Quality Management

Activity Title: The Case of the FDA Letter: 1

A Warning Letter was sent to a clinical investigator (CI) with objectionable conditions observed during the U.S. Food and Drug Administration (FDA) inspection conducted at the clinical investigator clinical site between August 5 and 25, 2015. Mrs. X representing the FDA, reviewed the conduct of the clinical investigator of following clinical investigations:

Protocol **(a)(4)**, "**(a)(4)**," of the investigation drug **(a)(4)**, performed for Dr. M **(a)(4)**
Protocol **(a)(4)**, "**(a)(4)**," of the investigational drug **(a)(4)**, performed for **(a)(4)**

The inspection was part of FDA's Bioresearch Monitoring Program, which included inspections designed to evaluate the conduct of FDA-regulated research to ensure that the data were scientifically valid and accurate, and to help ensure that the rights, safety, and welfare of the human subjects of those studies have been protected.
At the conclusion of the inspection, Mrs. X presented and discussed with the clinical investigator Form FDA 483, Inspectional Observations. They acknowledge receipt of the clinical investigator September 12, 2015 written response to the Form FDA 483.

The citation addressed the following:

Clinical Investigator failed to personally conduct or supervise the clinical investigations [21 CFR 312.60].

When the clinical investigator signed the Statement of Investigator (Form FDA 1572) for the above-referenced clinical trials, agreed to take on the responsibilities of a clinical investigator at her/his site. The general responsibilities as a clinical investigator include ensuring that the clinical trials are conducted according to the signed investigator statement, the investigational plan, and applicable regulations; protecting the rights, safety, and welfare of subjects under your care; and ensuring control of drugs under investigation [21 CFR 312.60]. By signing Form FDA 1572, the clinical investigator specifically agreed to personally conduct the clinical trial or to supervise those aspects of the trial that he/she did not personally conduct. While the clinical investigator may delegate certain study tasks to individuals qualified to perform them, as a clinical investigator he/she may not delegate his/her general responsibilities. The FDA investigation indicated that the CI supervision of personnel to whom he/she delegated study tasks was not adequate to ensure that the clinical trial was conducted according to the signed investigator statement, the

investigational plan, and applicable regulations, and in a manner that protects the rights, safety, and welfare of human subjects.

Specifically, for Protocol **(a)(4)**, the CI failed to supervise adequately the individuals to whom he/she delegated study tasks. The clinical investigator failure to supervise adequately the conduct of Protocol **(a)(4)** led to many of the violations noted in this letter. These violations included, but were not limited to, enrollment of subjects into the protocol when approval by the America University Medical Center (AUMC) Institutional Review Board (IRB) had lapsed; failure to obtain informed consent from 28 of 50 enrolled subjects; and randomization and administration of investigational drug to 10 subjects before obtaining their informed consent to participate in the study.

In the clinical investigator September 12, 2015 written response, he/she acknowledged that he/she did not provide adequate supervision or delegate the responsibilities of conducting the study appropriately nor provided additional training for appropriate personnel. The CI also acknowledged that it was his/her responsibility to ensure that the IRB-approved protocol was followed, and he/she stated that he/she "delegated this responsibility without providing the proper oversight."

As the clinical investigator, it was your ultimate responsibility to ensure that the studies were conducted properly and in compliance with FDA regulations in order to protect the rights, safety, and welfare of study subjects and to ensure the integrity of the study data. The CI lack of supervision and oversight over Protocol **(a)(4)** raised significant concerns about the adequacy of the CI protection of study subjects enrolled at the CI site in the studies mentioned above and also raised data integrity concerns generated for Protocol **(a)(4)**.

Quality Management

Activity Title: The Case of the FDA Letter: 2

A Warning Letter was sent to a clinical investigator (CI) with objectionable conditions observed during the U.S. Food and Drug Administration (FDA) inspection conducted at the clinical investigator clinical site between August 5 and 25, 2015. Mrs. X representing the FDA, reviewed the conduct of the clinical investigator of following clinical investigations:

Protocol **(a)(4)**, "**(a)(4)**," of the investigation drug **(a)(4)**, performed for Dr. M **(a)(4)**
Protocol **(a)(4)**, "**(a)(4)**," of the investigational drug **(a)(4)**, performed for **(a)(4)**

The inspection was part of FDA's Bioresearch Monitoring Program, which included inspections designed to evaluate the conduct of FDA-regulated research to ensure that the data were scientifically valid and accurate, and to help ensure that the rights, safety, and welfare of the human participants of those studies have been protected.
At the conclusion of the inspection, Mrs. X presented and discussed with the clinical investigator Form FDA 483, Inspectional Observations. They acknowledge receipt of the clinical investigator September 12, 2015 written response to the Form FDA 483.

