DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Center for Devices and
Radiological Health
2098 Gaither Road
Rockville, MD 20850

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OCT 3 2005

WARNING LETTER

Via Federal Express

Michelle A. Ross, MD
Atlanta Radiology Consultants
5665 Peachtree
Atlanta, GA 30341

Dear Dr. Ross:

The purpose of this Warning Letter is to inform you of objectionable conditions found during a recent Food and Drug Administration (FDA) inspection conducted at your clinical site. This letter also discusses your July 11, 2005, written response to the noted violations and requests that you promptly implement corrective actions. An investigator from FDA's Atlanta District Office conducted the inspection from May 5 through June 16, 2005. The purpose of the inspection was to determine if your activities as a Clinical Investigator (CI) of human research studies complied with applicable FDA regulations. The clinical trial that was the subject of the inspection was [redacted] using the [redacted], and sponsored by [redacted]. The product used in the study is a device as that term is defined in Section 201(h) of the Federal Food, Drug, and Cosmetic Act (the Act) [21 U.S.C. 321(h)].

The FDA conducted the inspection under a program designed to ensure that data and information contained in applications for Investigational Device Exemptions (IDE), Premarket Approval Applications (PMA), Product Development Protocols (PDP), or Premarket Notification [510(k)] submissions are scientifically valid and accurate. Another objective of the program is to ensure that human subjects are protected from undue hazard or risk during the course of the scientific investigation.

Our review of the inspection report prepared by the Atlanta District Office revealed serious violations of Title 21, Code of Federal Regulations (21 CFR), Part 812 - Investigational Device Exemptions and Part 50 - Protection of Human Subjects. At the close of the inspection, the FDA Investigator presented a Form FDA 483, "Inspectional Observations," to you for review, and discussed the listed deviations. The deviations noted on the FDA 483, our subsequent review of the inspection report, and your written responses to those deviations are discussed below:

1. **Failure to ensure that informed consent was obtained in accordance with 21 CFR Part 50 and failure to document informed consent [21 CFR 812.100, 21 CFR 812.140(a)(3)(i), and 21 CFR 50.20].**

   You failed to obtain and document that valid informed consent was obtained for each of the [redacted] subjects enrolled in the study as required by the above-stated regulations. Examples of this failure include but are not limited to the following:

   a.) Three consent forms (Subjects [redacted], and [redacted]) appeared to have subject signatures that did not match the signatures of these same subjects found in other parts of their clinic records.

   b.) The consent form approved by the IRB for use at your site required you, the CI, to sign each consent form at the time of consent. You failed to sign consent forms for at least fifteen subjects (Subjects [redacted], and [redacted]).

   c.) During the inspection, you were provided with the signature pages of the consent forms for Subjects [redacted] and asked to verify your signature. At that time, you expressed your belief that eleven of the consent forms (Subjects [redacted], and [redacted]) purportedly bearing your signature as the CI were not actually signed by you.

   d.) The consent form approved by the IRB for use at your site required each form to be signed by a witness at the time of consent. Study personnel and site auditors determined that many of the witness signatures observed on the consent forms could not be identified as true witnesses, and could not be verified as clinic or study personnel.

   In your response letter to FDA, dated July 11, 2005, you state that you only became aware of these issues when a new study coordinator was assigned to the study in August 2004, which was after forty-one subjects had already been enrolled in the study. In addition, you state that "virtually all of the serious documentation problems appear to have been the work of a single research coordinator who was delinquent in fulfilling her assigned study duties." This explanation is insufficient because, as the CI, it was your obligation to ensure that all of the requirements for obtaining and documenting informed consent were met. Your required signature on the informed consent forms implies that you have reviewed the documents for completeness and that the subjects were appropriately and adequately consented.

2. **Failure to ensure an investigation is conducted in accordance with the signed agreement with the sponsor, the investigational plan, applicable FDA regulations, and any conditions of approval imposed by FDA or the IRB [21 CFR 812.100, 21 CFR 812.110(b)].**

   You failed to adhere to the above-stated regulations. Examples of this failure include but are not limited to the following:

   a.) The Research Nurse Procedure Manual, which is part of the investigational plan, requires that paper copies of all the electronic case report forms must be maintained in the study charts. Copies of CRF-04 [redacted] Form) were missing from thirty-two of the [redacted] study charts. In addition, you did not provide the FDA investigator with access to the electronic records during the inspection, which resulted in an inability to perform a complete audit and

evaluation of the study records.

