Monitoring Guidance for Investigator Holders of IDE/IND

The following FDA excerpts on monitoring clinical trials were compiled for PIs who hold an Investigational New Drug/Investigational Device Exemption. Holders of IND/IDE are accountable for sponsor responsibilities as well as monitoring responsibilities. Industry sponsored studies are routinely monitored for regulatory and protocol compliance and to confirm that data are accurate, complete, and verifiable. Holders of IND/IDE are expected to assure the same for investigator sponsored studies.

Also see USC OPRS booklet "*Are you the holder of an IND or IDE?*" available at www.usc.edu/oprs/training/brochures

Selected FDA Excerpts…

- **"Guidelines for the Monitoring of Clinical Investigations"*:**

  The purpose of this guideline is to present acceptable approaches to monitoring clinical investigations. Existing requirements for sponsors of clinical investigations involving new drugs for human and animal use (including biological products for human use) and medical devices under 21 CFR Parts 312 and 511, and 812 and 813, respectively, require that a sponsor monitor the progress of a clinical investigation. The monitoring functions may be delegated to a contract research organization. Proper monitoring is necessary to assure adequate protection of the rights of human subjects and the safety of all subjects involved in clinical investigations and the quality and integrity of the resulting data submitted to the Food and Drug Administration (FDA).

  - A sponsor ***should*** establish written procedures for monitoring clinical investigations.
  - A standardized, written procedure (sufficiently detailed to cover the general aspects of clinical investigations) may be used as a basic monitoring plan (and supplemented by more specific or additional monitoring procedures tailored to the individual clinical investigation).
  - The monitoring plan should assure that:
    - The facilities continue to be acceptable for purposes of the study
    - The protocol/investigational plan is being followed
    - The investigator is carrying out the agreed-upon activities and has not delegated them to other previously unspecified staff
    - Changes to the protocol have been approved by the IRB and/or reported to the sponsor and the IRB
    - Records are accurate, current, and complete
    - Reports are being made to the sponsor and IRB
    - Information recorded in the investigator's report is complete, accurate, and legible
    - There are no omissions in the reports of specific data elements
    - Missing visits or examinations are noted in the reports
    - Subjects failing to complete the study and the reason for each failure are noted in the reports
    - Informed consent has been documented in accordance with 21 CFR Parts 50 and 56
  - The monitor or the sponsor should maintain a record of the findings, conclusions, and action taken to correct deficiencies for each on-site visit to an investigator.

* Excerpted from FDA "Guidelines for the Monitoring of Clinical Investigations" http://firstclinical.com/regdocs/doc/?showpage=1&db=FDA_Guidance_Monitoring

- **FDA Guidance on IDE*:**

  While the IDE regulation does not specify the content of the written monitoring procedures, the agency has published a guideline (53 FR 4723, February 17, 1988) on acceptable approaches to monitoring clinical investigations involving FDA-regulated products. The Center for Devices and Radiological Health (CDRH) has identified the following procedures that sponsors should follow with respect to monitoring clinical investigations:

  - Written monitoring procedures ***ARE NOT REQUIRED*** for sponsor-investigator studies where only one investigator is involved
  - Written monitoring procedures ***ARE*** required for all studies involving more than one investigator
  - IDE regulation does not specify the content of the written monitoring procedures
  - IDE regulation requires the sponsor to identify the name and address of the monitor and provide written monitoring procedures

Selected Excerpts…

FDA Regulations on IDE

General Responsibilities of Sponsors (21 CFR 812.40)

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. Additional responsibilities of sponsors are described in subparts B and G.

IDE Monitoring Investigations (21 CFR 812.46)

(a) *Securing compliance.* A sponsor who discovers that an investigator is not complying with the signed agreement, the investigational plan, the requirements of this part or other applicable FDA regulations, or any conditions of approval imposed by the reviewing IRB or FDA shall promptly either secure compliance, or discontinue shipments of the device to the investigator and terminate the investigator's participation in the investigation. A sponsor shall also require such an investigator to dispose of or return the device, unless this action would jeopardize the rights, safety, or welfare of a subject.

(b) *Unanticipated adverse device effects.* (1) A sponsor shall immediately conduct an evaluation of any unanticipated adverse device effect.

(2) A sponsor who determines that an unanticipated adverse device effect presents an unreasonable risk to subjects shall terminate all investigations or parts of investigations presenting that risk as soon as possible. Termination shall occur not later than 5 working days after the sponsor makes this determination and not later than 15 working days after the sponsor first received notice of the effect.

(c) *Resumption of terminated studies.* If the device is a significant risk device, a sponsor may not resume a terminated investigation without IRB and FDA approval. If the device is not a significant risk device, a sponsor may not resume a terminated investigation without IRB approval and, if the investigation was terminated under paragraph (b)(2) of this section, FDA approval.

* Excerpted from FDA Office of Device Evaluation "IDE Policies and Procedures"
http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm080202.htm

Selected Excerpts…

FDA Regulations on IND

IND General Responsibilities of Sponsors (21 CFR 312.50)

Sponsors are responsible for… ensuring proper monitoring of the investigation(s), ensuring that the investigation(s) is conducted in accordance with the general investigational plan and protocols contained in the IND, maintaining an effective IND with respect to the investigations, and ensuring that FDA and all participating investigators are promptly informed of significant new adverse effects or risks with respect to the drug.

IND Review of Ongoing Investigations (21 CFR 312.56)

(a) The sponsor shall monitor the progress of all clinical investigations being conducted under its IND.

(b) A sponsor who discovers that an investigator is not complying with the signed agreement (Form FDA-1572), the general investigational plan, or the requirements of this part or other applicable parts shall promptly either secure compliance or discontinue shipments of the investigational new drug to the investigator and end the investigator's participation in the investigation. If the investigator's participation in the investigation is ended, the sponsor shall require that the investigator dispose of or return the investigational drug in accordance with the requirements of 312.59 and shall notify FDA.

(c) The sponsor shall review and evaluate the evidence relating to the safety and effectiveness of the drug as it is obtained from the investigator. The sponsors shall make such reports to FDA regarding information relevant to the safety of the drug as are required under 312.32. The sponsor shall make annual reports on the progress of the investigation in accordance with 312.33.

(d) A sponsor who determines that its investigational drug presents an unreasonable and significant risk to subjects shall discontinue those investigations that present the risk, notify FDA, all institutional review boards, and all investigators who have at any time participated in the investigation of the discontinuance, assure the disposition of all stocks of the drug outstanding as required by 312.59, and furnish FDA with a full report of the sponsor's actions. The sponsor shall discontinue the investigation as soon as possible, and in no event later than 5 working days after making the determination that the investigation should be discontinued. Upon request, FDA will confer with a sponsor on the need to discontinue an investigation.