

Clinical trials: A compliance primer for physician practices

By Gregg D. Reisman, Esq. and Lara Jean Ancona, Esq.

Editor's note: Gregg D. Reisman, Esq. and Lara Jean Ancona are attorneys in the New York Garfunkel, Wild & Travis, P.C. Gregg may be reached by telephone at 516/393-2294 or by email greisman@gutlaw.com and Lara may be reached by telephone at 516/393-2245 or by email lancona@gutlaw.com

The conduct of human research, including clinical trial research; involving drugs, biologicals and devices; requires an understanding of, and compliance with, extensive and complicated federal and state laws, rules, and regulations. Traditionally, manufacturers have focused upon institutions, such as community hospitals and academic medical centers, to act as the sites for the conduct of their research. These institutions typically have substantial administrative infrastructure, often have long standing experience in conducting research, and many times even have their own institutional review boards (IRB). Therefore, these institutions are generally well equipped to handle the significant responsibility relating to the performance of clinical trials. This is often not the case for private practice physicians performing research in their private offices.

Because manufacturers are increasingly turning to physician offices as clinical trial sites, more and more physicians, who have little or no experience with clinical trials, or who have historically only acted as principal investigators

under the watchful guidance and oversight of a hospital, are now being faced with significant responsibility for which they may be unprepared. Physicians should carefully consider the capabilities of their office and their staff, and the obligations created by performing clinical research in their offices, prior to agreeing to act as a clinical trial site.

Failure to properly conduct research in compliance with the requirements of the applicable laws, rules and regulations, can result in serious consequences, including placing patients at risk, lawsuits, FDA enforcement actions and even licensure issues. This article will review certain of the considerations and concerns relating to the responsibilities of the physician conducting FDA related research in his or her office.

Overview of research obligations

Prior to agreeing to perform human research in his or her office, a physician and the staff of the office should be prepared to:

1. Adopt research policies and procedures;
2. Engage and communicate with an IRB;
3. Contract with a research sponsor;
4. Recruit subjects and obtain informed consents;
5. Comply with Form 1572 and the rules of Good Clinical Practice;
6. Comply with the applicable research protocol and maintain research records;
7. Report adverse events and maintain control of investigational drugs;
8. Train staff; and

9. Ensure that the human research is conducted in compliance with all applicable laws, rules and regulations, including FDA regulations and HIPAA.

Policies and procedures

All necessary research policies and procedures should be written, adopted and implemented by the principal investigator and his or her office prior to conducting human research. The policies and procedures should address:

1. Compliance with the FDA and good clinical practice rules;
2. The process for reviewing and evaluating research protocols;
3. Relationship with an IRB, including appointing officials to interact with the IRB;
4. Creation of informed consent and implementation of an informed consent process;
5. Monitoring procedures to ensure that the policies and procedures are followed and oversight activities are documented;
6. Reporting procedures for responding to adverse events and non-compliance and follow-up measures to deal with such reports;
7. Procedures for maintenance of research records;
8. Procedures to avoid the appearance or existence of a conflict of interest;
9. Procedures for use, storage and oversight of research drugs; and
10. Internal audit or self-assessment procedures in connection with FDA inspections or audits.

All research policies and procedures should then be made available to the personnel of the physician's office who are involved in conducting research, and all staff involved in research should

be required to comply with the policies and procedures. The personnel involved in performance of research must be trained in the policies and procedures for, and the process of, conducting research at the physician office.

Institutional review board

With few exceptions, all research must be conducted under the oversight and approval of an IRB. Traditionally, where a physician conducts hospital based research, the hospital's IRB is used. The principal investigator conducting human research at his or her office is responsible for locating and engaging an appropriate IRB. If the principal investigator is affiliated with a hospital, the hospital's IRB may be available. Hospital IRBs are often amenable to reviewing human research performed by members of the hospital's medical staff, even when the research is not conducted at the hospital. If a hospital IRB is not available, the principal investigator will have to engage an independent or non-institutional IRB. The process of engaging an IRB often involves contracting with the IRB and ensuring that the IRB is duly constituted and capable of providing review and continuing oversight of research involving human subjects.

