DEPARTMENT OF HEALTH & HUMAN SERVICES

Office of the Secretary
Office of Public Health and Science

Office for Human Research Protections
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December 22

Martin L. Doordan
President
Anne Arundel Medical Center
2001 Medical Parkway
Annapolis, MD 21401

RE: Human Research Subject Protections Under Federalwide Assurance (FWA) 3219
Research Project: Breast Cancer Research at the DeCesaris Cancer Institute, including "*PemFlex: Prospective Clinical Trial to Establish the Positive Predictive Value of PEM Flex PET Scanner in Detecting Additional Cancer Foci Among Women with at Least One Focus of Confirmed Primary Breast Cancer" (closed to accrual* November 21, 2005)
Principal Investigator: Dr. Lorraine Tafra

Dear Mr. Doordan:

The Office for Human Research Protections (OHRP) has reviewed the January 17, 2006 report of Anne Arundel Medical Center (AAMC) evaluating allegations of noncompliance with the Department of Human Services (HHS) regulations protecting human research subjects, 45 CFR part 46, pertaining to the above research.

Based upon its review, OHRP makes the following determinations with respect to allegations raised about the above research:

(1) HHS regulations at 45 CFR 46.116 require that investigators seek consent only under circumstances that provide prospective subjects sufficient opportunity to consider whether or not to participate and that minimize the possibility of coercion or undue influence. It was alleged that prospective subjects enrolling in breast cancer clinical trials at AAMC are not given sufficient time to consider enrollment after they receive a diagnosis of cancer. It was further alleged that a decisionally impaired subject's daughter, with authorized power of attorney, signed the informed consent document immediately prior to the subject's surgery.

OHRP finds that no evidence was presented to substantiate the allegation that prospective subjects in breast cancer clinical trials are not provided sufficient time to consider enrollment after they receive a diagnosis of breast cancer. OHRP notes AAMC's statement that an unannounced September 7, 2005 Joint Commission on Accreditation of Healthcare

Organizations (JCAHO) survey found that subjects at AAMC are afforded adequate time to decide whether to enroll in clinical trials.

OHRP further notes the following information from AAMC's January 17, 2006 letter. At the DeCasaris Cancer Institute, subjects are given consent forms and provided with information about clinical trials at an initial meeting with investigators. Investigators do not obtain consent at this time. The majority of subjects take consents home for further discussion with their families and will then call back with a decision regarding participation. However, it is not unusual to have subjects sign consent forms immediately prior to surgical intervention in a clinical trial. Frequently, subjects forget to bring signed research consent forms with them on the scheduled day of surgery at AAMC, or have no fax available to send the signed consent forms to AAMC prior to scheduled surgery.

(2) HHS regulations at 45 CFR 46.116(a) delineate basic elements required for informed consent, including, at section 45 CFR 46.116(a)(3), a description of any benefits to subjects or others that may reasonably be expected from the research. It was alleged that AAMC clinical trial investigators occasionally misstated the potential benefits of research participation as described in protocols. OHRP finds that no evidence was presented to substantiate these allegations.

(3) Under HHS regulations at 45 CFR 46.111(a)(1)(i), institutional review boards (IRBs), in order to approve research, must determine that risks to subjects are minimized by using procedures which are consistent with sound research design and which do not unnecessarily expose subjects to risk. It was alleged that AAMC failed to minimize research risks to subjects in a trial in which enrolled subjects were injected with radioisotope F-18 FDG at a PET/CT site, and then sent to another site across campus to have PET mammography.

