DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Center for Biologics Evaluation
and Research
1401 Rockville Pike
Rockville MD 20852-1448

November 1, 2010

By Facsimile Transmission and Overnight Delivery

Alan Niederman, M.D., Medical Director
Jim Moran Heart and Vascular Research Institute
Holy Cross Hospital
1951 NE 47th Street
Fort Lauderdale, Florida 33308

NOTICE OF INITIATION OF DISQUALIFICATION PROCEEDINGS AND OPPORTUNITY TO EXPLAIN

Dear Dr. Niederman:

Between September 15, 2009 and October 16, 2009, Ms. Colleen M. Aspinwall, representing the Food and Drug Administration (FDA, or the agency), conducted an inspection of the following clinical study and met with you to review your conduct as the clinical investigator of the study: *A Double-Blind, Prospective, Randomized, Placebo-Controlled Study to Determine the Tolerability, Efficacy, Safety, and Dose Range of Intramyocardial Injections of G-CSF Mobilized Auto-CD34+ Cells for Reduction of Angina Episodes in Patients with Refractory Chronic Myocardial Ischemia* (stem cell study). You conducted this study at the Holy Cross Hospital (HCH) in Fort Lauderdale, Florida, where you serve as the Medical Director of the Jim Moran Heart and Vascular Research Institute (JMHVRI).

This inspection was conducted as part of FDA's Bioresearch Monitoring Program, which includes inspections designed to monitor the conduct of research involving investigational products.

At the conclusion of the inspection, Ms. Aspinwall presented and discussed with you the items listed on Form FDA 483, Inspectional Observations. We have reviewed the inspection report, the documents submitted with that report, and your written response to the Form FDA 483 dated November 2, 2009 ("Response Letter"). We consider your response to be unacceptable in addressing the matters outlined in this letter.

Based on our evaluation of information obtained by the agency, we believe that you have repeatedly or deliberately violated regulations governing the proper conduct of clinical studies involving investigational new drugs, as set forth under *Title 21, Code of Federal Regulations* (CFR), Part 312. The regulations are available at http://www.access.gpo.gov/cgi-bin/cfrassemble.cgi?title=201021.

This letter provides you with written notice of the matters complained of and initiates an administrative proceeding, described below, to determine whether you should be disqualified from receiving investigational products as set forth under 21 CFR § 312.70.

A listing of violations follows. The applicable provisions of the CFR are cited for each violation.

1. You failed to fulfill the general responsibilities of an investigator. [21 CFR § 312.60].

As a clinical investigator, your general responsibilities under 21 CFR § 312.60 include ensuring that an investigation is conducted according to the signed investigator statement, the investigational plan, and applicable regulations; for protecting the rights, safety, and welfare of subjects under the investigator's care; and ensuring control of drugs under investigation. When you signed the investigator statement (Form FDA 1572) for the above-referenced clinical investigation, you specifically agreed to personally conduct the clinical studies or to supervise those aspects of the studies that you did not personally conduct. While you may delegate certain study tasks to individuals qualified to perform them, such delegation requires adequate supervision of those to whom you delegate authority. You are responsible for the oversight of study personnel and for reviewing the work of study personnel to ensure that they follow the investigational plan and procedures.

Our investigation indicates that you delegated to the study coordinator, Ms. Terri Kellerman, the conduct of all of the study screening visits and the completion of study records for such screening visits, including source documents and Case Report Forms (CRFs). There is no evidence that you adequately oversaw and reviewed the study activities you delegated to Ms. Kellerman. As described below, it appears that you failed to review study records generated by Ms. Kellerman with reasonable care. Your lack of supervision and personal involvement resulted in failure to ensure that the study was conducted according to the signed investigator statement, the investigational plan, and applicable regulations.

A. The radiology reports for the 12-month chest x-rays of subjects (b)(6) and (b)(6) appear to have been fabricated. These reports are identical to the radiology reports for the baseline chest x-rays for these subjects, with the exception that the reports for the 12-month x-rays do not include a date. The same unique report identification number is present on the baseline report and the 12-month x-ray report for each of these subjects. Had you reviewed the radiology reports for these two subjects with reasonable care, it would have been obvious to you that the subjects' 12-month x-ray reports had been fabricated.

