DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
9200 Corporate Boulevard
Rockville MD 20850

OCT 21 2005

NOTICE OF INITIATION OF DISQUALIFICATION PROCEEDING AND OPPORTUNITY TO EXPLAIN (NIDPOE)

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Mark S. Wholey, M.D.
Pittsburgh Vascular Institute
UPMC Shadyside Hospital
580 S. Aiken Avenue
Pittsburgh, PA 15232

Dear Dr. Wholey:

Between February 17, 2004 and March 23, 2004, a Food and Drug Administration (FDA) investigator from the Philadelphia District Office conducted an inspection at the Pittsburgh Vascular Institute (PVI) to review your conduct of the clinical investigation entitled "[redacted]), for which you served as principal clinical investigator from August 2000 through February 2002. This study of the [redacted] and of the [redacted], both investigational devices, was sponsored by [redacted] under [redacted]. Between March 30, 2004 and April 1, 2004, the FDA investigator conducted a second inspection at PVI to review your conduct of the clinical investigation entitled "[redacted]", for which you served as principal clinical investigator from July 1998 through May 2002. This study of the [redacted], an investigational device, was also sponsored by [redacted] under [redacted]. These inspections were conducted as part of the FDA's Bioresearch Monitoring Program, which involves inspections designed to monitor the conduct of research involving investigational products, including assuring that the rights and welfare of human subjects have been protected.

At the conclusion of each of these inspections, you were presented with a Form FDA 483, "Inspectional Observations." You responded in writing to these observations by letters dated April 6, 2004, and April 12, 2004.

Based on our evaluation of information obtained by the Agency, including your responses to the investigational observations, we believe that you have repeatedly or deliberately violated regulations governing the proper conduct of clinical studies involving investigational products as published under Title 21, Code of Federal Regulations (CFR), Part 812 – Investigational Device Exemptions and Part 50 - Protection of Human Subjects (copies enclosed). This letter provides you with written notice of the matters under complaint and initiates an administrative proceeding, described below, to determine whether you should be disqualified from receiving investigational products as set forth under 21 CFR 812.119.

A listing of the violations follows. The applicable provisions of 21 CFR Parts 812 and 50 are cited for each violation.

1. You failed to adequately supervise the conduct of the study. [21 CFR 812.100, 812.110].

When you signed the Investigator's Agreements for the above-referenced clinical investigations, you agreed to take on the responsibilities of a clinical investigator at your site. Your general responsibilities include ensuring that an investigation is conducted according to the signed agreement, the investigational plan and applicable FDA regulations, for protecting the rights, safety and welfare of subjects under the investigator's care, and for the control of devices under investigation. [21 CFR 812.100] The Investigator's Agreements that you signed required that you or your sub-investigators personally supervise all testing of the device involving human

subjects. In addition, regulations provide that an investigator shall permit an investigational device to be used only with subjects under the investigator's supervision. An investigator shall not supply an investigational device to any person not authorized to receive it, in accordance with 21 CFR Part 812. [21 CFR 812.110(c)]. Although you may delegate study tasks to individuals qualified to perform them, you may not delegate your general responsibilities as a clinical investigator.

You failed to supervise the study so as to ensure that your general responsibilities were fulfilled. As detailed in charges 2-6 below, there were numerous violations such as ones involving informed consent, including the falsification of your signature on informed consent documents; protocol violations, including enrollment of patients not meeting eligibility criteria and problems with follow-up visits; and record keeping violations, including the failure to maintain device accountability records. Despite the widespread nature of these problems, in most cases, you made no effort at correction until action was requested by study monitors or your IRB.