Once an IRB reviews and approves or disapproves proposed research, it will report such approval or disapproval to the principal investigator. Such approval will involve review of the protocol, informed consent, HIPAA authorization, investigator's brochure, proof of qualifications of researcher, and proposed advertising. Subsequently, the principal investigator will be responsible for continuing communication with the IRB, reporting protocol changes and obtain-

ing continuing IRB review of the research (required not less than once per year). The physician's office is also required to maintain adequate documentation of IRB activities, although such documentation can be maintained by the IRB on behalf of the physician's office. The documentation should include copies of all research proposals reviewed by the IRB, minutes of IRB meetings, records of continuing review activities, copies of all correspondence between the IRB and investigators, and statements of significant new findings provided to research subjects.

Contracting with the sponsor

A sponsor of research, such as a pharmaceutical company or device manufacturer, will usually require the physician's office (and often the physician acting as principal investigator for the research) to enter into a "clinical trial agreement." This Agreement is a legal document which places responsibilities for the research upon the physician's office (as the trial site) and the principal investigator (in conducting the trial) and the sponsor. The clinical trial agreement will also address (i) indemnification, if any, of the physician's office and principal investigator, in the event of subject's injury or death resulting from participation in the research; (ii) the budget for the reimbursement the physician will receive for conducting the clinical trial; (iii) the reporting requirements the physician must comply with; (iv) insurance requirements; (v) qualifications the investigators must meet; and (vi) termination rights.

Overall, it is important that the physician review and understand this Agreement before entering into it. Generally, the sponsor will provide the physician with a form of Agreement that

is beneficial to the sponsor. The physician may, therefore, find it necessary to negotiate certain of the terms contained in the Agreement and the budget and/or obtain counsel to complete this step in the process.

In negotiating this Agreement, the physician (and/or his or her counsel) must also ensure that neither the terms of the Agreement, or the research process, violates any federal or state fraud or abuse statutes, regulations or rules. The agreement must be for bona fide research; the payments being made by the sponsor must be fair market value for the services rendered by the principal investigator; and the payments cannot be in exchange for referrals from the principal investigator. A principal investigator has to be particularly careful in relation to these issues when entering into agreements to conduct post-marketing studies.

Informed consent and subject recruitment

Once research is approved by the IRB and a clinical trial agreement is executed, conduct of the research can begin. Initially, the principal investigator will need to recruit research subjects and ensure such recruitment is conducted in accordance with the requirements of the FDA regulations and the regulations under the Health Insurance Portability and Accountability Act of 1996 and related regulations ("HIPAA"). He or she will also be responsible for ensuring each research subject signs an appropriate informed consent prior to any participation in the clinical trial. Typically, the sponsor will provide an informed consent to be used. The IRB may require modifications to the form pro-

vided by the sponsor.

The process of obtaining informed consent from a research subject does not only involve ensuring that the research subject signs an IRB approved and appropriate informed consent. Rather, the signed informed consent is considered documented evidence of the entire informed consent process, e.g., the process of discussing the research with the subject to educate them regarding terms of the research and ensure that they understand the research purpose, risks, duration, procedures, alternatives and benefits. It is important that the informed consent form and the educational process be done in a manner that is understandable to the subject, e.g., in layman terms.

Under the FDA regulations, both the informed consent form and the informed consent process must contain/involve specific statements and discussions. There are at least 13 points that must be addressed in writing in the informed consent form and the entire form should be discussed with the subject during the informed consent process. The principal investigator should ensure that the process is completed correctly and that all subjects are given an opportunity to ask questions before entering into the research. The FDA website provides access to the regulations governing informed consent at <http://www.access-data.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=50> and provides guidance regarding the informed consent process at <http://www.fda.gov/oc/obrt/irbs/informedconsent.html#model>. In addition to the informed consent, the principal investigator shall ensure that each subject executes a HIPAA compliant authorization. A sample authorization

form and further information regarding this form can be obtained at <http://privacyruleandresearch.nih.gov/authorization.asp>. This form lets the research subject know how his or her protected health information will be used and disclosed and the circumstances under which his or her protected health information will remain confidential and those under which it will not.

