

FDA Warning Letters

The U.S. Food and Drug Administration (FDA) has made a number of different non-compliance oversight determinations at institutions over the last several years. The listing below contains excerpts from some of the violations that have occurred at institutions. Researchers should proactively review over these determinations to ensure their research protocols are being conducted in compliance with the federal regulations.

Failure to obtain Informed Consent from each human subject

Excerpt from FDA Warning Letter dated: May 19, 2009

The FDA cited an investigator for the following violations:

#2 Failure to obtain the informed consent of each human subject in accordance with 21 CFR part 50 [21 CFR 312.60].

Under 21 CFR 312.60, an investigator is required to obtain the informed consent of each human subject in accordance with 21 CFR part 50. FDA's regulations at 21 CFR 50.20 state that except as provided in 21 CFR 50.23 and 21 CFR 50.24, no investigator may involve a human being as a subject in research covered by the regulations unless the investigator has obtained the legally effective informed consent of the subject or the subject's legally authorized representative. The regulation specifies that an investigator shall seek such consent only under circumstances that provide the prospective subject or the subject's representative sufficient opportunity to consider whether or not to participate and that minimize the possibility of coercion or undue influence. Section 50.27 of FDA's regulations further provide that informed consent shall be documented by the use of a written consent document approved by the IRB, which is to be signed by the subject or subject's representative only after the subject or the subject's representative is given adequate opportunity to read the document.

Subject #0004 signed the original informed consent form to be enrolled into the study on February 7, 2006. In a letter dated March 1, 2006, the IRB informed your site that they had approved informed consent form version 021706 which included modifications that were made to the risks section. The IRB's letter further stated that current and new subjects were to sign the revised informed consent form. There was no documentation found during the FDA inspection to show that your site re-consented Subject #0004, who was still enrolled into the study at the time, with the revised informed consent form to inform them of the possible additional risks the subject may experience.

To review this Warning Letter in its entirety, visit FDA's Warning Letters site:

<http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/ucm166520.htm>

Failure to maintain adequate and accurate case histories

Excerpt from FDA Warning Letter dated: May 19, 2009

The FDA cited an investigator for the following violations:

#2 Failure to maintain adequate and accurate case histories that record all observations and other data pertinent to the investigation on each individual [21 CFR 312.62(b)].

In FDA's review of the source documents for the records audited during the inspection, there were numerous instances where either (a) information entered into the case report forms (CRFs) did not match the information in the source documents or (b) information in the source documents was changed after the subject had completed the study, up to two years post-completion, and it could not be determined where the information related to the change was derived.

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Failure to conduct the investigation according to the signed agreement, the investigational plan, and applicable FDA regulations

Excerpts from FDA Warning Letter dated: October 7, 2005

The FDA cited an investigator for failure to conduct the investigation according to the signed agreement, the investigational plan, and applicable FDA regulations. The following violations were observed:

#3 Failure to conduct the investigation according to the signed agreement, the investigational plan, and applicable FDA regulations. [21 CFR 812.100 and 21 CFR 812.110(b)]

In accordance to 21 CFR 812.100 and 812.110(b), clinical investigators are required to ensure that investigations are conducted according to the signed agreement, the investigational plan, and applicable FDA regulations, as well as any conditions of approval imposed by the IRB or FDA. In addition, federal regulations require that clinical investigators obtain prior approval from the sponsor before implementing any deviations from the investigational plan, except for deviations to protect the life or physical well being of a subject in an emergency. (21 CFR 812.150(a)(4)). If these changes or deviations affect the scientific soundness of the plan or the rights, safety, or welfare of the subjects, FDA and IRB approval are also required. (21 CFR 812.150(a)(4), 812.35(a)).

Our investigation revealed several deviations from the signed agreement and investigational plan, including but not limited to the following:

1) Under the protocol in effect at the time, inclusion criteria #3 states, "Patient requires treatment of a [redacted]. However, [redacted] had [redacted] treated during the index procedure.

In your response you state that at the time of treatment of this subject, the protocol did not list treatment of both [redacted] during the index procedure as an exclusion criteria. You do not disagree that the inclusion criteria at the time referred to treatment of a [redacted]. You state that you discussed enrollment of this subject with the sponsor and were given allowance to treat [redacted] as per standard of care and [redacted] as per the protocol. However, there is no documentation of this sponsor approval prior to enrolling this subject. You attached a letter from the sponsor dated January 28, 2003, clarifying treatment of additional [redacted] and stating they must be treated 24 hours prior to or after the index procedure, apparently to support your view that at the time of your enrollment and treatment of this subject, it was ambiguous as to whether or not subjects having more than [redacted] in need of treatment were to be excluded. You do not appear to rely on this letter as granting permission for the procedures done with regard to the subject in question, nor could you, as your subject was treated six weeks prior to the date of the letter, and you treated both lesions at the same time, not 24 hours apart, as mandated in the sponsor's protocol clarification.