In your responses to the two Form FDA 483s issued to you, you admitted generally that the noted deficiencies did occur, but in those responses as well as in your statements to the FDA investigator and in your correspondence with your IRB, you repeatedly attributed them to poor performance and lack of experience by research staff including your former study coordinator, and in some cases, to poor oversight by the study monitor. While your 483 responses also indicate that those staff have been replaced, that you yourself are no longer the principal investigator for these studies, and that new procedures have been implemented, these responses do not excuse your failure to adequately supervise the conduct of the studies during the period in which you were the principal investigator. We note that your IRB took an extensive role in initiating the corrective actions undertaken with respect to these studies. Your own statements indicate that you did not adequately supervise the conduct of the study. For example:

- You told the FDA investigator that you did not maintain daily oversight of the [redacted] study and delegated many of the study tasks to other people. Specifically, you stated that you delegated to [redacted], RN, one of the study coordinators, the responsibilities of device accountability, coordination of follow-up visits, decision to enroll subjects, Case Report Form (CRF) completion, and collection and reporting of adverse event information. As noted, several of these were areas in which widespread violations occurred, and as indicated below, you attribute these violations to the actions of [redacted] or other study staff.

- In your May 2, 2002 response to your IRB's internal study audit, which was conducted in April 2002, you explained that the issues noted regarding the conduct of the [redacted] study were due to such things as: "previous coordinator neglected to complete this requirement", "this was an oversight by the coordinator as well as the monitor," "this was apparently an oversight by the previous coordinator and monitor."

- In your April 6, 2004 letter to Thomas Gardine, FDA Philadelphia District Director, regarding the FDA 483 observations about the [redacted] study, you stated, "The majority of issues listed in the observations were due to study coordinator inexperience and failure to follow-up on protocol-required procedures, incomplete medical records, patient scheduling or a combination of these events...many of the problems in this case resulted from an overworked staff with insufficient research experience to recognize and correct deficiencies."

- Similarly, in your April 12, 2004 letter to Thomas Gardine, FDA Philadelphia District Director, regarding the FDA 483 observations about the [redacted] study, you stated, "The issues listed in the observations were due to study coordinator inexperience and occurred during his tenure between 2000 and 2002...many of the problems in this case resulted from an overworked staff with insufficient research experience to recognize and correct deficiencies."

- In a January 9, 2004 memo to the file, you admitted that someone other than you had signed your name on five informed consent forms in the [redacted] study. You attributed these false signatures to a former study coordinator. Although in that memo you stated that it was "apparent" that these signatures were not your own, you admitted that you were unaware of this falsification until that date, when the study monitor pointed it out to you. This falsification demonstrates your lack of oversight, because if you had looked at those forms at any point after they were signed, you would have noted the falsifications of your signature.

2. You failed to adhere to informed consent requirements. [21 CFR 812.100, 21 CFR 50.20, 50.25(a) and 50.27(a)].

An investigator is responsible for ensuring that an investigation is conducted in accordance with applicable FDA regulations, for protecting the rights, safety, and welfare of subjects under his care, and for ensuring that informed consent is obtained from those subjects in accordance with 21 CFR Part 50. [21 CFR 812.100]. The following examples of specific violations of part 50 demonstrate your failure to fulfill this requirement.

a. No investigator may involve a human being as a subject in FDA-regulated research unless the investigator has obtained the legally effective informed consent of the subject or his authorized representative. [21 CFR 50.20]. However, [redacted] Subjects [redacted] and [redacted] were randomized to study treatment prior to signing an Informed Consent document.

b. Informed consent must be documented by the use of a written consent form approved by the IRB and signed and dated by the subject or the subject's legally authorized representative at the time of consent, as set forth in 21 CFR 50.27(a). You violated this requirement. For example:

- In the [redacted] study, Subject [redacted] received a study device in 2002 without signing the applicable study informed consent form. Although this subject had signed an informed consent document for participation in the study in 1998, prior to receiving a first investigational [redacted], the study protocol and informed consent forms had been amended in the interim, and the second study procedure involved the use of an additional investigational device, the [redacted] device, not mentioned in the 1998 consent form. Therefore, for the 2002 use of the investigational device, the 1998 consent document does not constitute documentation of informed consent using a written form approved by the IRB.

- In the [redacted] Study, several informed consent documents were missing the dates that the subjects signed the forms. [redacted] Subjects [redacted], and [redacted] signed versions of the informed consent documents that were not the currently-approved form at the time of their signature and that lacked risk information contained in the proper, approved version in force at the time.