b.) You enrolled ineligible subjects into the study. Subjects with a history of [redacted] were specifically excluded by the study protocol, but at least six of the [redacted] enrolled subjects had previous [redacted] histories documented in their clinic charts.

c.) The protocol required that the [redacted] for enrolled subjects be performed within 90 days of receiving a [redacted]. You enrolled Subject [redacted] and performed the [redacted] 177 days after the [redacted].

d.) By letter dated October 22, 2004, the Institutional Review Board (IRB) at [redacted] directed that specific corrective actions be taken in response to the protocol deviation report you submitted to them concerning the existence of questionable witness signatures on some of the informed consent forms:

1. PI (Principal Investigator) must undergo training related to conducting clinical research and Good Clinical Practices and provide the IRB with documentation that such training has occurred;
2. written follow-up on the action plan submitted to the IRB on October 14, 2004, must be provided within 2 months (by December 2004);
3. documentation must be provided to the IRB showing that the [redacted] staff received training on Good Clinical Practices within two months from the date the action plan was submitted; and
4. [redacted] staff must undertake an audit of all previous studies involving the same study coordinator as the [redacted] study.

The study records provided to the FDA investigator during the inspection did not indicate that the corrective actions specified by the IRB had been completed. In your response letter, you assert that "[e]ach of the actions required by the IRB have in fact been addressed." However, we do not find your response to the IRB's requirement that you, as the principal study investigator, receive training related to clinical research and Good Clinical Practices, to be adequate. In this regard, your letter includes the following statement: "Clinical research training and GCP training for the PI were determined to be moot because the PI indicated that she would no longer be involved in clinical research as a principal investigator or in any other capacity. However, should the PI later reconsider this decision, she understands that she must complete such training prior to performing any study activities." Please provide this statement to us using first person language. The statement should be signed and dated by you.

With regard to the IRB's requirement that [redacted] perform an audit of all studies involving the previous study coordinator, your response letter states that, "An audit of all previous studies involving the previous Coordinator was conducted and a report received in May 2005. In summary, all studies were in order except one, where several questions were raised that are presently being answered and/or addressed." Please provide FDA with specific information related to the studies that were audited, including audit findings and subsequent actions taken, if any.

3. Failure to maintain accurate, complete, and current records relating to your participation in an investigation [21 CFR 812.140(a)].

You failed to adhere to the above-stated regulation. Examples of this failure include but are not limited to the following:

a.) The Protocol, the Research Nurse Procedure Manual, and the Case Report Form Manual required that each investigator use source document worksheets that were provided by the sponsor as a primary record for all data entries on the case report forms (CRFs). These worksheets were to be used to verify the data reported on the electronic CRFs. The following worksheets were not used as required, and therefore the study data could not be verified:

i. [redacted] Worksheet ([redacted]): this source data worksheet was blank, missing, or incomplete for thirty-nine of the [redacted] subjects enrolled in the study. This information was to be used to document and verify array selection and performance of [redacted].

ii. [redacted] Source Document ([redacted]): this source data worksheet was blank for ten of the [redacted] subjects enrolled in the study. This information was to be used to document [redacted].

iii. Study Subject Progress Notes ([redacted]): this document was blank or incomplete for thirty-three of the [redacted] subjects enrolled in the study. This information was to be used to document and verify the consent process, subject eligibility for the study, the completion of [redacted], and any initial subject reactions after [redacted]

iv. Subject Data Form Source Document ([redacted]): this document was incomplete, missing, or inaccurate for thirty-eight of the [redacted] subjects enrolled in the study. This information was to be used to document baseline medical and surgical history for the subjects.

b.) At least six of the [redacted] subjects had previous [redacted] histories documented in their clinic charts that were not documented in the eligibility criteria recorded in the study chart or reported in the CRFs. Subjects with a history of [redacted] were specifically excluded by the study protocol.

