Inspections, Compliance, Enforcement, and Criminal Investigations

Cleveland Clinic Response Letter

Cleveland Clinic

Ali R. Rezai, M.D.
Jane & Lee Seidman Chair in Functional Neurosurgery
Director of Neurological Innovations

April 28, 2009

Doreen Kezer
Food and Drug Administration
Center for Devices and Radiological Health
Office of Compliance
Division of Bioresearch Monitoring
9200 Corporate Boulevard
HFZ-311
Rockville, Maryland 20850

Re: Response to FDA Warning Letter Posting

Dear Ms. Kezer:

I am respectfully requesting the opportunity to post my submitted response to the FDA Warning Letter dated November 13, 2008. My response was submitted to the FDA on December 2, 2008 stating the follow-up actions related to the issues raised in the warning letter. The FDA acknowledged our response on December 11, 2008 and indicated that our corrective and preventive actions were sufficient.

Attached please find a disk containing both the Word and Adobe versions of my Warning Letter response and the FDA acknowledgement and follow-up letter.

I continue to take seriously my responsibilities as a Sponsor and Investigator and

thank you for the opportunity to post my response letter. Please contact me if there is any additional information that I need to provide.

Regards,

/s/

Ali R. Rezai, MD

The Cleveland Clinic Foundation
9500 Euclid Avenue /8-31
Cleveland, OH 44195
Tel 216-444-4720
Fax 216-636-3321

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Cleveland Clinic

Ali R. Rezai, M.D.
Jane and Lee Seidman Chair in Functional Neurosurgery
Director, Center for Neurological Restoration
Professor of Neurosurgery

December 2, 2008

Doreen Kezer
Food and Drug Administration
Center for Devices and Radiological Health
Office of Compliance
Division of Bioresearch Monitoring
9200 Corporate Boulevard
HFZ-310
Rockville, Maryland 20850

Dear Ms. Kezer:

I am responding to the FDA Warning letter dated November 13,2008 concerning my response to the Form 483 of the inspection dated September 2,2008 that took place at the Cleveland Clinic from July 22, 2008 through August 29, 2008.

I am dedicated to the highest standards for clinical research and I am taking very seriously the FDA Warning Letter. I have been and remain committed to resolving the objectionable conditions observed during this audit on the following studies:

(b)(4)

(b)(4)

(b)(4)

I understand my obligations as a Sponsor and Investigator, and I am committed to complying with all the applicable laws and regulations regarding clinical research. I have dedicated time and effort toward improving my clinical research program and remedying the deficiencies indentified by the FDA. In this regard, I will not enroll any new subjects in these studies until deficiencies are corrected and accepted by the FDA. I will submit a 30 day progress report in January 2009.

I want to thank you for the opportunity to respond.

Sincerely,

Ali R. Rezai, MD

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The Cleveland Clinic Foundation
9500 Euclid Avenue I S-31
Cleveland, Ohio 44195

Tel 216-444-8001
Fax 216-636-3321

Appt 216 444-2230

Citations related to my role and responsibilities as the sponsor of the above IDEs.

1. Failure to prepare and submit progress reports to the FDA at regular intervals and at least yearly.

I failed to submit reports for IDE **(b)(4)** in 2007 and 2008
I failed to submit reports for IDE **(b)(4)** for 2006
I failed to submit reports for IDE **(b)(4)** for 2005
I submitted the 2007 report for IDE **(b)(4)** in February of 2008, due date is December 12

Response:
As the Investigator/Sponsor, I recognize my responsibility for timely submission of the annual IDE report. Please allow me to clarify some of the findings from the audit. There were 5 annual reports identified by the auditors as deficient. We were delinquent with three annual reports (IDE **(b)(4)** 2007, IDE **(b)(4)** 2006, and IDE **(b)(4)** 2005). However according to our records one of the five reports was submitted to the FDA (IDE **(b)(4)** 2007). The FDA acknowledgment of this annual report is attached in (Appendix A: Annual Report & Acknowledgement of receipt of report from FDA).