In your Response Letter, you neither agree nor disagree with this observation. Instead, you note that good documentation practices have been reviewed with all members of your study team, that you now use a log to track the review of study-related documents, and that you intend to hire a Quality Assurance Specialist as a member of your study team.

B. FDA's inspection revealed discrepancies between the CRFs maintained by the study coordinator and medical records maintained by you. For example, the CRF for subject (b)(6) study visit on October 17, 2007, showed that this subject was prescribed four medications. The CRF for the next study visit, which occurred on December 10, 2007, shows no changes in concomitant medication. However, medical records from your private practice document that this subject's concomitant medication did in fact change during this period. First, on October 25, 2007, you saw subject (b)(6) for follow-up and discharged the subject on eight medications. Subsequently, you saw this subject for follow-up on November 29, 2007, and discharged the subject on eight medications, five of which had been changed from the October 25, 2007 visit. Had you reviewed the CRFs with reasonable care, you would have found that they did not reflect the changes in medication made by you during interim visits at your medical practice.

In your Response Letter, you neither agree nor disagree with this observation. Instead, you note that you have changed your documentation review practices such that all source documentation charts now contain a "Medications Log" that is used to readily identify concomitant medication use for the duration of a subject's participation in a study.

C. As described below in item 2.A.i, the medical history documentation prepared by the study coordinator was not adequate to support the enrollment of any of the seven subjects into the study under the inclusion/exclusion criteria set forth in the protocol. There is no evidence to show that you reviewed this documentation. Had you reviewed this documentation with reasonable care, you would have found that it was not adequate to support the enrollment of any of the subjects in the study.

In your Response Letter, you neither agree nor disagree with this observation. Instead, you note that you have since taken corrective action to ensure that adherence to a study protocol is accurately and appropriately documented.

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

A. Subject records indicate that none of the enrolled subjects were eligible for the study according to the inclusion/exclusion criteria specified in the study protocol.

i. Protocol section 8.1.1.3 provides that to be eligible for inclusion in the study, a subject's treatment regimen must include at least one statin at the maximum tolerated dose and at least two anti-anginal medications (AAMs) at the maximum tolerated dose. You enrolled all seven subjects in the study even though they did not meet this study inclusion criterion. First, study records indicate that the treatment regimens of subjects (b)(6) did not include a statin, while the treatment regimens of subjects (b)(6) (b)(6) did not include AAMs. Second, study records indicate that subjects whose treatment regimens included statins and/or AAMs were not prescribed the maximum dosage of these medications, as determined under the "Monthly Prescribing Reference" (December 2007 version) provided to the FDA investigator as the reference used by your study site. Nothing in your records indicates that the subjects whose treatment regimens did not include statins and/or AAMs were unable to tolerate them, or that the subjects whose treatment regimens did include statins and/or AAMs were unable to tolerate the maximum dose. The following table summarizes information from the study records concerning each subject's treatment regimen prior to enrollment.

Subject	Medication Category	Medication Prescribed	Dose Prescribed	Maximum Dose from Monthly Prescribing Reference
	Statin	Lipitor	40 mg daily	80 mg once daily
	AAM #1	Lopressor	50 mg twice per day	100 mg – 450 mg daily
	AAM #2	Imdur	60 mg daily	Increase to 120 mg once daily; usual maximum dose is 240 mg once daily
	Statin	None	--	--
	AAM #1	Atenolol	50 mg daily	100 mg daily
	AAM #2	Procardia	30 mg daily	120 mg daily
	Statin	Lipitor	40 mg daily	80 mg once daily
	AAM #1	None	--	--
	AAM #2	None	--	--
(b)(6)	**Statin** **AAM #1** **AAM #2**	Unclear. Subject's form is blank; two medication lists are discrepant and undated.	Unclear.	--
	Statin	None	--	--
	AAM #1	Nitrodur patch	0.6 mg per hour daily	0.8 mg per hour daily
	AAM #2	Lisinopril	20 mg daily	40 mg daily
	Statin **AAM #1** **AAM #2**	Unclear. Subject's form states "See list in folders." No list was located.	Unclear.	--
	Statin	None	--	--
	AAM #1	Imdur	60 mg daily	Increase to 120 mg once daily; usual maximum dose is 240 mg once daily
	AAM #2	Toprol	100 mg daily	400 mg daily

In your Response Letter, you neither agree nor disagree with this observation. Instead, you note that you have since taken corrective action to ensure that adherence to a study protocol is accurately and appropriately documented.

ii. Protocol section 8.1.2.14 provides that a clinically significant abnormal laboratory result discovered during screening of a potential subject is a basis for study exclusion. There is no evidence to show that you assessed screening laboratory test results to evaluate subject eligibility prior to enrolling subjects in this study. As shown in the table below, for three of the subjects, your records show that the subjects' screening laboratory test results were reviewed after the subject had been enrolled in the study and the baseline study visit had been completed.