The citation addressed the following:

You failed to obtain informed consent in accordance with the provision of 21 CFR part 50 [21 CFR 312.60 and 21 CFR 50.20].

As a clinical investigator, it is his/her responsibility to obtain informed consent 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 participant in research covered by the regulations unless the investigator has obtained the legally effective informed consent of the participant or the participant's legally authorized representative. The CI failed to obtain legally effective informed consent. Specifically:

a. the following 28 of 50 participants who were enrolled in Protocol **(a)(4)**: Participants C1, C4 through C7, C9 through C12, C17, C19, C20, C22 The CI failed to obtain informed consent from, C26, C28, C30, C31, C33, C34, C37 through C42, C45, A3, and A5.
b. The CI enrolled 10 participants into Protocol (a) (4) and gave the investigational drug before each signed the informed consent document. These participants are listed in the Table below.

Participant	**Date Participant first given investigational drug**	**Date Participant first signed the Informed Consent Document**
C15	September 15, 2010	December 10, 2010
C 16	September 15, 2010	September 22, 2010
C 21	November 28, 2010	December 17, 2010
C 24	December 17, 2010	December 23, 2010
C 25	December 20, 2010	December 28, 2010
C 32	May 19, 2011	June 16, 2011
C 36	January 26, 2011	February 9, 2011
C 43	April 7, 2011	April 26, 2011
C 44	May 10, 2011	May 27, 2011
C 47	April 29, 2011	May 26, 2011

In the clinical investigator September 12, 2015 written response to the Form FDA 483 [pages 3-4] he/she agreed that he/she failed to obtain consent from the 28 participants listed in Item 2.a. above and that the CI gave investigational drug to the additional 10 enrolled participants listed in item 2.b. above, prior to participant signing the informed consent document. In addition, in that written response the CI stated, "I acknowledge and take full responsibility for not providing the instruction and oversight of the research staff delegated to recruiting and obtaining informed consent."

We acknowledge the CI summarized written response, actions that the America University Medical Center Institutional Review Board (AUMC IRB) and the Department of Obstetrics and Gynecology (Department) have taken. The CI indicated that after serious noncompliance and the potential risk to participants was discovered, on August 19, 2011, the AUMC IRB and the Department suspended Protocol **(a)(4)**, the Department performed an audit of all available study records and, at the direction of the IRB, all 50 participants were notified of the violations in the consent process and study procedures.
We also acknowledge the CI corrective action plan that includes the following:

- Re-education of investigators involved in Protocol **(a)(4)**;
- Department approval of all research so that appropriate safeguards and monitoring can be initiated;
- Establishment of a Department requirement for assigning a research coordinator to each investigator-initiated FDA regulated research study;
- Performance of quarterly monitoring by the Department Quality Assurance (QA) Research Monitor, and;
- Use of an Informed Consent Process Checklist to assist in the documentation of the consent process.

The written response of the CI is inadequate as it relates to the findings noted in Item 2 above. We are concerned that the majority of the corrective actions appear to represent actions taken by America University Medical Center and do not reflect corrective actions that you personally have taken. Please note that, as the clinical investigator, the CI are ultimately responsible for ensuring that informed consent is obtained in accordance with 21 CFR part 50.

We are also concerned about the CI plans to use the Informed Consent Process Checklist to ensure that the consent process is documented appropriately. This checklist does not address the timing of consent and, therefore, does not appear adequate to acquire informed consent prior to a participant's participation in clinical research. In addition, the checklist refers to consent forms printed from "Rascal." We request clarification on the "Rascal" system as it relates to study data tracking, such as informed consent.

Your failure to obtain informed consent prior to involving participants in research jeopardizes the safety and welfare of participants by denying them an opportunity to assess the risks and benefits of their participation in the clinical investigation.

Quality Management

Activity Title: The Case of the FDA Letter: 3

A Warning Letter was sent to a clinical investigator (CI) with objectionable conditions observed during the U.S. Food and Drug Administration (FDA) inspection conducted at the clinical investigator clinical site between August 5 and 25, 2015. Mrs. X representing the FDA, reviewed the conduct of the clinical investigator of following clinical investigations:

Protocol **(a)(4)**, "**(a)(4)**," of the investigation drug **(a)(4)**, performed for Dr. M **(a)(4)**
Protocol **(a)(4)**, "**(a)(4)**," of the investigational drug **(a)(4)**, performed for **(a)(4)**

The inspection was part of FDA's Bioresearch Monitoring Program, which included inspections designed to evaluate the conduct of FDA-regulated research to ensure that the data were scientifically valid and accurate, and to help ensure that the rights, safety, and welfare of the human participants of those studies have been protected.
At the conclusion of the inspection, Mrs. X presented and discussed with the clinical investigator Form FDA 483, Inspectional Observations. They acknowledge receipt of the clinical investigator September 12, 2015 written response to the Form FDA 483.

