Dear Dr. Boyce:

This Warning Letter informs you of objectionable conditions observed during the U.S. Food and Drug Administration (FDA) inspection conducted at your clinical site between August 24 and September 15, 2011, by Krista Flores, representing the FDA, to review your conduct of a clinical investigation [Protocol \(\text{(b)(4)}\) entitled \(\text{(b)(4)}\) of the investigational drug \(\text{(b)(4)}\) performed for \(\text{(b)(4)}\)].

This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to evaluate the conduct of FDA-regulated research to ensure that the data are 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, Ms. Flores presented and discussed with you Form FDA 483, Inspectional Observations. We acknowledge receipt of your October 5, 2011, written response to the Form FDA 483.

From our review of the establishment inspection report, the documents submitted with that report, and your October 5, 2011, written response, we conclude that you did not adhere to the applicable statutory requirements and FDA regulations governing the conduct of clinical investigations. We wish to emphasize the following:

1. **You failed to assure that an Institutional Review Board (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 expired on May 11, 2010, for the above-mentioned clinical investigation. The following
five subjects were enrolled at your site after IRB approval had expired:

a. Subject 23/015852 was enrolled on May 19, 2010;
b. Subject 24/001699 was enrolled on May 23, 2010;
c. Subject 25/015964 was enrolled on June 23, 2010;
d. Subject 26/001970 was enrolled on July 5, 2010; and
e. Subject 27/016052 was enrolled on July 26, 2010.

In your written response to the Form FDA 483, you note that the protocol and revised informed consent document were submitted to the IRB on April 7, 2010, for continuing review approval; and that, in response, the IRB communicated stipulations required to be met prior to IRB approval. Specifically, you noted that the IRB’s letter stipulated that subinvestigators needed to complete updated training in Good Clinical Practice (GCP) and to sign a conflict of interest statement before IRB approval could be granted. You further note that your study coordinator was delegated the responsibility of ensuring that the IRB’s stipulations were addressed, and that IRB approval was obtained. You indicate that your failure to obtain IRB approval was the result of the actions of your study coordinator, and that you were not aware that IRB approval of your clinical investigation had expired until after all five of the above listed subjects were enrolled.

We acknowledge that you have provided a corrective action plan that includes placing expiration/renewal dates for studies on your personal calendar; seeing the actual IRB approval letter and approved informed consent; using a clinical research associate meeting form to inquire if the clinical research associate has any concerns about documents or processes; and conducting a clinical study with two coordinators.

Your response is incomplete because you have not provided documentation of procedures to ensure that IRB review and approval are obtained. Without this information, we cannot conduct an informed evaluation of the potential use of your corrective actions to prevent the recurrence of this type of violation in the future. Moreover, it was your responsibility as a clinical investigator to ensure that an IRB that complied with 21 CFR part 56 was responsible for the initial and continuing review and approval of Protocol (b)(4). Please note that, although you indicate that your current employer closely monitors protocols nearing expiration of IRB approval, it remains your responsibility as a clinical investigator to ensure IRB review and approval.

Your failure to ensure IRB approval of Protocol (b)(4) raises concerns about the extent to which subjects’ rights and welfare were protected at your site.

2. You failed to maintain adequate and accurate case histories that record all observations and other data pertinent to the investigation on each individual administered the investigational drug or employed as a control in the investigation [21 CFR 312.62(b)].

As a clinical investigator, you are required to prepare and maintain adequate and accurate case histories that record all observations and other data pertinent to the investigation on each individual administered the investigational drug or employed as a control in the investigation. Case histories include the signed and dated consent forms. You have failed to maintain adequate and accurate case histories by using informed consent forms that inaccurately indicated they had been approved by the IRB. Specifically:

Informed consent forms for the five subjects enrolled at your site after IRB approval for your study had expired (Subjects 23/015852, 24/001699, 25/015964, 26/001970, and 27/016052) were found to have stamps on the documents inaccurately indicating that they had been approved by the IRB. The stamps on these informed consent forms inaccurately showed an IRB approval date of May 11, 2010, and an IRB approval expiration date of May 9, 2011.

According to your September 15, 2011, affidavit, you were not aware until August 30, 2010, that IRB approval had expired on May 11, 2010, and you were informed by your site manager on September 9, 2010, that your study coordinator had purchased a custom-made stamp at Office Depot, which he had used to stamp the informed consent documents that were used to enroll five subjects after the study’s IRB expiration date.

In your written response to the Form FDA 483, you indicate that the above finding was the “egregious act of one rogue employee.” We acknowledge that your written response provided a
corrective action plan that includes placing expiration/renewal dates for studies on your personal calendar; seeing the actual IRB approval letter and approved informed consent prior to enrolling subjects in any study; using a clinical research associate meeting form to inquire if the clinical research associate has any concerns about documents or processes; and conducting a clinical study with two coordinators.

Your response is incomplete because you have not provided documentation of procedures for regulatory oversight of studies that you conduct. Without this information, we cannot conduct an informed evaluation of the potential use of your corrective actions to prevent the recurrence of this type of violation in the future. Moreover, it was your responsibility as a clinical investigator to prepare and maintain adequate and accurate case histories for Protocol (b)(4). Please note that, although you indicate that your current employer has internal processes for helping to ensure that updated informed consent documents are used, it remains your responsibility as a clinical investigator to prepare and maintain adequate and accurate case histories.

You failed to prepare and maintain adequate and accurate case histories because the case histories for your study included informed consent documents that inaccurately indicated they had been approved by the IRB. By doing so, as also noted below, you may have caused Subjects 23/015852, 24/001699, 25/015964, 26/001970, and 27/016052 to be misled regarding the status of IRB approval of the informed consent documents they were signing, thus raising concerns about the adequacy of human subject protections at your site.

