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Financial Disclosure by Investigators

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On March 23, 2010, President Obama signed the the Patient Protection Affordable Care Act.[1] This act includes the Physician Payment Sunshine Provision, which requires pharmaceutical and medical device companies to create publicly accessible websites that report payments to physicians exceeding $100 in any year. Payments are defined broadly and include items such as cash, cash equivalents, in-kind services, gifts, food, entertainment, research grants, charitable contributions, license fees, dividends, clinical study fees, and just about any "other transfer of value the Secretary determines appropriate." Regulations implementing the law presumably will be published before the reporting requirement takes effect in March 2013. In preparation for this reporting tsunami, it is a good time to review clinical investigator reporting under current regulations.

Regulations and Guidance

Federal regulation 21 CFR 54 requires "anyone who submits a marketing application of any drug, biological product or device to submit certain information concerning the compensation to, and financial interests of, any clinical investigator conducting clinical studies covered by the rule."

Regulations 21 CFR 312.64(d) and 21 CFR 812.110(d) require clinical investigators to provide sponsors with "sufficient accurate financial information to allow an applicant to submit complete and accurate certification or disclosure statements as required under part 54 of this chapter. The clinical investigator shall 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." Regulations 21 CFR 312.53 and 21 CFR 812.43 require sponsors to obtain this information "before permitting an investigator to begin participation in an investigation."

FDA Guidance for Industry - Financial Disclosure by Clinical Investigators provides FDA's perspectives on how to implement the regulations.

According to this Guidance, the following financial arrangements should be disclosed:

- Compensation made to the investigator in which the value of compensation could be affected by study outcome.
- A proprietary interest in the tested product, including, but not limited to, a patent, trademark, copyright or licensing agreement.
- Any equity interest in the sponsor of a covered study, i.e., any ownership interest, stock options, or other financial interest whose value cannot be readily determined through reference to public prices.
- Any equity interest in a publicly held company that 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; and
- Significant payments of other sorts, which are payments that have a cumulative monetary value of $25,000 or more made by the sponsor of a covered study to the investigator or the investigators' institution to support activities of the investigator, exclusive of the costs of conducting the clinical study or other clinical studies, (e.g., a grant to fund ongoing research, compensation in the form of equipment, retainers

for ongoing consultation, or honoraria) during the time the clinical investigator is carrying out the study and for one year following completion of the study.

The Financial Disclosure Guidance states that, for financial disclosure purposes, "for drugs and biological products, the terms investigators and subinvestigators include persons who fit any of these criteria: sign the Form FDA 1572, are identified as an investigator in initial submissions or protocol amendments under an IND, or are identified as an investigator in the NDA/BLA… For medical devices, clinical investigators are defined as individual(s), under whose immediate direction the subject is treated and the investigational device is administered, including follow-up evaluations and treatments… In general, investigators and subinvestigators sign 'investigator agreements' in accordance with 21 CFR 812.43(c) and it is these individuals whose interests should be reported." The reporting requirements apply to both U.S. and foreign investigators in IND and IDE studies.

The regulations do not define the phrase, "completion of the study," so the Guidance clarifies that "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." It further clarifies that "the sponsor may consider completion of the study to be when the last study site is complete, or may consider each study site individually as it is completed." The second option is more practical for investigators. The date of the close-out visit is convenient to use for the completion date of the study.

While the regulations require updates for the entire reporting period, they do not require investigators to file a final report at the end of the reporting period. Nevertheless, some sponsors may require final reports or remind investigators to update their disclosures, if necessary.

The regulations require clinical investigators to "promptly update this information if any relevant changes occur during the reporting period." However, they do not define the term "relevant changes." The Guidance clarifies: "In light of the potential volatility of stock prices, FDA recognizes that the dollar value of an investigator's equity holding in a sponsoring/applicant company is likely to fluctuate during the course of a trial. 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 that equity interest fluctuates below that threshold."

The guidance provides various examples of "significant payments of other sorts." The guidance clarifies one example, "compensation in the form of equipment": "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 trial, the payment would be considered a significant payment of other sorts and should be reported… Payments made to the institution or to other nonstudy participating investigators that are not made on behalf of the investigator do not need to be reported." In other words, if the investigator gains personal financial benefit from donated equipment outside the clinical study, the value of that benefit should be reported.

The regulations set the reporting thresholds of $25,000 and $50,000 in February, 1998, when the Consumer Price Index was 162.[4] The Index is now 218, so the inflation-adjusted thresholds would be $34,000 and $67,000. On the other hand, the thresholds do not consider the lower income levels in low-resource countries, where $5,000 or less might impose an equivalent financial conflict.

The regulations do not explicitly require disclosure of employment relationships. Nevertheless, if consulting fees qualify as significant payments of other sorts, wages and

salaries should also qualify. Certainly, an employee-investigator's compensation could be affected by study outcome.

The regulations and guidance do not explicitly state whether the thresholds apply to the investigator, spouse and dependent children individually or collectively, but "collectively" makes more sense from the perspective of incentives. Also, the above definition of "clinical investigator" "includes the spouse and each dependent child of the investigator."

Sponsors do not pass the investigators' financial disclosure forms along to the FDA. Instead, they summarize the information on two FDA forms. They use FDA Form 3454 – Certification: Financial Interests and Arrangements of Clinical Investigators to certify that they "have not entered into any financial arrangement with the listed clinical investigators."[5] They use FDA Form 3454 – Disclosure: Financial Interests and Arrangements of Clinical Investigators to report clinical investigators who "participated in financial arrangements or hold financial interests that are required to be disclosed."[6] There is no regulation against financial conflicts. However, FDA takes them and any "steps taken to minimize the potential bias of clinical study results by any of the disclosed arrangements or interests" into consideration when reviewing marketing applications.

European Union Privacy Laws

European Union (EU) privacy laws are stricter than U.S. laws. The European Union Privacy Directive defines "personal data" as "any information relating to an identified or identifiable natural person ('data subject'); an identifiable person is one who can be identified, directly or indirectly, in particular by reference to an identification number or to one or more factors specific to his physical, physiological, mental, economic, cultural or social identity." (Article 2(a))[7] Some sponsors therefore obtain informed consent to use and process personal information (in which the investigator must provide clear, freely given, specific and unambiguous informed consent) from the investigator in their financial disclosure forms.

This approach makes some sense, but financial information is only one type of personal information covered by the EU law. Any information that can directly or indirectly identify the investigator is covered by the EU privacy laws, so a more general consent is required. The sponsor should obtain consent from investigators in European and perhaps other countries before transferring any of this information outside the European Economic Area (EEA).

Furthermore, if a financial disclosure form includes private information that could identify a spouse or adult child, the sponsor should obtain consent from that person as well.
To complicate matters, if the sponsor transfers private personal information into the EEA, transferring it back out to a third country outside of the EEA, e.g., to a data entry contractor in India, still requires investigator consent, unless other safeguards are in place to adequately protect the personal information, as specified in the EU privacy laws.

A Standard Form

On behalf of Model Agreements and Guidelines International (MAGI), the author reviewed financial disclosure forms from 18 pharmaceutical, medical device, and contract research organizations. There are substantial differences among the forms. These differences create confusion and place an unnecessary reporting burden on investigators and clinical research sites. Some of the forms are superior to others in eliciting the correct information.

A standardized form, based on the best features of current forms and compliant with both the letter and spirit of the rules, reduces the burden and supports complete and accurate

reporting. This form is located on MAGI's website at http://www.magiworld.org/standards. Suggestions for improvement are invited.

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