- There was no documentation that informed consent was obtained from [redacted] subjects [redacted] and [redacted] and [redacted] subjects [redacted], and [redacted]

c. An investigator is responsible for providing each subject with an explanation of the investigation that includes a description of the procedures to be followed. [21 CFR 50.25(a)(1)]. You treated eight [redacted] subjects with [redacted] although the informed consent forms that they signed did not disclose that this would be a procedure under the protocol. (The informed consent form omitted this information because you failed to seek IRB approval for the protocol amendment and revised informed consent form that addressed this possibility, and thus failed to ensure that the requirements of part 56 were met for this study.) Your April 4, 2004, response to the inspectional observations admitted that incorrect copies of the informed consent were used to consent these patients.

d. An investigator is also responsible for providing each subject with an explanation of whom to contact for answers to pertinent questions about the research and the research subjects' rights, and whom to contact in the event of a research-related injury. [21 CFR 50.25(a)(7)]. In the [redacted] study, Subjects [redacted] and [redacted] signed informed consent documents, which were missing the names and phone numbers of whom to contact for answers to pertinent questions about the research and research subjects' rights, and whom to contact in the event of a research-related injury.

3. You failed to conduct the investigation in accordance with the signed agreement with the sponsor and the investigational plan. [21 CFR 812.110(b), 812.100].

An investigator shall conduct an investigation in accordance with the signed agreement with the sponsor and the investigational plan. (21 CFR 812.110(b), 812.100). You signed Investigator Agreements for both the [redacted] and [redacted] studies, which stated that you would conduct the Clinical Study in accordance with the

Protocol. In addition, FDA regulations require that clinical investigators obtain prior approval from the sponsor before implementing any deviations from the investigational plan, except for deviations to protect the life or physical well-being of a subject in an emergency. (21 CFR 812.150(a)(4)). If these changes or deviations affect the scientific soundness of the plan or the rights, safety, or welfare of the subjects, FDA and IRB approval are also required. (21 CFR 812.150(a)(4), 812.35(a)).

You failed to follow the investigator agreement that you signed for the [redacted] study, which stated "I will not transfer any device to anyone other than the [redacted] Clinical Research Department," when you "loaned" three study devices to another study site. There is no documentation that this deviation from the agreement was approved by the study sponsor. In your April 4, 2004 letter, you admit that you sent two [redacted] to site 239 in Greenville, S.C.

There are also numerous examples of your failure to follow the investigational plan for the [redacted] study. You do not have evidence of prior sponsor approval for these deviations. Many of the examples listed below also affect the scientific soundness of the plan or the rights, safety and welfare of the subjects, but you have no record of FDA or IRB approval. You also did not document that any of these deviations were needed to protect the life or physical well-being of a subject in an emergency. You failed to report these deviations to the IRB within five working days, as required by 21 CFR 812.150(a)(4), and reported them only after they were discovered by study monitors who instructed you to report them.

For example, in the [redacted] Study:

- According to the protocol, you were required to notify the IRB of any changes in research activity. By letter of March 2, 2001, [redacted], the study sponsor, suspended enrollment at your study site, but you did not notify the IRB. This suspension continued until March 16, 2001.

- Surgeons who were not listed in the protocol as investigators and who had not signed any investigator agreements were allowed to perform surgical procedures or participate in the insertion of the study devices on study Subjects.

- Two [redacted] began performing protocol-mandated evaluations for the [redacted] study at its inception in August 2000, but you did not notify the IRB and seek its approval of a protocol amendment naming them as sub-investigators until January 2001. The protocol in effect at that time required that these tests be performed by "a [redacted] listed on the Statement of Investigator form".

- According to the protocol, subjects who satisfy inclusion and exclusion criteria but are deemed to be too high risk for surgery should be entered into the [redacted] Registry and not randomized. Subjects [redacted] and [redacted] had documentation that a non-study surgeon had advised that these individuals were too high risk for surgical treatment, yet they were randomized in the study.

- Subjects [redacted] and [redacted] were enrolled despite failure to meet eligibility criteria as required by the study protocol.