The citation addressed the following:

The Clinical Investigator (CI) failed to ensure that the investigation was conducted according to the investigational plan [21 CFR 312.60].

As a clinical investigator, he/she is required to ensure that your clinical studies are conducted in accordance with the investigational plan. The investigational plan for Protocol **(a)(4)** required the CI to administer the protocol-specified dose of investigational drug to each participant according to their assigned study arm, and to obtain study-related laboratory tests. The CI failed to adhere to these requirements. Examples of this failure include but are not limited to the following:

Protocol **(a)(4)** contained two study arms: (1) a "traditional" **(a)(4)** treatment arm, and (2) a "stair-step" arm. The "traditional" treatment arm required that the participant receive 50 mg of **(a)(4)** daily for 5 days on Day 5 - 9 of the first menstrual cycle during the study. If the participant did not develop a positive response (i.e., follicles of at least 17 mm in size) after the first menstrual cycle, the protocol required that the dose be increased to 100 mg on the second menstrual cycle. If the participant did not develop a positive response after the second cycle, the protocol

required that the dose be increased to 150 mg on the third cycle. The "stair-step" arm required that the participant receive the same dosing of **(a)(4)** (50 mg to 150 mg) in an attempt to induce a positive response, but in a shorter timeframe and without having to wait for the next menstrual cycle before increasing the **(a)(4)** dose from 50 mg to 100 mg or from 100 mg to 150 mg.

For Protocol **(a)(4)**, four participants were not dosed according to their protocol-specified study arm (standard dosing or stair-step dosing). Specifically:

a. Participant C4 was enrolled in Protocol **(a)(4)** on October 10, 2010 and assigned to the "traditional" or "standard" dosing arm. The participant's dosing log shows that Participant C4 received the protocol-required **(a)(4)** dose of 50 mg and 100 mg during Cycles 1 and 2, respectively. However, the dosing log shows that for Cycle 3, the participant again received 100 mg daily for 5 days rather than 150 mg daily for 5 days as required by the protocol. The Progress Note Addendum for Participant C4 states that the Participant responded to 50 mg of **(a)(4)** and no further assessment was needed, but this statement is not supported by the dosing log.

In the CI written response to the Form FDA 483, he/she indicate that Participant C4 received 50 mg daily for 5 days, responded with the development of one preovulatory follicle, and then exited the study. The CI response is inadequate because it lacks supporting documentation and an explanation as to why the dosing records described above conflict with the Progress Note Addendum and your response.

b. Participant C6 was enrolled in Protocol **(a)(4)** on December 17, 2010 and assigned to the "stair-step" dosing arm. The participant's dosing log shows that Participant C6 received **(a)(4)** 50 mg daily from January 11 to 15, 2011, and from March 31 to April 6, 2011, and then received 75 mg daily from April 7 to 14, 2011, rather than the protocol-required stair-step dosing. The Progress Note Addendum for participant C6 states that the participant responded to 50 mg of **(a)(4)** and became pregnant. The Progress Note Addendum conflicts with the dosing log.

The CI written response to the Form FDA 483, you indicate that Participant C6 received 50 mg of **(a)(4)** for 5 days, responded with the development of a preovulatory follicle, and exited the study. Your response is inadequate because it lacks supporting documentation and an explanation as to why the participant participant's dosing log conflicts with your response.

c. Participant C19 was enrolled in Protocol **(a)(4)** on December 13, 2010 and assigned to the "stair-step" dosing arm. The participant's dosing log shows that Participant C19 received **(a)(4)** 25 mg daily from December 13 to 17, 2010, and from February 15 to 19, 2011, rather than the protocol-required stair-step dosing. The Progress Note Addendum notes the participant received 50 mg of **(a)(4)** for each cycle. The Progress Note Addendum conflicts with the dosing log.

In your written response to the Form FDA 483, you state that participant C19 "had a hyper-response to 50 mg for 5 days and exited the study; she required a dose decrease with her next cycle." Your response is inadequate because it lacks supporting documentation and an explanation as to why the participant's dosing log and Progress Note Addendum conflict with your response.

d. Participant C35 was enrolled in Protocol **(a)(4)** on January 21, 2011 and assigned to the "traditional" or "standard" dosing arm. According to the participant's dosing log, Participant C35 received **(a)(4)** 100 mg daily for 5 days during Cycles 1, 2, and 3 rather starting with the protocol-required dose of 50 mg in Cycle 1 and progressing to 100 mg and 150 mg in Cycles 2 and 3, respectively. The Progress Note Addendum indicates the participant's first treatment cycle was for 50 mg, followed monthly by three 100 mg cycles.