Treating this subject was a protocol deviation. There is inadequate documentation of notification of the sponsor and IRB of these deviations from the investigational plan.

Please provide copies of policies, procedures, and training with expected completion dates, which are being developed and implemented to ensure deviations from the investigational plan are reported in accordance with the FDA regulations and your IRB's policy.

2) The investigational plan requires anticipated and unanticipated adverse events and complications to be recorded on the Adverse/Serious Adverse Event CRF and reported to the local IRB and coordinating center. In addition, reporting of serious adverse events occurring in the study are to be reported within 24 hours of the investigator's knowledge to the coordinating center for the principal study investigator to review. However, you did not report serious adverse events in accordance with these requirements. For example, [redacted] complained of pain in the right leg during a non-scheduled study visit on 1/31/2005. In February, the subject was seen 'by Sub-Investigator [redacted], at which time he documented clotting of the superficial femoral artery, "probably in the area of the stent." The adverse event CRF was not completed until the FDA inspection on 6/28/2005. Please note, the adverse event CRF is missing the date of the event. Furthermore, there is no documentation of the event being reported to the IRB or sponsor.

In your response you note this event was inadvertently not documented on the CRF or reported to the sponsor and IRB due to the study staff attempting to contact the subject to set up the 24 month follow-up visit. In accordance with the protocol, this event should have been reported to sponsor and IRB within 24 hours of you becoming aware of this event. Your response is incomplete ; it does not include a plan to ensure proper reporting of serious adverse events. Please provide copies of policies and procedures with expected completion dates, that are being developed and implemented to ensure reporting of serious adverse device effects are in accordance with the investigational plan and IRB policy.

Failure to appropriately maintain investigational records:

Excerpts from FDA Warning Letter dated: October 7, 2005

The FDA cited an investigator for failure to appropriately maintain investigational records. The following violations were observed:

#4 Failure to maintain investigational records for a period of two years after the latter of the date on which the: investigation is terminated or completed or the date the records are no longer needed to support a PMA [21 CFR 812.140(d)]

You failed to maintain records of Duplex Flow Scans and Index Extremity X-Rays or Fluoroscopy for two years after the study completion. Examples of records not available for all subjects enrolled in trial the are the following:

1. Duplex Flow Scans at discharge, 9 months, 24 months, and non-scheduled visits: and
2. Index Extremity X-Rays or Fluoroscopy at baseline, 9 month, and 24 month.

In your response you state the records of the Duplex Flow Scans and the Index Extremity X-Rays for all subjects were not retained by the hospital. The originals were sent to the [redacted], and the original X-Rays were forwarded to the [redacted]. You also note you have contacted the labs to obtain the originals and will retain them with the study binders for at least two years. Your response is incomplete. Although you have requested the aforementioned records, you do not indicate what policies and procedures, with expected completion dates, are being developed and implemented to ensure proper maintenance of study-related source records in the future.

The above-described deviations are not intended to be an all-inclusive list of deficiencies that may exist in this clinical study. It is your responsibility as a clinical investigator to assure adherence to each requirement of the Act and all applicable federal regulations. Within 15 working days after receiving this letter please provide written documentation of the additional, specific steps you have taken or will take to correct these violations and prevent the recurrence of similar violations in current and future studies. Any submitted corrective action plan must include projected completion dates for each action to be accomplished. Failure to respond to this letter and take appropriate corrective action could result in the FDA taking regulatory action without further notice to you. In addition, FDA could initiate disqualification proceedings in accordance with 21 CFR 812.119. Send your response to: Food and Drug Administration, Center for Devices and Radiological Health, Office of Compliance, Division of Bioresearch Monitoring, Special Investigations Branch, HFZ 311, 9200 Corporate Road, Rockville, Maryland 20850, Attention : Doreen Kezer, Chief, Special Investigations Branch.

Conducting an unapproved device trial while serving as a sponsor-investigator:

Excerpts from FDA Warning Letter dated: April 3, 2007

According to a warning letter from the FDA (summary follows):

A physician who started an investigator-initiated trial of a significant-risk implanted device failed to get FDA approval before starting the study and did not get signed agreements for himself and the other physicians working as subinvestigators.

Thomas Davis of the Cardiology Division of St. John Hospital and Medical Center acted as both sponsor and clinical investigator in a study of a significant-risk device but failed to submit an investigational device exemption (IDE) application to the FDA, according to the warning letter, which was based on an inspection conducted Nov. 20 to Dec. 12, 2006. In all, five different devices were implanted into 68 subjects without approval.

Davis told the FDA he was not aware that an IDE was required for an FDA-approved device to be used off-label, that there was no risk assessment from the institutional review board and that he was not aware that he met the definition of a sponsor-investigator. However, the letter said, "As a sponsor, you are required to obtain a new IDE if a device that is approved for one indication is intended to be used in a clinical study for a new indication."

The warning letter can be accessed at: http://www.fda.gov/foi/warning_letters/b6324d.htm