DEPARTMENT OF HEALTH & HUMAN SERVICES

Office of the Secretary
Office of Public Health and Science

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August 21, 2008

James Mulshine, M.D.
Associate Vice Provost for Research
Rush University Medical Center
1735 W. Harrison, Suite 206
Chicago, IL 60612

Robert R. Simon, M.D.
Chief
Cook County Bureau of Health Services
1900 W. Polk Street, Suite 200
Chicago, IL 60612

RE: Human Research Protections Under Federalwide Assurance FWA-482 and FWA-1802

Research Project: A Phase II Trial of Doxorubicin & Docetaxel in the Neoadjuvant Treatment of Locally Advanced Breast Cancer with Correlation of Clinical, Molecular and Biological Prognostic Factors
Principal Investigators: Elizabeth Marcus, M.D. and Shalina Gupta-Burt, M.D.

Dear Drs. Mulshine and Simon:

The Office for Human Research Protections (OHRP) has received your respective reports of November 29, 2007 and December 5, 2007 regarding allegations of noncompliance with Department of Health and Human Services (HHS) regulations for the protection of human research subjects (45 CFR Part 46) involving the above-referenced research. We note that all subjects in the research study were recruited by, and enrolled at, Cook County Hospital (Cook County) where the majority of research related interventions took place and that Rush University Medical Center (Rush) in its report grants deference to Cook County in responding to all allegations.

The allegations involve the following:

(1) Failure of the institutional review board (IRB) to determine that criteria for IRB

approval are satisfied, as required by HHS regulations at 45 CFR 46.111(a). Specifically, the complainant alleged that:

(a) Risks to subjects were not minimized because all subjects were required to undergo Modified Radical Mastectomy (MRM).

(b) Selection of subjects was not equitable because the research targeted impoverished black women.

(2) Enrollment procedures did not minimize the possibility of coercion or undue influence, as required by HHS regulations at 45 CFR 46.116. Specifically, the complainant alleged that impoverished women were offered undue influence of money to enroll in the research.

(3) Failure of IRB to review and approve protocol changes, in contravention of HHS regulations at 45 CFR 46.103(b)(4)(iii). Specifically, the complainant alleged that the researchers added an investigator and payment to subjects without prior IRB review and approval.

A. Determinations regarding the above-referenced research

(1) We find no evidence supporting the allegation of IRB failure to minimize risks to subjects by requiring all subjects to undergo MRM, in violation of HHS regulations at 45 CFR 46.111(a)(1). While Cook County IRB minutes documenting approval of the research were not provided to us (the study was voluntarily suspended in 1999 and, according to Cook County, IRB minutes are no longer available), we note Cook County's statement that MRM was the standard of care for locally advanced breast cancer (LABC) at Cook County Hospital and Rush Medical Center at the time the protocol was conducted, and was the standard of care for the surgeons involved in the research. We also note the contradicting medical opinion of Cook County's Department of Surgery Chair in his November 18, 1999 memorandum stating that breast conservation therapy is a recognized surgical option for patients who have substantial tumor response to neoadjuvant treatment of locally advanced breast cancer, and advising that the above study not be allowed to proceed. OHRP makes no determination regarding the safety or risks of surgical alternatives to MRM for treatment of LABC at the time the study was approved.

Regardless of whether there were acceptable treatment alternatives to MRM for LABC at the time this research study was approved, subjects apparently were not required to undergo MRM in order to participate in the study. We note the following statement in the research protocol document:

> **2.2.2 Choice of Surgical Procedure:** Patients with a complete response [to induction chemotherapy], partial response and stable disease will receive modified radical mastectomy. Neoadjuvant chemotherapy results in 80-90% overall response for LABC [locally advanced breast cancer]. Some of the patients achieve a complete response, therefore raising the question of whether or not breast conservation is a feasible option. These studies that have utilized breast conservation in this setting have had very short follow up. They were nonrandomized and didn't always correlate clinical CR [complete response] with pathological CR. More importantly, there is little long term data to support the premise that locally advanced breast cancer behaves biologically like early cancers where local control does not impact on survival. There has been no randomized study to date to show that conservative surgery in LABC is equal to mastectomy in terms of local control. While there may [be] a group of patients in whom breast conservation is a viable option offering equivalent local control and survival, currently such a group cannot be identified.

Despite this protocol language, Cook County states that two study subjects elected surgical options other than MRM but still received the neo-adjuvant therapy as part of the protocol. Furthermore, no documentation has been presented of subjects who responded well to neoadjuvant therapy but were denied surgical options other than MRM. In short, the evidence before us does not indicate that all subjects in this study were forced to undergo MRM in order to participate in the research.

(2) Based on the documentation provided in Cook County's December 5, 2007 correspondence, we determine to be unproven the allegation of IRB failure to ensure equitable selection of subjects for the above research, in violation of HHS regulations at 45 CFR 46.111(a)(3). Specifically, no evidence was presented to us indicating that the above research targeted impoverished black women. According to Cook County's report, there were 2 White women, 5 Hispanic women, and 18 African-American women enrolled in the research, which reflected "rather precisely" the racial and ethnic characteristics of the population served by Cook County Hospital. In addition, according to Cook County's report, African-American women are more often diagnosed with later stage breast cancer (locally advanced disease) as compared with White women. Since LABC, the study diagnosis, is overrepresented in African-American women, it is not surprising that the study population here is primarily African-American women.