In your written response to the Form FDA 483, you indicate that Participant C35 received **(a)(4)** 50 mg for 5 days, had a delayed response, had a dose increase to **(a)(4)** 100 mg at the next cycle, and then achieved a normal response and exited the study. Your response is inadequate because it lacks supporting documentation and an explanation as to why the participant's dosing log conflicts with your response as well as the Progress Note Addendum.

In your July 11, 2013 written response to the Form FDA 483, you stated, "I agree that the IRB-approved protocol-specific dosing regimens were not followed for all participant \s, resulting in protocol violations." You further explained that, "A review of participants' charts noted that many of the participant were treated according to clinical standards, instead of adhering to the strict dose and schedule in the IRB-approved protocol."

In your written response, you also acknowledged your responsibility to ensure that the IRB-approved study protocol is followed and acknowledged that you were "responsible for these errors." You also stated that you "will supervise and monitor for protocol violations and report to the IRB and the sponsor, accordingly."

The CI written response is inadequate because he/she failed to provide sufficient details with respect to your corrective action plan. For example, the CI did not provide details regarding how he/she will carry out the plan to supervise and monitor protocol violations. Without having these details, we are unable to determine whether the CI corrective action appears sufficient to prevent similar violations in the future.

Failure to administer investigational drug to participant according to the protocol-required dosing schedule compromises the validity and integrity of data generated at your site for Protocol **(a)(4)**.

Quality Management

Activity Title: The Case of the FDA Letter: 4

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Protocol **(a)(4)**, "**(a)(4)**," of the investigation drug **(a)(4)**, performed for Dr. M **(a)(4)**
Protocol **(a)(4)**, "**(a)(4)**," of the investigational drug **(a)(4)**, performed for **(a)(4)**

The inspection was part of FDA's Bioresearch Monitoring Program, which included inspections designed to evaluate the conduct of FDA-regulated research to ensure that the data were scientifically valid and accurate, and to help ensure that the rights, safety, and welfare of the human participants of those studies have been protected.
At the conclusion of the inspection, Mrs. X presented and discussed with the clinical investigator Form FDA 483, Inspectional Observations. They acknowledge receipt of the clinical investigator September 12, 2015 written response to the Form FDA 483.

The citation addressed the following:

You failed to assure that an IRB that complies with the requirements set forth in part 56 was responsible for the initial and continuing review and approval of the proposed clinical study [21 CFR 312.66].

As a clinical investigator, you are required to assure that an IRB that complies with 21 CFR part 56 reviews and approves a proposed clinical investigation. **You failed to assure that an IRB that complies with 21 CFR part 56 reviewed and approved a proposed clinical study.**

Specifically, **IRB approval to conduct Protocol (a)(4) lapsed from March 30 to June 3, 2011.** During this lapsed period, **you enrolled six participants** (Participants C42 through C47) into this protocol and gave them the investigational drug.

In your July 11, 2013 written response to the Form FDA 483, you acknowledged that you "failed to ensure that continuing IRB approval was maintained" and that "participants were enrolled and treated during a lapse in IRB approval." In that response, you **also described corrective actions** that you will take, including

monitoring the protocol for continuing IRB approval and ensuring that no study-related procedures are performed without IRB approval or during a period in which IRB approval has lapsed.

Your **response is inadequate with respect to the conduct of study activities without IRB approval.** Specifically, you did not provide details regarding how you will ensure that you will monitor protocols for continuing IRB approval or how you will ensure that no study-related procedures are performed without IRB approval or during a period in which IRB approval has lapsed. Without having these details, we are unable to determine whether your corrective action appears sufficient to prevent similar violations in the future.

Your failure to ensure continuing IRB review and approval of Protocol **(a)(4)** impeded the IRB's ability to review your application to conduct Protocol **(a)(4)** and make a determination regarding the adequacy of that application.

This letter is not intended to be an all-inclusive list of deficiencies with your clinical study of an investigational drug. It is your responsibility to ensure adherence to each requirement of the law and relevant FDA regulations. **You should address these deficiencies and establish procedures to ensure that any ongoing or future studies will comply with FDA regulations.**

Within fifteen (15) working days of your receipt of this letter, you should notify this office in writing of the actions you have taken to prevent similar violations in the future. Failure to address the violations noted above adequately and promptly may result in regulatory action without further notice. If you believe you have complied with FDA regulations, include your reasoning and any supporting information for our consideration.