Corrective Action:
IDE #**(b)(4)** I acknowledge that the 2007 annual report was not submitted to the FDA. The data collected in 2007 was included in the final annual report submitted 9/2/2008. (Appendix A: Acknowledgement of receipt of report from FDA). This study has subsequently been closed since all subjects have completed protocol required follow-up. I have submitted the final annual report sent 9/2/2008**. (Appendix A)**

IDE #**(b)(4)** I acknowledge that the 2006 annual report was not submitted to the FDA. The data collected in 2006 was included in the annual report submitted 9/2/2008 to close enrollment. **(Appendix A)**.

IDE **(b)(4)** I acknowledge that the 2005 annual report was not submitted to the FDA. I will submit a comprehensive annual report on or before 12/12/2008 (our annual renewal date) which will include data from 2005. Our records indicate that the 2007 annual report was submitted to the FDA 2/21/2008. **(Appendix A)**

Preventive Plan:
As the Investigator/Sponsor I understand that it is my responsibility for the completion of the annual report per 21 CFR 812.150 (b)(5). I have developed and implemented a standard operating procedure to ensure that annual reports are appropriately submitted to the FDA and IRB. This SOP (Appendix B: Annual Report SOP and checklist) includes a checklist and due dates to ensure that all requirements for progress reports to both the FDA and IRB are done in a timely manner.

In addition, I have spoken with **(b)(6)** Director of our IRB and requested synchronized due dates for the IRB study renewal and the FDA annual report. The IRB renewal process includes an automated notification two months prior to the renewal date. This will provide an additional check and reminder regarding the progress reports to the FDA and IRB are completed.

I have also scheduled training for myself and the research coordinators with our IRB to review the reporting requirements and ensure that all study personnel are comfortable and knowledgeable. An additional institute mechanism at Cleveland Clinic now has an IND/IDE office to assist Sponsor Investigators and will serve as resource for training and guidance. I will be working collaboratively with **(b)(6)** RN. I have coordinated a training session regarding the progress reports as described in 21 CFR 812. Furthermore all new research personnel will have to undergo specific training regarding the 21 CFR 812 regulations.

Additionally, I have also set up a system for both myself and the research coordinator's schedule using **(b)(4)** and have activated preset reminders for all my annual reports to appear 2 months prior to their due date. This will allow enough time for the research team to compile the needed information for each report.

Citations related to my role and responsibilities as the sponsor of the above IDEs.

2. Failure to obtain from each participating investigator a signed agreement that includes sufficient accurate financial disclosure information to allow the sponsor to submit a complete and accurate certification or disclosure statement.

Response:
I recognize the importance of completing a signed Investigator agreement that includes Investigator Financial Disclosure information.

Corrective Action:
I am collecting Financial Disclosure Forms and Investigator Agreements from the active Cleveland Clinic investigators. My study coordinator and I have requested

and are collecting those documents. Five of the seven Cleveland Clinic investigators have signed the investigator agreements. **(Appendix C: Signed Investigator Agreements)** Copies of the remaining documents will be forwarded to the FDA upon receipt, no later than January 30, 2009.

Regarding our off-site investigators (IDE# **(b)(4)**, they have been contacted for the information and I have given them a deadline of January 30, 2009 to respond appropriately or I will proceed as required by Federal Regulations.

Preventive Plan:
All new investigators will sign the aforementioned investigator agreement and financial disclosure documents. Failure to do so will preclude the investigator from participating in the research trial. Each investigator will be queried annually for updates to the financial disclosure, a duty I have delegated to our research manager Despina Mavrakis.

Updated financial disclosure information has been added to our annual report checklist that will be completed by the study coordinator and then reviewed by me to ensure all elements of the annual report are complete. **(Appendix B: Annual Report SOP and checklist)**

Moving forward, I have developed an additional Standard Operating Procedure with an associated checklist on Regulatory Document Collection for Site Initiation prior to initiation of any further Investigator held IDEs. My team members have been trained on this SOP. You will find the SOP and training document which includes language regarding financial disclosures **(Appendix D: Regulatory Document Collection SOP and Checklist).**

I plan to use a contract research organization, M3, to audit the regulatory documents of each site prior to site initiation on new IDEs. If there are any missing documents, I will not approve site initiation until each document has been collected. **(See Appendix E: (b)(4) Checklist and (b)(4) Checklist)**

Citations related to my role and responsibility as a clinical investigator of the above IDEs.