(3) Based on the documentation provided in Cook County's December 5, 2007 correspondence, we determine to be unproven the allegation that enrollment procedures for the above research study did not minimize the possibility of coercion or undue influence, as required by HHS regulations at 45 CFR 46.116. Specifically, no evidence has been presented that impoverished women were

induced to enroll in the research by offers of excessive financial remuneration. Subjects were offered a $20 grocery store coupon for each study visit for neoadjuvant therapy and data collection. This compensation plan was, according to Cook County, consistent with an informal IRB policy permitting compensation of subjects for the cost of volunteering at a rate of $20-$25 per visit. The IRB policy was formalized in writing in March of 2001. The "per visit" compensation policy was superseded in June of 2007 by a new IRB policy which changed the basis for paying subject expenses from a "per visit" amount to $10-$12 per hour, in addition to reimbursement for travel, parking and childcare.

We note that the compensation provided to subjects in this research study was not in any way linked to subjects' choices regarding MRM versus other surgical options. The principal investigator stated that she chose not to communicate the food coupon compensation policy in the informed consent form in order to avoid the possibility that the compensation for time and expenses might coerce patients to enroll. We note that compensation for time and expenses is not a benefit which must be described to subjects under 45 CFR 46.116(a)(3).

(4) We determine that because the Cook County IRB was not specifically informed of the investigators' intention to compensate subjects in the above research study with a $20 grocery store coupon at each hospital visit, the IRB was unable to make required determinations under 45 CFR 46.111. Specifically, the IRB's lack of knowledge about the intended compensation plan prior to review and approval of the research study prevented the IRB from determining whether subject consent was to be obtained under circumstances that minimize the possibility of coercion or undue influence in accordance with 45 CFR 46.116. Moreover, the IRB's lack of knowledge about the intended compensation plan prevented the IRB from determining whether the compensation plan would result in an inequitable selection of economically disadvantaged subjects, in violation of 45 CFR 46.111(a)(3).

Corrective Action: Under the Cook County IRB's current Policies and Procedures, researchers must disclose to the IRB the exact amount and circumstances of any payments to subjects. Although this corrective action substantially addresses our determination, we note that a separate IRB Human Participant Research Policy dated June, 2007 titled "Payments to research subjects" states that investigators are "encouraged to discuss payments to research subjects with the Board" and could be misleading to investigators. We recommend that the June, 2007 Policy either be deleted or revised to reflect the requirement of disclosure to the IRB of payments to subjects set forth in Cook County's Policies and Procedures.

(5) We determine that the hiring of a physician assistant as a study coordinator for the

above project does not constitute a protocol change for which the IRB needed to provide prior review and approval under 45 CFR 46.103(b)(4)(iii). Cook County's internal investigation revealed that a physician assistant hired through Cook County's fiscal intermediary, the Hektoen Institute for Medical Research, was added to study staff after the IRB had approved the study. The physician assistant was not credentialed by the medical staff at Cook County hospital but her training and licensure were verified by the Hektoen Institute prior to employment. The physician assistant was not a co-investigator in the research study. We note that current Cook County Guidelines for Investigators and Sponsored Projects, (revised 1/07, page 34) states that all changes in key personnel (e.g., co-investigators) are to be reported to the IRB.

B. Determinations regarding your institution's system for protecting human subjects

In addition to the matter complained about, we make the following determinations:

(1) We have reviewed the Guide to Conducting Human Subjects Research at Rush University Medical Center, provided in response to our request for a copy of any written description of IRB policies and procedures, and we have determined that the Guide does not contain the following required written procedures:

(a) Procedures which the IRB will follow for determining which projects require review more often than annually and which projects need verification from sources other than the investigators that no material changes have occurred since previous IRB review, as required by HHS regulations at 45 CFR 46.103(b)(4); and

(b) Procedures for ensuring prompt reporting to the IRB, appropriate institutional officials, and any Department or Agency head [Federal Sponsor] of (a) any unanticipated problems involving risks to subjects or others; (b) any serious or continuing noncompliance with 45 CFR Part 46 or the requirements or determinations of the IRB; and (c) any suspension or termination of IRB approval, as required by HHS regulations at 45 CFR 46.103(b)(5).

Required Action: Please provide a corrective action plan to address this determination by adopting appropriate written procedures.

C. Questions and concerns regarding the above-referenced research

(1) [Redacted]

[Redacted]

(2) [Redacted]

Please provide us with responses to the above determinations and concerns by October 3,

2008. Feel free to contact me if you would like guidance in developing any additional corrective action you deem appropriate.

We appreciate your institution's continued commitment to the protection of human research subjects.

Please do not hesitate to contact me should you have any questions.

Sincerely,

Carol J. Weil
Division of Compliance Oversight

cc:

Ms. Mary Jane Welch, Director, Human Subjects Protection, Rush University Medical Center
Dr. Allen C. Korenblit, IRB Chair, Rush University Medical Center, IRB #1
Dr. Howard M. Kravitz, IRB Chair, Rush University Medical Center, IRB #1
Dr. Shalina Gupta-Burt, Rush University Medical Center
Ms. Lynda Brodsky, Director, Research Affairs, Cook County Bureau of Health Services
Dr. Audrey French, IRB Chair, Cook County Bureau of Health Services/Stoger Hospital
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Commissioner, FDA
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