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

Center for the Improvement of Human Functioning International, Inc. IRB 7/3/12

Department of Health and Human Services

Public Health Service
Food and Drug Administration
Silver Spring, MD 20993

WARNING LETTER

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Ref: 12-HFD-45-06-01

Brian Riordan
President and CEO
Center for the Improvement of Human Functioning International, Inc. IRB
822 Greenwich Street, 3C
New York, NY 10014

Dear Mr. Riordan:

This Warning Letter informs you of objectionable conditions observed during the U.S. Food and Drug Administration (FDA) inspection conducted of your Institutional Review Board (IRB) between July 6 and July 8, 2011, by Mr. Richard Rutherford, representing FDA. The purpose of this inspection was to determine whether the IRB procedures for the protection of human subjects complied with Title 21 of the Code of Federal Regulations (CFR), parts 50 and 56. These regulations apply to clinical investigations of products regulated by FDA. 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, Mr. Rutherford presented and discussed with you Form FDA 483, Inspectional Observations. We acknowledge receipt of your September 29, 2011, written response to the Form FDA 483, but note that this response was received past the 15 working days from close of the inspection. Thus, while we have reviewed the response, we have not included a discussion of the response in this letter, as per the Commissioner's Enforcement Initiative announced August 11, 2009.

In addition, interviews of three clinical investigators were conducted between January 23 and February 1, 2012. These clinical investigators submitted protocols to your IRB. From our review of the establishment inspection report, the documents submitted with that report, and the documents collected from the clinic investigators interviewed, we conclude that your IRB did not adhere to the applicable statutory requirements and FDA regulations governing the protection of human subjects. We wish to emphasize the following:

1. The IRB failed to prepare, maintain, and follow required written procedures governing the functions and operations of the IRB [21 CFR 56.108(a), 21 CFR 56.108(b), and 21 CFR 56.115(a)(6)].

In order to fulfill the requirements of the IRB regulations, each IRB must prepare, maintain, and follow written procedures describing IRB functions and operations specified in the regulations.

Our inspection revealed that the IRB had no written procedures, and therefore did not follow adequate written procedures for the IRB’s functions and operations. IRB procedures need to include

the following:

a. Written procedures for conducting its initial and continuing review of research and for reporting its findings and actions to the investigator and the institution [21 CFR 56.108(a)(l)].

b. Written procedures for determining which projects require review more often than annually and which projects need verification from sources other than the investigator that no material changes have occurred since previous IRB review [21 CFR 56.108(a)(2)].

c. Written procedures for ensuring prompt reporting to the IRB of changes in research activitie [21 CFR 56.108(a)(3)].

d. Written procedures for ensuring that changes in approved research, during the period for which IRB approval has already been given, may not be initiated without IRB review and approval except where necessary to eliminate apparent immediate hazards to the human subjects [21 CFR 56.108(a)(4)].

e. Written procedures for ensuring prompt reporting to the IRB, appropriate institutional officials, and the FDA of any unanticipated problems involving risks to human subjects or others [21 CFR 56.108(b)(l)].

f. Written procedures for ensuring prompt reporting to the IRB, appropriate institutional officials, and the FDA of any instance of serious or continuing noncompliance with these regulations or the requirements or determinations of the IRB [21 CFR 56.108(b)(2)].

g. Written procedures for ensuring prompt reporting to the IRB, appropriate institutional officials, and the FDA of any suspension or termination of IRB approval [21 CFR 56.108(b)(3)]

Please submit a corrective and preventive action (CAPA) plan to address the citation above. With your CAPA plan, submit a copy of your written procedures, or any draft procedures in development, and a timeline for the implementation of any new procedures.

Please provide a description of any training provided to IRB staff on the new procedures and a list of attendees, or a projected timeline of planned training.

2. The IRB failed to prepare and maintain adequate documentation of IRB activities, including copies of all research proposals reviewed, approved consent documents, and progress reports submitted by investigators [21 CFR 56.115(a)(1)].

An IRB is required to prepare and maintain adequate documentation of IRB activities including, but not limited to, copies of research proposals reviewed, approved consent documents, and progress reports. Your IRB failed to adhere to this requirement.

Specifically:

a. On November 14, 2007, the IRB approved the FDA-regulated study "**(b)(4)**." The full protocol contained 127 pages. However, the IRB's documentation is limited to eight pages of the protocol dated May 5, 2006. Therefore, the documentation maintained by the IRB is incomplete.

b. A December 31, 2008, letter from Dr. James Jackson, an IRB member, refers to approving a change in the consent form for the **(b)(4)** study. No copy of any consent form for this study was located among the IRB's records.

c. A December 21, 2010, letter from the IRB Chair to Dr. Hunninghake states that the **(b)(4)** study is approved to continue. No progress reports for the **(b)(4)** study were located among the IRB's records.

Please submit a CAPA plan to address the citation above. Please include in your CAPA plan any preventive actions you plan to take to avoid recurrence of this violation.

3. The IRB failed to prepare and maintain adequate documentation of IRB activities, including minutes of IRB meetings [21 CFR 56.115(a)(2)].

An IRB shall prepare and maintain adequate documentation of IRB activities, including minutes of IRB meetings, which shall be in sufficient detail to show attendance at the meetings, actions taken by the IRB, the vote on these actions, including the number of members voting for, against, and

abstaining, the basis for requiring changes in or disapproving research, and a written summary of the discussion of controverted issues and their resolution. Your IRB failed to adhere to the above-stated regulations.