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

Response:
I recognize the importance of adherence to the protocol throughout clinical investigations. The only occasion when we would deviate from the investigational plan would be to protect the life or physical well-being of a subject in an emergency. Such notice will be given as soon as possible, but in no event later than 5 working days after the emergency. Except in an emergency, prior approval

by the FDA and IRB will be obtained before changes or deviations from the plan are implemented.

IDE (b)(4)

The protocol required that subjects be implanted bilaterally with model **(b)(4)** however, I deviated from the protocol by implanting only one device in Subject **(b)(6)**

Corrective Action:
I recognize that this is a protocol deviation. However in certain medical circumstances ensuring patient safety is my priority. During surgery, I discovered that an electrode could not be implanted on the right side of the subject's brain for fear of rupturing a blood vessel that was recognized once the surgery had begun. This abnormality can only be detected during the surgical procedure and not before. The subject had anatomical abnormalities and in order to minimize risk of hemorrhage a decision was made to implant the subject unilaterally. I should have reported this protocol deviation to the IRB and FDA immediately. I have reported this to both the FDA and the IRB as a protocol deviation since the initial audit. **(Appendix F: Deviation Report)**

The protocol required that two post surgical functional magnetic resonance imaging (fMRI) be performed; however I did not document the second post-surgery fMRI on any of the three subjects enrolled.

Corrective Action:
I recognize that this is a protocol deviation; however, in certain medical circumstances it is unavoidable as I must ensure patient safety. As a part of specific patient care, I determined that the information from a second fMRI would not provide me with data that would improve clinical care or my research program. As such, to decrease the additional testing on subjects, I decided not to do the fMRI. This should have been reported as a protocol deviation followed by a protocol amendment reported to the IRB and FDA. A protocol amendment will be forthcoming and submitted to the FDA. A protocol deviation has been reported to the FDA and the IRB since the initial audit **(Appendix G: Deviation Report Submission to the FDA and IRB with acknowledgements from both FDA and IRB).**

IDE (b)(4)
The protocol required that pulse generators (Soletra model 7426) be implanted. I deviated from the protocol by implanting a different pulse generator in two subjects.

Corrective Action:
I recognize that this is a protocol deviation; however, in certain medical

circumstances it is unavoidable as I must ensure patient safety. The **(b)(4)** systems are implanted on the right and the left sides of the brain. The two subjects noted had multiple previous brain surgeries including a shunt placement for hydrocephalus. The shunt tubing was in the way. In addition further distorted anatomy as a result of a brain surgery, craniotomy, burr holes and skull removal from a previous head trauma prevented implantation of the **(b)(4)** system. The **(b)(4)** system requires implantation on both sides of the body. The specific patient circumstance prevented us from safely implanting the **(b)(4)** system on the one side. I thus used an alternative FDA approved and routinely used **(b)(4)** pulse generator system which allows for implantation on only one side of the body. When I made this decision, I should have amended the protocol immediately and provided this information to the FDA and IRB. The Amendment will include the option to use the **(b)(4)** or **(b)(4)** model. This will be submitted by the end of the year. This protocol deviation was reported on 9/24/2008 to the FDA and IRB sine the initial audit. **(Appendix F Deviation report to the FDA and IRB including acknowledgement from both the FDA and IRB)**

Preventive Plan:
I have developed the following comprehensive process to prevent any of these issues.
This includes:

1- Additional training for all research staff for reporting and reviewing the protocol deviations. My team will be educated on this new Standard Operating Procedure **(Appendix G: Protocol Deviation SOP and Protocol Deviation CRF).** Prior to the enrollment of the next patient I will provide protocol training to all current investigators outside of the Cleveland Clinic via Webcast Teleconference. Attendance will be mandatory and recorded. We will submit these records to the FDA upon completion.