OHRP finds that no evidence was presented to substantiate these allegations. OHRP notes that AAMC's investigation of these allegations revealed a protocol entitled "Prospective Clinical Trial to Establish the Positive Predictive Value of PemFlex PET Scanner in Detecting Additional Cancer Foci Among Women with at Least One Focus of Confirmed Primary Breast Cancer (hereinafter, PemFlex)." In the PemFlex protocol, subjects received F-18 FDG injections in one location and were then sent to a separate location for PET mammography. At the PET mammography site, specialized PET breast images were created with a PET camera attached to a stereotactic biopsy table. There was no storage or direct use of F-18 at the PET mammography site. The quality control sources associated with the camera (Na-22 and Ge-68) were all in the microcurie range. The QC sources were stored in a case when not in use and radiation levels associated with these cases were equal to background. Patients were offered shuttle service from one site to the other. According to AAMC's Radiation Safety Officer, board certified in internal medicine and nuclear medicine, subjects were not in danger from having to move or be moved after receiving the injection.

(4) Under HHS regulations at 45 CFR 46.111(a)(7), IRBs, in order to approve research, must determine that there are adequate protections to protect the privacy of subjects and to maintain the confidentiality of data. The following allegations were raised with respect to the protection of subject privacy and the confidentiality of research data at AAMC.

(a) It was alleged that AAMC clinical trial records containing private identifiable information were lost or missing.

OHRP finds that no evidence was presented to substantiate this allegation. OHRP notes AAMC's statement that during the September 7, 2005 JCAHO survey at AAMC, the surveyor found no research records missing in 25 randomly selected research charts chosen from a list of the last 100 subjects enrolled in Breast Center protocols at AAMC.

(b) It was alleged that there is no plan for protecting the confidentiality of information obtained in the course of clinical trials at AAMC.

OHRP finds that no evidence was presented to substantiate this allegation. OHRP notes that AAMC provided the following relevant information to OHRP. AAMC policy requires patient record keeping departments to provide for physical security of patient records by controlling circulation, securing storage areas, locking file cabinets and a key control program. The AAMC Clinical Trials Department staff maintain research protocols and subjects' medical records in a cipher locked room at the DeCasaris Cancer Institute not accessible to other staff. The electronic database is limited to the clinical research staff and is password protected. All AAMC employees receive an annual inservice training on policies and procedures relating to relating to confidentiality and are required to sign a Confidentiality Pledge ensuring that health information is obtained and communicated only on a "Need to Know" basis, and that computer passwords will not be disclosed. AAMC IRB Policies and Procedures require investigators to consider applying for Certificates of Confidentiality when the results of research participation would yield information that could lead to social stigmatization or discrimination, or information potentially damaging to subjects' financial standing, employability or reputation.

(c) It was alleged that clinical trial data was evaluated for clinical care purposes, contrary to protocol specifications.

AAMC investigated this allegation and determined that, with respect to a subject enrolled in the above-described ***PemFlex*** protocol, a radiologist reported the findings from a research scan and recommended additional imaging. Blinding procedures in the ***Pemflex*** protocol require that "[t]he radiologist performing the PEM scan will record estimates of the index lesion's size prior to the pathological determinations, and will therefore be unprejudiced by the pathology results." According to AAMC , the radiologist did not violate these blinding procedures. OHRP notes that the informed consent document for the ***Pemflex*** study states:

> The PEM Flex results could affect your medical care by bringing x-ray abnormalities to the attention of your doctor, which might not otherwise have been considered important. Any decisions that would affect your medical care will be made on the basis of what your doctors see on x-ray mammograms and on results from your biopsies.

Based upon the above facts, OHRP finds no evidence that AAMC violated subject privacy or the confidentiality of subject data. OHRP notes that following the above incident, AAMC (i) developed case report forms which use an electronic database that prevents unblinding, and (ii) implemented an intensive educational program for researchers and IRB staff on the regulations protecting human research subjects, including an institutionally-approved web-based course and specific training for radiologists involved in clinical trials.

OHRP has the following question about the above research:

(5) [Redacted]

Please respond to OHRP's question in (5) above by January 26, 2007.

OHRP appreciates AAMC's commitment to the protection of human research subjects. Feel free to contact me if you have any questions.

Sincerely,

Carol J. Weil, J.D.
Compliance Oversight Coordinator
Office for Human Research Protections

cc: Dr. Bernard Schwetz, OHRP
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