- Subjects [redacted] and [redacted] were enrolled prior to performance of all study-required eligibility procedures.

- You treated eight [redacted] subjects with [redacted], although the version of the protocol, which your IRB had approved, did not provide for this. After this treatment occurred, in July 2001, you provided the IRB with an informational copy of [redacted] Study Protocol Amendment #1, dated 8/16/00, which did include this treatment, but neither sought nor received IRB approval, as this protocol amendment had been superseded by that time and the sponsor had discontinued use of [redacted] under the protocol.

- Of the [redacted] subject records reviewed during the inspection, although required by the protocol:

- Subjects [redacted] and [redacted] did not have the [redacted] to confirm eligibility;
- Subjects [redacted], and [redacted] did not have the baseline [redacted] exam or [redacted] performed;
- Subjects [redacted], and [redacted] did not have baseline [redacted] levels performed;
- Subjects [redacted] and [redacted] did not have the 8 to 12-hour post-procedure [redacted] levels performed;
- Subjects [redacted] and [redacted] did not have the 18 to 24-hour post-procedure [redacted] levels performed;
- Subjects [redacted], and [redacted] did not have post-procedure [redacted] performed;
- Subjects [redacted] and [redacted] did not have post-procedure [redacted] exams or [redacted] performed;
- Subjects [redacted] and [redacted] did not have post-procedure [redacted] performed;
- Subjects [redacted] and [redacted] did not have the 30-day post-procedure [redacted] performed;
- Subjects [redacted] and [redacted] did not have the 30-day post-procedure [redacted] exams or [redacted] performed.

In your April 4, 2004, letter of response to FDA's inspectional observations, you admitted that these procedures were not done.

- Protocol-required tests and procedures were not performed within the specified time-frames. For example:
  - The protocol required a screening [redacted] within 30 days prior to the study procedure. Subject [redacted] screening [redacted] was done on 8/22/00 and the study procedure was done on 11/7/00; Subject [redacted] screening [redacted] was done on 9/12/00, and the study procedure was done on 10/21/00; Subject [redacted] screening [redacted] was done 11/16/00 and the study procedure was done on 1/29/01.
  - Subject [redacted] 1-year follow-up visit, which should have been performed 11-13 months after the study procedure on 12/7/00, was not performed until 2/28/02.
  - Subject [redacted] post-procedure [redacted] should have been performed within 48 hours of the study procedure on 1/29/01, but was not performed until 2/7/01. The 1-year follow-up visit, which should have been performed 11-13 months after the study procedure on 1/29/01, was not performed until 4/11/02.
  - Subject [redacted] 30-day follow-up visit, which included [redacted] exam and [redacted], should have been performed 30-44 days following the study procedure on 10/17/00, but was not performed until 1/9/01.

Of note, your April 4, 2004, letter of response to FDA's inspectional observations indicated that patient scheduling may have contributed to failure to meet specified time frames.

- The protocol required follow-up visits at 6 months, 1 year, 2 years, and 3 years following the study procedure, to include a [redacted] exam, [redacted], collection of adverse events, and quality-of-life assessments. The protocol did not allow for follow-up visits to be conducted by telephone, and telephone visits could not accomplish the [redacted] and [redacted] exams required by the protocol. However, there were numerous instances of missed study visits or visits conducted over the telephone. For example:
  - Subject [redacted] had no 6-month, 1-year, or 2-year follow-up visits documented.
  - Subject [redacted] had the 6-month and the 2-year follow-up visits conducted by telephone, so no follow-up testing was done.
  - Subjects [redacted] and [redacted] had their 6-month visits conducted by telephone, so no testing was done.
  - Subject [redacted] had 6-month, 1-year, and 2-year follow-up visits conducted by telephone, so no testing was done.
  - Subject [redacted] had the 6-month and 1-year visits conducted by telephone, so no testing was done.