Subject	Screen Date	Baseline Visit Date	Laboratory Test Results	Review Date	Comment
(b)(6)	7/19/07	9/7/07	Coagulation panel, CK-MB, troponin	9/11/07	Results reviewed
	9/25/07	11/2/07	Coagulation panel, CK-MB, troponin	1/7/08	Lab reported no specimen received
				2/7/08	Results reviewed
	11/1/07	12/14/07	Coagulation panel, CK-MB, troponin	1/25/08	Lab reported no specimen received
				2/7/08	Results reviewed

In your Response Letter, you neither agree nor disagree with this observation. Instead, you note that screening laboratory results for subjects (b)(6) and (b)(6) were "available prior to treatment". For subject (b)(6), you state that the screening laboratory results were "reviewed prior to treatment." You do not state whether these subjects' screening results were reviewed prior to enrolling the subjects in the study.

iii. Protocol section 15.1.5 requires that a clinical investigator should not implement any deviations or changes to the protocol without agreement from the sponsor and prior review and agreement from the Institutional Review Board (IRB), except that prior approval from the IRB is not required if the deviation or change is to eliminate an immediate hazard to trial subjects.

a. Subject (b)(6) was enrolled in the study on July 19, 2007, even though the subject did not meet the inclusion criterion in protocol section 8.1.1.5 requiring a coronary angiogram obtained within the last 12 months. An eligibility exception was signed by the sponsor's medical monitor on April 8, 2008, nine months after the subject was enrolled. There is no evidence that the IRB ever reviewed or approved this deviation from protocol.

Similarly, subject (b)(6) was enrolled in the study on October 22, 2007, despite not meeting the study protocol inclusion criterion requiring a coronary angiogram obtained within the last 12 months. There is no evidence that the IRB was ever notified of this deviation from protocol. During the FDA inspection, you indicated that you did not seek approval from the IRB to waive these subjects into the study because you were concerned that this might exclude some subjects from participating in the study.

In your Response Letter, you neither agree nor disagree with this observation. Instead, you explain why you decided to waive these two subjects into the study.

b. Subject (b)(6) was enrolled in the study on September 25, 2007. At the time, this subject was on Clopidogrel and had a platelet count of 83,000 per microliter. The protocol excludes subjects on Clopidogrel with platelet counts below 100,000 per microliter. The sponsor's medical monitor verbally approved a waiver for this subject on October 2, 2007, provided that the subject was informed of the increased risks for bleeding and tamponade. An email from the medical monitor specifically requests that you confirm "that if allowed to go ahead, this subject will not be exposed to unforeseen or undisclosed risks or risk severity, keeping in mind that abnormal coagulation may increase the severity of any bleeding, including tamponade following cardiac perforation." There is no documentation that this discussion with the subject occurred. The IRB granted a waiver allowing you to enroll this subject on October 16, 2007, three weeks after you enrolled the subject in the study.

In your Response Letter, you agree with this observation. You state that the subject was "well known to me and we did, in fact, have this conversation related to his participation in this study." You acknowledge, however, that "An entry should have been made in the subject's chart clearly documenting this conversation."

B. Serious Adverse Events (SAEs) were not reported to the sponsor as required by the protocol. Hospitalization is considered an SAE according to protocol section 10.2.3.2.1 and is required to be reported to the sponsor within 24 hours of its occurrence.

i. Subject (b)(6) was hospitalized on (b)(6) (b)(6). These four hospitalizations were not reported to the sponsor.

