

U.S. Food and Drug Administration
Protecting and Promoting *Your* Health

Taber, Louise A., MD Response Letter 11/4/14

Arizona Research Center

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November 4, 2014

Via email to constance.cullity@fda.hhs.gov (<mailto:constance.cullity@fda.hhs.gov>)

Via Fedex 771737175065

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Dear Dr. Cullity,

The purpose of this letter is to respond to the Food and Drug Administration's Warning Letter with FDA reference number 3641239, which we received in our office on October 17, 2014. I am also writing to share with you a Corrective Action Plan which is designed to ensure that, in the future, my research records will be fully compliant with regulations. As a Principal Investigator (PI) in good standing at Arizona Research Center, I fully understand the need for accurate and reliable data that support the sponsor's submission and are collected in a manner that respects the safety and welfare of the study subjects.

I am responding to each concern listed in the Warning Letter and discussing corrective actions to address each concern. I am also providing a separate corrective action plan document, which is attached to this letter as Attachment 1.

RESPONSE TO WARNING LETTER

1) 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)].

During the course of the conduct of study HYD3003, the study coordinator, Ms. **(b)(6)**, was delegated the task of maintaining study records, including the pure-tone audiometry reports. Unfortunately, Ms. **(b)(6)**, misunderstood certain instructions from the study monitor and this resulted in her redacting all of the identifying information on the source records that you cited in the letter. When I noticed what I believed to be **(b)(6)**'s error, I called the monitor to clarify exactly what should have been redacted. The monitor had asked Ms. **(b)(6)**, to remove only the subjects' names and to leave the subjects' initials and ID numbers on the records. I then asked Ms. **(b)(6)** to re-enter the identifying information (ID number and initials) onto the records. Ms. **(b)(6)**, hastily entered incorrect identifying information, resulting in four inaccurately labeled records that are described in the Warning Letter.

The corrective action for this situation would be to re-train and/or re-assign Ms. **(b)(6)**, within the organization so that she could be adequately trained to maintain accurate records. However, as of August 23, 2013, Ms. **(b)(6)**, is no longer working at Arizona Research Center. I have confirmed that her personnel record is annotated as "not eligible for re-hire". Please see Attachment 2 for a screen shot of her personnel record that captures Ms. **(b)(6)**'s status.

I fully understand that, as the PI, I have the ultimate responsibility for the accuracy of the study records. Therefore, I routinely review all of the study records. When I reviewed these records for accuracy, the documents that I reviewed were **photocopies of the original**. Because the photocopying process further obscures the readability of the data underneath the black marker, I was unable to see the original identifying data on the copies. For that reason, I did not know that Ms. **(b)(6)**, had mistakenly entered the incorrect identifiers. During our FDA inspection, the inspector reviewed the **original** records and not the **photocopies**, and showed me that, when held up to the light, the original identifying information was still visible on the original records.

As part of my corrective action plan, going forward, if I ever encounter a similar situation, I will use the technique that the FDA inspector demonstrated in order to verify the accuracy of the records and will only look at the originals, not photocopies. Additionally, an email message had been distributed to all of the study coordinators at our site to advise them that, if they are asked to redact identifying information on any study records, they should maintain, at a minimum, the subject's study ID number. (Attachment 3) This will result in our ability to correctly associate study records with the correct study subject.

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

I would like to address this concern by first clarifying my response to the 483 item related to the missed audiograms for 7 of the 16 enrolled subjects whose study records were reviewed. As is true for most clinical studies, the sponsor relied on our site to create what you describe in the Warning Letter as the "template document for

capturing study information”. I mistakenly referred to that item as the “source document” but in fact it is actually the **template** that we use to record source data. I regret the misuse of the term “source document” as I realize it refers to the original record of study data and, of course, that would never be in “draft” form. What I was trying to say is as follows: At our site Ms.

(b)(6), the current Document Specialist, is responsible for creating the template documents that capture study information. At the time of study start in 2011, our **former** Study Coordinator Manager **(b)(6)** had the assignment of creating all template documents that capture study information, and did so for study HYD3002. Ms. **(b)(6)** created this document, the lead coordinator reviewed it; however I did not perform a quality check on the document. The required procedure of an audiometry test prior to randomization was not included on the template document. When I realized that it was missing from the template document, I revised the document. As a result, the procedure was included on the template form from that time forward and we then performed the study procedures as required by the protocol.

Our corrective action plan for this includes implementation of new procedures. The first procedure will require the Document Specialist to work with the lead study coordinator in preparation of the template. Then, a physician investigator for the study will review the document to ensure that all of the study required procedures are captured. When template documents are finalized, the Regulatory Department will maintain a set of final documents for the study and will institute version numbers on these records. By implementing this 3-step process, our template documents will correctly capture the study procedures. Furthermore, when study amendments result in changes that are related to data collection, we will have excellent document controls in place for the templates. We have instituted the term “Data Collection Documents” or “DCDs” for these records and will no longer refer to the templates as “source documents”. Please see Attachment 4 for a copy of the email I distributed to all staff describing this new terminology. Our current “Source Documentation” SOP is under revision to also include proper document control by assigning version numbers to these documents.

As another step in our corrective action plan, we will conduct a pre-study meeting for each new study, prior to enrollment of the first subject. These will be in addition to the site initiation meetings. At these meetings a physician investigator and the lead study coordinator, as well as other associated staff, will formally discuss the study and review the procedures required for the study. We will maintain a record of attendance and minutes at these meetings. A new SOP is being created to describe this additional step. Finally, Arizona Research Center’s Director has informed our research staff that attendance at these meetings is required. (Attachment 5)

CORRECTIVE ACTION PLAN

The details of Arizona Research Center’s corrective action plan are captured in the table attached to this letter as Attachment 1. Some of the items listed in the plan are already underway or completed. I have provided target completion dates for each item. We have adequate staff and resources to accomplish the plan according to the timeline indicated in the table. I firmly believe that instituting these objectives will

result in improved quality to our records and better document controls.

I recognize the importance of the baseline audiometry reports since these tests were a key safety endpoint in these studies. The safety of our volunteers is of paramount importance to me as a physician and PI and to my co-workers at Arizona Research Center. Furthermore, we want to uphold the highest standard of accuracy for all records and data collected at our site. The significance of maintaining subject safety and ensuring accuracy is reflected in our corrective action plan.

I have chosen to focus my career on clinical research and have maintained current certification as a Certified Physician Investigator by ACRP since 2005 (Attachment 6) and have completed the CITI training course in Good Clinical Practice every two years since January 2008. (Attachment 7) Additionally I have completed many Continuing Medical Education (CME) courses that are research specific (see Attachment 8). Along with the management and staff at Arizona Research Center, I recognize the importance of accurate data that are collected while respecting subject safety and I am highly committed to carrying out the corrective action plan. Thank you for the opportunity to address the concerns raised in the Warning Letter. I look forward to improving performance and accuracy in our future studies with the corrective steps we are taking at Arizona Research Center.

Sincerely,

/s/

Louise A. Taber, MS, RD, MD, FACP, CPI

Attachments:

Attachment 1 Arizona Research Center Corrective Action Plan

Attachment 2 Personnel Record, **(b)(6)**

Attachment 3 Email from N. Dell'Erario, Director, regarding redacting

Attachment 4 Email from Louise Taber, MD regarding DCDs terminology

Attachment 5 Email from N. Dell'Erario, Director, regarding required attendance at pre-study meetings

Attachment 6 ACRP Certified Physician Investigator Certificate

Attachment 7 CITI training in Good Clinical Practice completion report

Attachment 8 Dr. Taber Continuing Medical Education activity 2004-2014

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