4. You failed to maintain accurate, complete and current records. [21 CFR 812.140(a)].

a. An investigator is required to maintain accurate, complete, and current records of receipt, use and disposition of the device (21 CFR 812.140(a)(2)). These records must include the type and quantity of the device, the date of its receipt, and the batch number or code mark. (21 CFR 812.140(a)(2)(i)). They must also include the names of all persons who received each device. (21 CFR 812.140(a)(2)(ii)). They must also document why and how many units of the device have been returned to the sponsor, repaired, or otherwise disposed of. (21 CFR 812.140(a)(2)(iii)). You had numerous examples of failures to meet these requirements:

- The original device accountability records for both the [redacted] study and [redacted] study were lost and had to be re-created by the study monitors. You acknowledged in your April 4, 2004, letter that the original device accountability log is missing.

- Lot numbers of both the [redacted] study devices and [redacted] study devices were not recorded in the device accountability logs.

- There was no documentation of the lot numbers of the study devices inserted into [redacted] Subjects [redacted], and [redacted]

- Three [redacted] study devices [redacted] were "borrowed" by another study site with no documentation of the disposition of the devices or of approval by the study sponsor. In your April 4, 2004 response to the 483, you stated that the "borrowed" [redacted] were sent to site 239 in Greenville, S.C., and were noted as received by that site, but you do not provide documentation to support this and do not address the lack of documented approval by the study sponsor.

b. An investigator is required to maintain accurate, complete, and current records of each subject's case history and exposure to the investigational device. (21 CFR 812.140(a)(3)). Such records must include documents indicating for each individual subject that informed consent was obtained prior to participation in the study. (812.140(a)(3)(i)). These records must also include all relevant observations, information and data on the condition of each subject upon entering, and during the course of, the investigation, including information about relevant previous medical history and the results of all diagnostic tests. [812.140(a)(3)(ii)]. In addition, you must maintain records of the exposure of each subject to the investigational device, including the date and time of each use, and any other therapy. [812.140(a)(3)(iii)]. You failed to fulfill these requirements. For example:

- The informed consent documents for [redacted] subjects [redacted] and [redacted] were not accurate because they were signed with your name but the signatures were not in your handwriting. When this falsification was pointed out to you by the study monitor in January 2004, several years after the documents were signed, you admitted in a memo to the file that the signatures were not yours.

- There was no documentation that informed consent was obtained from [redacted] Subjects [redacted] and [redacted] or [redacted] Subjects [redacted] and [redacted]

- There was no documentation that [redacted] Subjects [redacted], and [redacted] met enrollment eligibility criteria.

- There was no documentation of the lot numbers of the study devices inserted into [redacted] Subjects [redacted] and [redacted]

Your April 4, 2004, response to the FDA inspectional observations admitted generally that case history records were incomplete, which you attributed to the actions of research staff and to the fact that dedicated research charts or shadow charts were not used consistently.

This letter is not intended to be an all-inclusive list of deficiencies with your clinical studies of investigational medical devices. 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 and it proposes that you be disqualified as a clinical investigator. You may reply to the above stated issues, including an explanation of why you should remain eligible to receive investigational products 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 812.119.

Within fifteen (15) days of receipt of this letter, write or call Michael E. Marcarelli, Pharm.D., Director, Division of Bioresearch Monitoring, Office of Compliance, Center for Devices and Radiological Health at (240) 276-0125 to arrange a conference time or to indicate your intent to respond in writing. Your written response must be forwarded within thirty (30) days of receipt of this letter. Your reply should be sent to:

Food and Drug Administration
Center for Devices and Radiological Health, Office of Compliance
Division of Bioresearch Monitoring, Program Enforcement Branch (HFZ-310)
9200 Corporate Boulevard, Rockville, Maryland 20850
Attention: Michael E. Marcarelli, Pharm.D.

Should you request an informal conference, we ask that you provide us with a full and complete explanation of the above listed violations. You should bring with you all pertinent documents, and you may be accompanied by a representative of your choosing. 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 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 products. 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 (enclosed) and 21 CFR 812.119. Before such a hearing, FDA will provide you with 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 free from bias or prejudice and who has not participated in this matter will conduct the hearing. Such a hearing will determine whether or not you will remain entitled to receive investigational products. 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,

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

Enclosures