institution must be "for direct support of the investigator" and that payments "not made on behalf of the investigator do not need to be reported."[27]

The guidance offers two examples: (1) if the sponsor gives the investigator equipment or money to purchase equipment for use in a laboratory, the payment should be tracked as SPOOS unless the payment is in relation to the conduct of a clinical trial; and (2) if the sponsor provides the investigator with software or with money to purchase the software needed for a clinical trial, that payment would not be trackable as SPOOS.[28] These examples do not begin to cover the range of situations that might be SPOOS.

The determination of whether a payment was "for direct support of the investigator" or "made on behalf of the investigator" can be a slippery slope. At one end of the spectrum, the sponsor could disclose all payments to the institution (other than for clinical studies) that support work in the doctor's specialty, namely knee surgery in this example, under the theory that the investigator arguably benefits at least indirectly from the payment because it supports work done by the knee doctors in the investigator's department.

This proposed over-disclosure goes beyond the regulatory requirements. Further, this approach could turn investigators who otherwise would not have a disclosable financial interest into "interested" investigators. In that case, the sponsor would have to include these additional investigators in the analysis of financial interest for its marketing submission to FDA, which could change the impact of financial interest on study results.

At the other end of the spectrum, the sponsor might choose to disclose payments to the investigator's institution only if the payments were earmarked for the investigator. As further suggested in the examples below, this second approach may result in under-disclosure. Ultimately, sponsors must wrestle with the following question: at what point is the support to the investigator so attenuated that the regulations and guidance do not require disclosure?

An additional judgment call that many medium to large-sized companies often have to make is when to stop digging deeper into records to determine the exact nature of the payment to the investigator's institution. If a sponsor's accounting system shows a payment to the investigator's institution, sometimes reviewing the invoice will resolve the issue. If the invoices do not yield enough information, the next step may involve phone calls to the payee or review of the contract under which the payment was made. The FDA guidance directs the sponsor to use due diligence in obtaining the financial disclosure information,[29] so the sponsor should be prepared to defend its decision to stop delving further into records and the basis for its conclusion that payments to the investigator's institution did not need to be disclosed.

At smaller companies, often one person has the institutional memory of the financial arrangements with the investigators and their institutions. The prudent company will document and track these arrangements from the start in an organized fashion with an eye to the financial disclosure regulatory requirements.

The second article in this series will explore in greater depth common SPOOS to investigators' institutions. It will review the three other types of financial arrangements covered by the regulations. The article will also discuss the changing landscape within and outside FDA regarding transparency of financial interests, and conclude with proactive steps companies can take to help stay in compliance.

References

1. *Guidance for Industry: Financial Disclosure by Clinical Investigators.* FDA website. http://www.fda.gov/RegulatoryInformation/Guidances/ucm126832.htm. Published 20 March 2001. Accessed 15 September 2009.
2. 21 CFR 54.1(b).
3. 21 CFR 54.2(f).
4. 21 CFR 54.2(e).
5. Ibid 1.
6. 21 CFR 54.4.
7. 21 CFR 54.4.
8. 21 CFR 54.2(a).
9. 21 CFR 54.2(c).
10. 21 CFR 54.2(b).
11. 21 CFR 54.2(f).
12. 21 CFR 54.2(d).
13. 21 CFR 812.110(d); 21 CFR 812.43(c)(5); Ibid 1, Question 15.
14. 21 CFR 54.2(g).
15. 21 CFR 812.43(c)(5); Ibid 1, Question 6.
16. Ibid 1, Questions 14 and 15.
17. 21 CFR 54.5.
18. *The Food and Drug Administration's Oversight of Clinical Investigator's Financial Information*. Office of Inspector General website. Appendix F, p. 5: http://oig.hhs.gov/oei/reports/oei-05-07-00730.pdf, Appendix F: Agency Comments, p. 5. Published 12 January 2009. Accessed 12 May 2009.
19. 21 CFR 54.5(c).
20. 21 CFR 54.2(f).
21. 21 CFR 54.2(f).
22. 21 CFR 54.4(a)(3)(ii).
23. Ibid 1, Question 26.
24. Ibid.
25. 21 CFR 54.2(f).
26. 21 CFR 54.2(f).
27. Ibid 1, Question 25.
28. Ibid.
29. Ibid 1, Question 3.

Author

Katherine R. Leibowitz is an attorney at the law firm of Hogan Lovells US LLP and practices in the firm's Philadelphia office.

Leibowitz would like to thank Dr. Steven Datlof, Esq., who also practices in the firm's Philadelphia office, for his contribution to this article.