In your Response Letter, you acknowledge that these hospitalizations should have been reported promptly to the study sponsor.

ii. The following hospitalizations for subject (b)(6) were not reported to the sponsor within 24 hours:

a. Subject (b)(6) was hospitalized on (b)(6), due to "angina /non cardiac". According to your study records, this hospitalization was not reported to the sponsor until September 27, 2007.

b. Subject (b)(6) was hospitalized on (b)(6), for "chest pain, non-cardiac". According to your study records, this hospitalization was not reported to the sponsor until October 8, 2007.

c. Subject (b)(6) was hospitalized on (b)(6), for "dizziness/chest discomfort/non cardiac origin". According to your study records, this hospitalization was not reported to the sponsor until October 17, 2007.

In your Response Letter, you acknowledge that these hospitalizations should have been reported promptly to the study sponsor.

C. Protocol section 8.2.4.3.5 requires that a 12-month chest x-ray be performed for each subject. There is no evidence to show that a 12 month chest x-ray was performed for five of the seven enrolled subjects (subjects (b)(6)).

In your Response Letter, you acknowledge this deviation from protocol.

3. You failed 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, including case report forms and supporting data. [21 CFR § 312.62(b)].

An investigator is required to prepare and maintain adequate and accurate case histories on each study subject. As defined by the regulation, case histories include CRFs and supporting data including, for example, subject medical records and signed and dated consent forms indicating that informed consent was obtained prior to participation in the study.

A. As noted above in item 1.A, the radiology reports for the 12-month chest x-rays of subjects (b)(6) and (b)(6) appear to have been fabricated.

In your Response Letter, you neither agree nor disagree with this observation. Instead, you note that good documentation practices have been reviewed with all members of your study team, that you now use a log to track the review of study-related documents, and that you intend to hire a Quality Assurance Specialist as a member of your study team.

B. The informed consent documentation for this study contains significant irregularities. The dates of informed consent are overwritten on many pages of the informed consent documents for subject (b)(6) obtained on July 19, 2006, September 7, 2007, and March 17, 2008. These informed consent documents also contain signatures and initials that are inconsistent in appearance and appear to have been altered. Additionally, the informed consent document for subject (b)(6) appears to have been altered from a date of November 1, 2007, to a date of October 19, 2007, in multiple locations in the consent form. We note that, according to a letter from the IRB, the study was in a non-approved status on November 1, 2007.

In your Response Letter, you neither agree nor disagree with this observation. Instead, you describe your current process for ensuring the completeness and accuracy of informed consent documentation.

C. As noted above in item 1.B, discrepancies were noted between subjects' medical records and the CRFs for the study. For example, the CRF for subject (b)(6) study visit on October 17, 2007, showed that this subject was prescribed four medications. The CRF for the next study visit, which occurred on December 10, 2007, shows no changes in concomitant medication. However, medical records from your private practice document that this subject's concomitant medication did in fact change during this period. First, on October 25, 2007, you saw this subject for follow-up and discharged the subject on eight medications. Subsequently, you saw the subject for follow-up on November 29, 2007 and discharged the subject on eight medications, five of which had been changed from the October 25, 2007 visit.

In your Response Letter, you neither agree nor disagree with this observation. Instead, you note that you have changed your documentation review practices such that all source documentation charts now contain a "Medications Log" that is used to readily identify concomitant medication use for the duration of a subject's participation in a study.

D. As described above in item 2.A.i, the inspection revealed that the medical history documentation was inadequate in that it was not sufficient to demonstrate that the seven subjects enrolled in the study were in fact eligible for enrollment.

In your Response Letter, you neither agree nor disagree with this observation. Instead, you note that you have since taken corrective action to ensure that adherence to a study protocol is accurately and appropriately documented.

4. You failed to assure that an IRB that complies with the requirements set forth in 21 CFR Part 56 was responsible for the continuing review and approval of the study. [21 CFR § 312.66].

Under 21 CFR § 312.66, an investigator is required to assure that an IRB is responsible for the initial and continuing review and approval of the clinical study. FDA's inspection revealed that you violated this regulation because you conducted study-related procedures when IRB approval had lapsed. For example, laboratory records show that study screening/visit 1 for subject (b)(6) occurred on November 1, 2007. A letter from the IRB indicates that the study was not in an approved status on that date.

In your Response Letter, you agree with this observation.

5. You failed to report promptly to the IRB all changes in the research activity and all unanticipated problems involving risk to human subjects or others. [21 CFR § 312.66].

21 CFR § 312.66 requires an investigator to promptly report to the IRB all changes in the research activity and all unanticipated problems involving risk to human subjects or others.

