

- Research Professional's Tip Sheet -

April 2008

FDA Warning Letters issued to clinical investigators conducting drug or device studies present a great opportunity to reinforce and enhance our own knowledge regarding the conduct of clinical research. This tip sheet is intended to highlight a single FDA Warning Letter submitted to an investigator after an FDA inspection and the findings of non-compliance described within. Each finding cited includes examples illustrating the finding, if available, and a reference to applicable MCW IRB Standard Operating Procedures. Overall, these examples of non-compliance are powerful reminders that we must pay careful attention to the regulations governing all clinical research.

In 2007 the FDA conducted an inspection of a device study at a healthcare organization. The inspection was conducted under a program designed to ensure that data contained in marketing applications was scientifically valid and accurate and that human subjects were protected from undue hazard or risks during the course of the investigation. The subsequent Warning Letter highlighted numerous violations of the regulations governing the proper conduct of the clinical study involving an investigational device and the monitoring of the study.

The individual conducting the device study was also the sponsor of the study. A sponsor-investigator is an individual who both initiates and conducts an investigation and under whose immediate direction an investigational device or drug is administered, dispensed or used. The responsibilities of a sponsor-investigator conducting a device study include those of both a sponsor and an investigator (**21 CFR 812 subpart C and E**). Therefore, sponsor-investigators of device studies are required to comply with the FDA regulations at 21 CFR 812 for both sponsors and investigators.

Finding #1

The investigator failed to ensure the study was conducted in accordance with the investigational plan, applicable FDA regulations and any conditions of approval imposed by FDA or the IRB.

(21 CFR 812.100, 21 CFR 812.110(b))

- Several individuals, who did not meet eligibility criteria, were enrolled in the study.
- All adverse events and medical complications were not documented in accordance with the IRB approved study protocol. The study required detailed descriptions of the adverse events and complications as well as the outcome.
- The investigator did not use the device in the manner specified by the protocol.
- Serious adverse events and complications were not reported to the IRB as required by the study protocol and the IRB policy.

FDA reminder: The principal investigator is responsible for ensuring that all study staff are adequately trained and qualified to perform study tasks delegated to them. The investigator may delegate tasks to other qualified personnel but cannot delegate the principal investigator's responsibility to ensure that all study tasks are correctly performed.

An investigator is responsible for ensuring that an investigation is conducted according to the signed agreement, the investigational plan and applicable FDA regulations, for protecting the rights, safety, and welfare of subjects under the investigator's care, and for the control of devices under investigation. An

investigator also is responsible for ensuring that informed consent is obtained in accordance with part 50 of this chapter. (21 CFR 812.100, 21 CFR 812.110(b))

MCW SOP 7.1.1(b)(i), (iii) describes the general responsibilities of investigators. **MCW SOP 7.1.1(b)(i)** states investigators are responsible for protecting the rights and welfare of the human subjects and for complying with all applicable (FDA and DHHS) regulations, all IRB policies, and any conditions of approval imposed by an MCW IRB. **MCW SOP 7.1.1(b)(iii)** states investigators must conduct the research study in accordance with the MCW IRB approved research study investigational plan.

MCW SOP 7.1.4 describes the responsibility of investigators who conduct research studies involving investigational devices to report any serious adverse event that occurs during a study as soon as possible but not later than 10 days after the investigator learns of the serious adverse event.

IRB Reportable Events Policy, dated 11.15.07 requires Immediate Reporting (within 72 hours) of All Unanticipated Problems, whether internal or external: any incident, experience, or outcome that meets all of the following criteria as defined by OHRP: (a) unexpected with reference to expected risks defined in initial IRB application, (b) possibly, probably, or definitely related to participation in the research study, and (c) resulting in harm or places subjects or others at greater risk of harm.

Finding #2

The sponsor-investigator failed to maintain accurate, complete and current records relating to an investigation. (21 CFR 812.140(a))

- There was no documentation in the study records to indicate that these individuals were evaluated regarding their eligibility for the study prior to enrollment.
- All study data was entered into an electronic data base. There was no audit trail or log of data changes made to the information in the database. The data could not be verified against source documents, since these records weren't maintained.

21 CFR 812.140(a) requires a participating investigator to maintain accurate, complete, and current records relating to the investigator's participation in an investigation. This includes the following:

- All correspondence with another investigator, an IRB, the sponsor, a monitor, or FDA, including required reports.
- Records of receipt, use or disposition of a device that relate to:
 - The type and quantity of the device, the dates of its receipt, and the batch number or code mark.
 - The names of all persons who received, used, or disposed of each device.
 - Why and how many units of the device have been returned to the sponsor, repaired, or otherwise disposed of.
- Records of each subject's case history and exposure to the device. Case histories include the case report forms and supporting data including, for example, signed and dated consent forms and medical records including, for example, progress notes of the physician, the individual's hospital chart(s), and the nurses' notes. Such records shall include:
 - Documents evidencing informed consent and, for any use of a device by the investigator without informed consent, any written concurrence of a licensed physician and a brief description of the circumstances justifying the failure to obtain informed consent. The case history for each individual shall document that informed consent was obtained prior to participation in the study.

- All relevant observations, including records concerning adverse device effects (whether anticipated or unanticipated), information and data on the condition of each subject upon entering, and during the course of, the investigation, including information about relevant previous medical history and the results of all diagnostic tests.
- A record of the exposure of each subject to the investigational device, including the date and time of each use, and any other therapy.
- The protocol, with documents showing the dates of and reasons for each deviation from the protocol.
- Any other records that FDA requires to be maintained by regulation or by specific requirement for a category of investigations or a particular investigation.

As noted under "Finding #1," MCW investigators are responsible for complying with all requirements applicable to investigators conducting research studies involving investigational devices or drugs (MCW SOP 7.1.1(b)(i), (iii)).

Finding #3

The sponsor-investigator failed to ensure proper monitoring of the study. (21 CFR 812.40)

- There were no records to indicate that the study monitor verified the eligibility of the subjects, who did not appear to meet the eligibility criteria.
- There were no monitoring records to show that the protocol deviations observed by the study monitor or that any actions were taken to correct the observed violations.
- There were no monitoring records to show that the unanticipated adverse events were evaluated.

21 CFR 812.40 states: Sponsors are responsible for selecting qualified investigators and providing them with the information they need to conduct the investigation properly, ensuring proper monitoring of the investigation, ensuring that IRB review and approval are obtained, submitting an IDE application to FDA, and ensuring that any reviewing IRB and FDA are promptly informed of significant new information about an investigation.

MCW SOP 7.1.6 describes the responsibilities of the sponsor-investigator. Sponsor-investigators are responsible for complying with all requirements applicable to Sponsors and Investigators conducting a research study involving an investigational drug or device.

Follow up to initial findings listed in the Warning letter: The FDA required the investigator to provide a corrective action plan that included a written procedure to ensure study protocol compliance, written verification of study staff training on study procedures and requirements, a plan for ensuring accurate and complete study subject records and adverse events, a plan ensuring proper monitoring of the study and corrective actions that have been or will be implemented to prevent recurrence of problems in the future.

(Taken/adapted from the OHRP Guidance Documents, Code of Federal Regulations, MCW IRB Standard Operating Procedures, and Warning Letters issued by the FDA)