Your response letter to FDA and your verbal responses to these observations during the inspection are not adequate. As noted above, your response letter states that "virtually all of the serious documentation problems appear to have been the work of a single research coordinator who was delinquent in fulfilling her assigned study duties." During the inspection, you also told the FDA investigator that you relied solely on the research coordinator to recruit and enroll subjects, and you did not review source data or the CRFs, other than [redacted] forms ([redacted]). You also told the FDA investigator that since this was your first research project, you did not understand your responsibilities. However, you signed a Clinical Study Agreement on December 9, 2003, in which you agreed to the following:

"The Clinical Study shall be conducted under the direction and supervision of the Investigator;"

"The Investigator shall be responsible for ensuring that all participating staff and hospital personnel are adequately informed and trained as to the procedures specified in the Protocol. The Investigator shall conduct the Clinical Study in accordance with the terms of this Agreement; the Protocol, the applicable FDA regulations and guidelines and in compliance with all other applicable federal, state or local laws, and regulations;" and, "The Investigator and the Institution shall bear responsibility for the collection, management and reporting to the Sponsor of all Data obtained from the Clinical Study and shall maintain adequate and accurate records relating to the Clinical Study."

These statements in the agreement you signed clearly outline your responsibilities in the study. Your delegation of some study tasks to another individual does not relieve you of responsibility for ensuring that the rights, safety, and welfare of the subjects participating in the study are protected, and that the study is conducted correctly and in accordance with the signed agreement, the investigational plan, and applicable federal regulations.

4. **Failure to make available for inspection and copying all records relating to an inspection [21 CFR 812.145 (b), 21 CFR 812.150(a) (7)].**

Clinical investigators are required to permit authorized FDA employees to inspect and copy all records relating to an inspection. [21 CFR 812.145(b)]. In addition, "an investigator shall, upon request by ... FDA, provide accurate, complete, and current information about any aspect of the investigation." [21 CFR 812.150(a) (7)]. You failed to adhere to the above-stated regulations. Examples of this failure include but are not limited to the following:

a.) The FDA investigator began the inspection of your study site on May 5, 2005, at which time she requested the clinic charts for the [redacted] subjects enrolled in the study. The charts were provided a few at a time and only after repeated requests by the FDA investigator. Only thirty-six of the [redacted] charts had been provided to the investigator by May 31, 2005, at which time the investigator notified [redacted] that she was concluding her review. The FDA investigator allowed ample time for you and your staff to locate and provide the clinic charts for all of the enrolled subjects but, after nearly four weeks, nineteen charts had still not been located.

b.) Because some of your study records are maintained electronically, FDA investigators must be allowed to access to these electronic files in order to adequately conduct inspections. As the clinical investigator, it is your responsibility to ensure that FDA investigators are granted such access.

Please provide assurance that records will be maintained and provided during future inspections at your clinical site.

Your response letter, which was signed jointly by you and William Schaeffer, Acting President of St. Joseph Research Institute (SJRI), notes that SJRI has implemented several corrective actions to prevent reoccurrences of the problems found during the inspection. Please provide us with written documentation providing specific details regarding the following procedures mentioned in the response letter:

- The competency assessment program for current coordinators;

- The compliance and ethics policy, including the code of conduct for research and requirements for reporting suspected violations;
- The internal audit process;
- The required training program for new principal investigators.

The above-described deviations are not intended to be an all-inclusive list of deficiencies that may exist at your clinical site. It is your responsibility to ensure adherence to each applicable requirement of the Act and all pertinent Federal regulations when conducting clinical research, and to ensure that any staff or personnel who are delegated study tasks are knowledgeable regarding the Investigational Plan and are directly supervised by you.

Please acknowledge receipt of this letter **within 15 working days**, including supporting documentation of the specific steps you have taken or will take to correct these violations and prevent the recurrence of similar violations in current and future studies. Any submitted corrective action plan must include projected completion dates for each action to be accomplished.

In addition, please provide a complete list of all clinical trials in which you have participated for the last five years, including the name of the study and test article, the name of the sponsor, the number of subjects enrolled, and the current status of the study.

Failure to respond to this letter and take appropriate corrective action could result in FDA taking regulatory action without further notice to you. In addition, FDA could initiate disqualification proceedings against you in accordance with 21 CFR 812.119. Send your response to: Food and Drug Administration, Center for Devices and Radiological Health, Office of Compliance, Division of Bioresearch Monitoring, Special Investigations Branch, (HFZ-311), 9200 Corporate, Rockville, Maryland 20850; Attention: Ms. Doreen Kezer, Branch Chief.

We are also sending a copy of this letter to the FDA's Atlanta District Office, Food and Drug Administration, 60 Eighth Street, N.E., Atlanta, GA 30309. We request that you copy the District Office on your response. If you have any questions, please contact Ms. Doreen Kezer by phone at (240) 276-0125, or by email at dmk@cdrh.fda.gov.

Sincerely yours,

Timothy A. Ulatowski
Director
Office of Compliance
Center for Devices and
Radiological Health