Complying with Form 1572 and the rules of good clinical practice

In connection with FDA related research, the principal investigator is required to complete a Form 1572. By signing this Form the principal investigator is agreeing, among other things to:

1. Conduct the study in accordance with the applicable research protocol;
2. Personally conduct or supervise the research;
3. Complete the informed consent process;
4. Report adverse events to the sponsor;
5. Read and understand the investigator brochure;
6. Maintain adequate records;
7. Comply with FDA regulations and rules and rules of good clinical practice;
8. Obtain IRB approval of the trial and informed consent; and
9. Ensure that all other investigators are informed of, and comply with, these requirements.

A copy of the form can be obtained at: www.fda.gov/opacom/morechoices/fdaforms/default.html.

Additionally, all research must be conducted in compliance with the rules of good clinical practice. These rules require principal investigators (and all other investigators involved in a clinical trial) to (i) comply with the general fed-

eral regulations, (ii) control the investigational drug; (iii) create and retain records, (iv) create reports, and (v) obtain appropriate IRB review. Guidance regarding the rules of good clinical practice can also be obtained on the FDA website at <http://www.fda.gov/cder/guidance/959fnl.pdf>.

Complying with the research protocol and maintaining records

The principal investigator is responsible for ensuring that the research proceeds in compliance with the applicable research protocol. The protocol contains the criteria for admitting subjects into the study, the procedure for administering the study drug or device, detail regarding testing of each study subject and all follow up tests required for each study subject. Failure to strictly follow the protocol can result in sanction by both the study sponsor and the FDA. Moreover, once a protocol has been approved by an IRB, an investigator cannot make changes to such protocol without the IRB approving changes. Moreover, often times, the research sponsor will require its approval of all changes as well.

Further, the actual conduct of the clinical trial will require the creation and maintenance of research records as set forth in the protocol and FDA regulations. These records shall include records of disposition of drugs or the device, case histories, regulatory correspondence, and a delegation log indicating responsibilities of all those involved in the research. Even following completion of the trial, the principal investigator will often be required to maintain certain records and conduct certain follow up activities.

Reporting adverse events and maintaining control of investigational drug

A principal investigator is responsible for reviewing and understanding the applicable FDA regulations and for reporting all adverse results of the study to the proper individuals at the IRB and sponsor. The principal investigator must strictly monitor all study subject reaction to participation in the study and report, in a very timely manner, an adverse response of such study subject. The principal investigator will also be responsible for making all progress reports, safety reports, final reports, derivation reports, financial disclosures, reports on changes in research activities and reports on unanticipated problems involving risks to subjects to the IRB,

sponsor and FDA. Further the principal investigator will be responsible for keeping accurate records of the use, storage and disposal of any study drug used in the research.

Conclusion

As noted above, failure to properly conduct research in compliance with the requirements of the applicable laws, rules and regulations, can result in serious consequence to the physician and staff conducting the research. As part of its monitoring and oversight responsibilities, the FDA conducts periodic audits of research sites. Should a FDA audit result in the FDA's determining that the research site is not operating in accordance with applicable laws, rules and regulations, the

FDA may issue a Warning Letter to the researchers or the research site regarding their failures. All Warning Letters issued by the FDA are posted on the FDA website and are publicly available at <http://www.fda.gov/foi/warning.htm>.

Failure to timely and satisfactorily respond to an FDA Warning Letter can lead to more significant consequences such as FDA enforcement actions. To avoid the consequences, it is very important that any physician interested in conducting research in his or her office understand the requirements and obligations surrounding such research before moving forward. ■