A. FDA's inspection revealed that you failed to report promptly to the IRB serious unanticipated problems involving sterility concerns with the study site's stem cell laboratory and the subsequent decision to transfer the remaining subjects to a new study site for mobilization, apheresis, and stem cell treatment. In your emails to the sponsor's medical monitor, you noted that you were "very concerned with this problem" and that "from a patient safety standpoint, I nonetheless feel contrite as this has never happened to me in the 20 years I have been doing research." However, you never reported these concerns, or the subsequent decision to change sites, to the IRB. Although the FDA investigator found a letter in the study files that purported to notify the IRB of the transfer of two subjects to a new site, the letter was dated three months after the sterility concerns were first raised. The letter did not mention that the decision to transfer

the subjects was made due to patient safety concerns involving the original lab. Furthermore, during the FDA inspection, the FDA investigator was informed that this letter was never received by the IRB.

In your Response Letter, you agree with this observation, noting that "these issues are reportable events and should have been communicated to the IRB in a timely fashion".

B. As described in items 2. A. iii. a. above, you failed to report to the IRB that you enrolled subjects (b)(6) and (b)(6) in the study even though they did not meet the protocol inclusion criterion for a coronary angiogram 12 months prior to enrollment. During the FDA inspection, you indicated that you did not seek approval from the IRB to waive these subjects into the study because you were concerned that this might exclude some subjects from participating in the study. Your failure to notify the IRB of this change in research activity deprived the IRB of the opportunity to evaluate whether it was appropriate to waive these subjects into the study.

In your Response Letter, you neither agree nor disagree with this observation. Instead, you explain why you decided to waive these two subjects into the study.

This letter is not intended to contain an all-inclusive list of deficiencies with your clinical study of investigational stem cells. It is your responsibility to ensure adherence to each requirement of the law and relevant regulations.

On the basis of the above listed violations, FDA asserts that you have repeatedly or deliberately failed to comply with the cited regulations. Accordingly, FDA proposes that you be disqualified as a clinical investigator. You may reply to the above stated issues, including any explanation of why you should remain eligible to receive investigational articles and not be disqualified as a clinical investigator, in a written response or at an informal conference in my office. This procedure is provided for by regulation 21 CFR § 312.70.

Within fifteen (15) working days of receipt of this letter, write me to arrange a conference time or to indicate your intent to respond in writing. Your written response must be forwarded within thirty (30) working days of receipt of this letter. If you do not respond within fifteen (15) working days, the right to file a response will be waived. Your reply should be sent to:

Mary A. Malarkey, Director
Office of Compliance and Biologics Quality
Center for Biologics Evaluation and Research
1401 Rockville Pike, Suite 200N
Rockville, Maryland 20852-1488

Should you request an informal conference, we ask that you provide us with a full and complete explanation of the violations listed above. You should bring with you all pertinent documents. A representative of your choosing may accompany you. Although the conference is informal, a transcript of the conference will be prepared. If you choose to proceed in this manner, we plan to hold such a conference within thirty (30) days of your request.

At any time during this administrative process, you may enter into a consent agreement with FDA regarding your future use of investigational articles. Such an agreement would terminate this disqualification proceeding. Enclosed you will find a proposed agreement between you and FDA.

The Center will carefully consider any oral or written response. If your explanation is accepted by the Center, the disqualification process will be terminated. If your written or oral responses to our allegations are unsatisfactory, or we cannot come to terms on a consent agreement, or you do not respond to this notice, you will be offered a regulatory hearing before FDA, pursuant to 21 CFR Part 16 and 21 CFR § 312.70 (available at the internet address identified on page 1 of this letter). Before such a hearing, FDA will provide you notice of the matters to be considered, including a comprehensive statement of the basis for the decision or action taken or proposed, and a general summary of the information that will be presented by FDA in support of the decision or action. A presiding officer who has not participated in this matter will conduct the hearing. The Commissioner will determine whether or not you will remain entitled to receive investigational articles. You should be aware that neither entry into a consent agreement nor pursuit of a hearing precludes the possibility of a corollary judicial proceeding or administrative remedy concerning these violations.

Sincerely yours,

Mary A. Malarkey, Director
Office of Compliance and Biologics Quality
Center for Biologics Evaluation and Research

Enclosures: (1)