Examples of this failure include, but are not limited to, the following:

a. During the inspection, the IRB Chair indicated that the IRB met twice per year and had beer in business for over 20 years. However, the field investigator was only able to locate one set o meeting minutes dated June 25, 1997.

b. The IRB had no meeting minutes documenting any action related to the **(b)(4)** study.

Please submit a CAPA plan to address the citation above. Please include in your CAPA plan any preventive actions you plan to take to avoid recurrence of this violation.

4. The IRB failed to maintain copies of all correspondence between the IRB and investigators [21 CFR 56.115(a)(4)].

An IRB shall prepare and maintain adequate documentation of IRB activities, including copies of all correspondence between the IRB and the investigators. Your IRB failed to adhere to the above-stated regulations. Examples include, but are not limited to, the following:

a. The IRB did not maintain the following items of correspondence that were obtained by the FDA investigator:

1. A letter dated November 14, 2007, from James Jackson, IRB Chair, to Dr. Hunninghake, stating that the **(b)(4)** study was approved.

2. A letter dated December 31, 2008, from James Jackson, IRB Chair, to Dr. Hunninghake, stating that the revised informed consent document for the **(b)(4)** study had been approved by all IRB members.

3. Five letters dated December 31, 2008, from James Jackson, IRB Chair, to IRB members (Dr. **(b)(6)**, Mr. **(b)(6)**, Mr. **(b)(6)**, Dr. **(b)(6)**, and **(b)(6)**), requesting tha they review the changes to the **(b)(4)** study informed consent document, sign, and sen back their approval.

4. A letter dated December 28, 2009, from James Jackson, IRB Chair, to Dr. Hunninghake, stating that the study was approved to continue.

b. The IRB's records include a March 23, 2011, letter from Dr. Hinshaw, the current IRB Chair, to the Medical Monitor for the **(b)(4)** study. The letter discusses six serious adverse event reports (SAEs) and Dr. Hinshaw's concern over their attributions. However, copies of the original SAEs were not maintained by the IRB.

Please submit a CAPA plan to address the citation above. Please include in your CAPA plan any preventive actions you plan to take to avoid recurrence of this violation.

5. The IRB failed to prepare and maintain a list of IRB members identified by name; earned degrees; representative capacity; indications of experience sufficient to describe each member's chief anticipated contributions to IRB deliberations; and any employment or other relationship between each member and the institution [21 CFR 56.115(a)(5)].

An IRB is required to prepare and maintain a list of IRB members in accordance with the regulations.

During the inspection, the only IRB roster that the FDA Investigator was given was part of a letter dated October 3, 2007, and did not include each IRB member's earned degree, representative capacity, and indications of experience sufficient to describe the member's chie anticipated contributions to the IRB deliberations.

Please submit a current IRB roster that includes names; earned degrees; representative capacities; indications of experience sufficient to describe each member's chief anticipated contributions to IRB deliberations; and any employment or other relationship between each member and the institution. With your response, please address how you will prevent reoccurrence of this violation.

As noted in the citations above, the IRB lacks procedures to define how it operates, and has failed to maintain adequate documentation of its activities. Documentation of an IRB's activities allows FDA to ascertain (1) what material was reviewed by the IRB; (2) that initial and continuing review were performed; (3) what controverted issues were discussed, if any; (4) who reviewed the studies, and whether they were qualified to review the research; and (5) what correspondence took place between the IRB and investigators. Such information helps to ensure that the rights, safety, and welfare of human subjects are protected.

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 that your written response to the Form FDA 483 dated September 29, 2011, fully explains the actions you have taken to prevent similar violations in the future, please communicate that to us in writing within fifteen (15) business days. You may reference your written response dated September 29, 2011, in your response to this letter.

We recommend that you visit the following FDA Web page for information on human subject protections. This information may assist you in your efforts to bring the IRB into compliance with FDA regulations:

http://www.fda.gov/ScienceResearch/SpecialTopics/RunningClinicalTrials/default.htm[1]

We appreciate the cooperation shown to FDA Investigator Rutherford during the inspection. If you have any questions, please contact Catherine Parker, R.N., at 301-796-5553; FAX 301-847-8748. Your written response and any pertinent documentation should be addressed to:

Catherine Parker, R.N.
Acting Branch Chief, Human Subject Protection Branch
Office of Scientific Investigations
Office of Compliance
Center for Drug Evaluation and Research
Food and Drug Administration
Building 51, Room 5247
10903 New Hampshire Avenue
Silver Spring, MD 20993

Sincerely,

{See appended electronic signature page}

Leslie K. Ball, M.D.
Acting Office Director
Office of Scientific Investigations
Office of Compliance
Center for Drug Evaluation and Research
Food and Drug Administration

Cc:

Charles T. Hinshaw, M.D.
Laboratory Director and IRB Chair
Center for the Improvement of Human Functioning International, Inc. IRB
3100 North Hillside Avenue
Wichita, KS 67219

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

LESLIE K BALL
07/03/2012

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Note: If you need help accessing information in different file formats, see Instructions for Downloading Viewers and Players.

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Links on this page:

1. http://www.fda.gov/ScienceResearch/SpecialTopics/RunningClinicalTrials/default.htm