2-Development of a specific case report from for protocol deviation **(Appendix H)**

3-Documentation oversight-All protocol deviations will be disclosed to the research manager within 5 working days of the recognition of the event. The research manager will notify me and I will ensure that all appropriate documentation related to the protocol deviation is complete including the FDA and IRB disclosure documentation along with the protocol deviation CRF. I will review all deviations and discuss with the relevant investigator the appropriateness of such actions. I will perform a detailed review of each deviation to determine a course of action necessary to prevent reoccurrence this may include a proactive amendment of the protocol if that is deemed necessary. All protocol deviations will be reported to the FDA, IRB and the Data Safety Monitoring Board at the specified regular meeting times and annually or earlier if necessary.

4-Additional Monitoring- I have contracted with an independent monitoring group

(b)(4) review each case after the subject is implanted. I will not implant another subject until I review each protocol deviation and assess the need for additional education and/or a protocol amendment. **(b)(4)** has agreed to issue a report as to the status of the adherence to the protocol and protocol deviations. We will provide the FDA with a copy of that report once completed.

5- I will proactively make amendments to the protocol and I will provide details about implant options in future protocols that would allow the use of one or the other alternative system to accommodate patient anatomical and structural differences. In this context, we are in the process of amending the protocol for IDE **(b)(4)** to allow for the ability to implant devices based on best medical action for each patient. This amendment will be submitted to the FDA and Cleveland Clinic IRB by January 30, 2009. There will not be any change in the process until the FDA and IRB approve the request for an amendment.

4. Failure to maintain accurate, complete and current case histories

IDE **(b)(4)**

The protocol preoperative studies included the (b)(4) scales and pre surgical baseline follow up test batteries to be performed by a psychiatrist or specially trained interviewer. Additional studies include the **(b)(4)**

For all five of the subjects enrolled in this study, records were incomplete.

Subject **(b)(6)** Subject Identification (ID), the examiner's initials, and the date of the visit are missing

Subject **(b)(6)** Examiner's initials missing and subject ID are missing

Subject **(b)(6)** Subject ID, dates and examiner's initials are missing

Subject **(b)(6)** Subject ID, dates and examiner's initials are missing

Subject **(b)(6)** Subject ID, dates and examiner's initials are missing

IDE **(b)(4)**

The protocol states that clinician rated scales will be performed by a psychiatrist or specially trained interviewer. The records for subject **(b)(6)** are incomplete in that pages are missing and subject ID, dates and examiner's initials.

Response:
I understand the importance of complete and accurate case history source documents. Our records indicate the case histories did include the details for clinical scales listed above. Unfortunately, however, the source documents

contained in the case history did not clearly identify the examiner, the date or subject ID.

Corrective Action:
IDE **(b)(4)** is now closed and IDE **(b)(4)** is now closed to enrollment. I have counseled and retrained the two individuals who have been conducting the assessments listed above. The psychiatrist **(b)(6)** has been involved in the study since inception. **(Appendix H Assessment counseling and sign off)**

Preventive Plan
I will retrain the psychiatrist and research nurse in maintaining accurate, complete and current case histories that identify the subject indicate the dates and examiner's initials. The monitors will also be trained to review source documents for completeness. If these mechanisms detect any incomplete records, there will be no additional enrollment until the cause for the incomplete records are determined and a plan of action for resolution and prevention is established.

Preventive Plan
I will retrain the psychiatrist and research nurse in maintaining accurate, complete and current case histories that identify the subject indicate the dates and examiner's initials. The monitors will also be trained to review source documents for completeness. If these mechanisms detect any incomplete records, there will be no additional enrollment until the cause for the incomplete records are determined and a plan of action for resolution and prevention is established.

Only one-two individuals will act as examiner for the various neuro-psych assessments; **(Appendix,H assessment counseling and sign off).** Once training is complete I will sign off a training log and the individual will then be allowed to assess the patients.

I would like to thank you for the opportunity to respond and provide further details regarding remedying the citations. I take my responsibility very seriously and will continue to work with you to provide a compliant research program. I would like to emphasize again that I will not enroll any additional patients in these IDE's until these objectionable conditions and deficiencies are corrected and deemed acceptable by the FDA.

If you have any questions, feel free to contact me at any time.

/s/

Ali Rezai

cc: Cincinnati District Office
6751 Steger Drive
Cincinnati, Ohio 45237