3. You failed to ensure that the investigation was conducted according to the investigational plan [21 CFR 312.60].

As a clinical investigator, you are required to ensure that your clinical studies are conducted in accordance with the investigational plan. The investigational plan for Protocol (b)(4) requires, among other things, that postoperative day (POD) visits occur and electrocardiograms (ECGs) be recorded at specified times. You failed to adhere to these requirements. Specifically:

a. The protocol requires that the office visit on POD 28 occur no earlier than 28 full days after study drug administration. For six subjects (20/001483, 23/015852, 24/001699, 25/015964, 26/001970, and 27/016052) out of the nine subjects whose POD 28 assessments were reviewed during the inspection, POD 28 assessments either were not performed or were performed earlier than 28 full days after study drug administration.

b. The protocol requires that standard 12-lead ECGs be recorded at 24 hours and 96 hours after completion of surgery and at discharge. For seven subjects (17/015693, 18/001401, 21/015769, 23/015852, 25/015964, 26/001970, and 27/016052) out of the nine subjects whose ECG records were reviewed during the inspection, ECGs were not performed at certain required times.

In your written response to the Form FDA 483, you concur with the findings noted in Item 3a. above as they relate to Subjects 20/001483, 23/015852, 24/001699, 25/015964. Regarding the missing ECGs (see the findings in Item 3b. above), you state in your written response that the reason why ECGs were missing is that hospital staff and the study coordinator did not obtain ECGs a required by the protocol.

We acknowledge that you have provided a corrective action plan to prevent future recurrence of similar violations. As part of your corrective action plan, you state that you will continue to ensure that hospital and research staff are aware of the importance of following study procedures, and that you will escalate findings of noncompliance to a written report when appropriate. Furthermore, in your response, you state that your current employer has an internal process for reporting protocol deviations, and that coordinators must report deviations to the regulatory team for submission to the IRB.

Your response is incomplete because you have not provided documentation of procedures that you will use for oversight of studies that you conduct. Without this information, we cannot conduct an informed evaluation of the potential use of your corrective actions to prevent the recurrence of this type of violation in the future. Moreover, as the clinical investigator, you were ultimately responsible for ensuring that Protocol (b)(4) was conducted according to the investigational plan.

Your failure to ensure that Protocol (b)(4) was conducted according to the investigational plan,
raises concerns about the extent to which the rights, safety, and welfare of subjects were protected, and about the validity and integrity of the data at your site. Of note, obtaining data for the POD 28 assessment prior to 28 full days after study drug administration may have affected the primary efficacy endpoint of first occurrence of the composite of all-cause death, nonfatal stroke, or need for mechanical support for severe left ventricular dysfunction (SLVD) occurring during and following \( (b)(4) \) surgery through POD 28. In addition, failure to obtain protocol-required ECGs in seven of the nine subjects undergoing cardiac surgery is a significant safety concern, and further raises concerns about the validity and integrity of the data collected at your site.

4. You failed to obtain informed consent in accordance with the provisions of 21 CFR part 50 [21 CFR 312.60, 21 CFR 50.27].

As a clinical investigator, it is your responsibility to obtain informed consent in accordance with 21 CFR part 50. Except as provided in 21 CFR 56.109(c), informed consent shall be documented by the use of a written consent form approved by the IRB and signed and dated by the subject or the subject’s legally authorized representative at the time of consent. You failed to properly document informed consent. Specifically:

The informed consent form signed by Subject 26/001970 was not dated.

In addition, as noted above, the informed consent forms for the five subjects enrolled at your site after IRB approval for your study had expired (Subjects 23/015852, 24/001699, 25/015964, 26/001970, and 27/016052) were not approved by the IRB, and were found to have stamps on the documents inaccurately indicating that they had been approved by the IRB.

In your written response to the Form FDA 483, you acknowledge that the informed consent form for subject 26/001970 was not dated. As a corrective action, you state that you will emphasize to your research staff the importance of dating documents as required. Furthermore, you state that a second research staff person will inspect the informed consent forms for completeness. In your written response, you also provide corrective actions related to the use of informed consent documents that were not approved by the IRB, including placing expiration/renewal dates for studies on your personal calendar; seeing the actual IRB approval letter and approved informed consent prior to enrolling subjects in any study; using a clinical research associate meeting form to inquire if the clinical research associate has any concerns about documents or processes; and conducting a clinical study with two coordinators.

Your response is incomplete because you have not provided documentation of procedures that you will use for oversight of studies that you conduct, or of training that study staff have received on the new procedures. Without this information, we cannot conduct an informed evaluation of the potential use of your corrective actions to prevent the recurrence of this type of violation in the future. Moreover, as the clinical investigator, you were ultimately responsible for ensuring that informed consent was obtained in accordance with 21 CFR part 50. Of note, your use of informed consent forms that inaccurately indicated they had been approved by the IRB, may have caused Subjects 23/015852, 24/001699, 25/015964, 26/001970, and 27/016052 to be misled regarding the status of IRB approval of the informed consent documents they were signing.

Your failure to obtain informed consent in accordance with 21 CFR part 50 prior to involving subjects in research, raises significant concerns about your protection of study subjects enrolled at your site in the study mentioned above.

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 be in compliance 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 have any questions, please contact Constance Cullity, M.D., M.P.H., at 301-796-3397; FAX 301-847-8748. Your written response and any pertinent documentation should be addressed to:
Constance Cullity, M.D., M.P.H.
Branch Chief
Good Clinical Practice Enforcement Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations
Office of Compliance
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Sincerely yours,
/S/
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