DEPARTMENT OF HEALTH & HUMAN SERVICES

Office of the Secretary
Office of Public Health and Science

Office for Human Research Protections
The Tower Building
1101 Wootton Parkway, Suite 200
Rockville, Maryland 20852
Telephone: 240 453-8297
FAX: 240 453-6909

September 25, 2006

Patrice M. DiMario, M.S., R.N.
Sr. Vice President, Patient Support Services
Women & Infants Hospital of Rhode Island
101 Dudley Street
Providence, R.I. 02905

RE: Human Research Subject Protections Under Federalwide Assurance FWA-56

Research Project: A Phase III Randomized Trial of Paclitaxel and Carboplatin vs. Triplet or Sequential Doublet Combinations in Patients with Epithelial Ovarian or Primary Peritoneal Carcinoma
Principal Investigator: Paul A. DiSilvestro, M.D.
Project Number: GOG Protocol 182

Dear Ms. DiMario:

The Office of Human Research Protections (OHRP) has received Women & Infants Hospital of Rhode Island's (WIH) September 7, 2005 report of WIH's investigation of allegations of noncompliance with U.S. Department of Health and Human Services (HHS) regulations protecting human research subjects at 45 CFR part 46.

Based on its review of your report, OHRP makes the following findings with respect to the above research project at WIH:

(1) In its July 11, 2005 letter to WIH, OHRP presented allegations raised by a complainant that (a) chemotherapy drugs were mixed by a secretary and (b) the complainant, an enrolled subject, received incorrect medication. OHRP finds the allegation that chemotherapy drugs were mixed by a secretary to be not substantiated by the evidence presented by WIH. However, OHRP notes WIH's finding that a randomization error occurred with respect to the complainant when an inaccurate chemotherapy order was sent to the hospital pharmacy for arm 5 instead of arm 2 drugs. OHRP also notes that WIH enacted a corrective action plan requiring (a) written confirmation of randomization signed by the research coordinator, pharmacist and physician signing the chemotherapy orders for each subject, and (b) reconciliation of the written randomization form and chemotherapy order sheet.

(2) HHS regulations at 45 CFR 46.103(a) and 46.103(b)(5) require that institutions have written institutional review board (IRB) procedures for ensuring prompt reporting to the IRB, appropriate institutional officials, and OHRP 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. OHRP finds that the randomization error noted in finding (1) represented an unanticipated problem involving risk to the subject and the investigators involved in GOG protocol 182 at WIH failed to report this unanticipated problem to the WIH IRB.

Required Action: Please provide OHRP with a corrective action plan to address the finding in (2) above.

(3) HHS regulations at 45 CFR 46.111(a)(7) require that in order to approve research, the IRB must determine that, when appropriate, there are adequate provisions to protect the privacy of human subjects and the confidentiality of data. The complainant alleged that the principal investigator failed to protect the confidentiality of her data by discussing her medical care with her personal physician. OHRP finds that although the principal investigator had one or more conversations concerning the subject with the subject's personal physician, the weight of evidence does not indicate that the principal investigator either sought or provided information about the subject's medical condition or treatment.

(4) HHS regulations at 45 CFR 46.103(b) and 46.109(a) require prior review and approval by an IRB before research involving human subjects is conducted. OHRP finds the allegation that research involving the GOG protocol 182 was conducted on July 13, 2004 after the protocol was terminated on June 30, 2004 to be not substantiated by the evidence. According to the WIH IRB file, GOG protocol 182 remained open on June 30, 2004 and was closed to subject enrollment on September 1, 2004.

(5) HHS regulations at 45 CFR 46.116(a)(8) require that human subjects be permitted to discontinue participation in research at any time without penalty or loss of benefits to which they are otherwise entitled. It was alleged that researchers attempted repeatedly to obtain follow-up medical information about a subject after the subject expressed a clear desire to discontinue participation in the above research. OHRP makes no finding regarding this allegation. OHRP notes that the subject clearly expressed to WIH researchers her desire to withdraw from chemotherapy at WIH and that WIH did not interpret this decision as a withdrawal from participation in GOG protocol182.

OHRP has the following additional concern regarding the above research project at WIH:

(6) [Redacted]

OHRP makes the following recommendations to WIH regarding its written IRB procedures:

(7) OHRP recommends that WIH's written IRB procedures more fully describe all of the following activities required by HHS regulations at 45 CFR 46.103(a) and 46.103(b)(4) and (5), including operational details:

(a) The procedures which the IRB will follow for conducting its initial review of research.

(b) The procedures which the IRB will follow for conducting its continuing review of research.

(c) The procedures which the IRB will follow for reporting its findings and actions to investigators and the institution.

(d) The procedures which the IRB will follow for determining which projects require review more often than annually.

(e) The procedures which the IRB will follow for determining which projects need verification from sources other than the investigators that no material changes have occurred since previous IRB review.

(f) The procedures which the IRB will follow for ensuring prompt reporting to the IRB of proposed changes in a research activity, and for ensuring that such changes in approved research, during the period for which IRB approval has already been given, may not be initiated without IRB review and approval except when necessary to eliminate apparent immediate hazards to the subject.

(g) The procedures for ensuring prompt reporting to the IRB, appropriate institutional officials, any Department or Agency head, and OHRP 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.

OHRP's July 11, 2002 *Guidance on Written IRB Procedures* (http://www.hhs.gov/ohrp/humansubjects/guidance/irbgd702.htm) contains OHRP's recommendations regarding the required elements and operational

details of written IRB procedures under 45 CFR Part 46.

OHRP requests that WIH provide the requested corrective action plan and response to the stated concern no later than October 3, 2006.

OHRP appreciates the continued commitment of WIH to the protection of human research subjects. Please feel free to contact me should you have any questions.

Sincerely,

Carol J. Weil, J.D.
Compliance Oversight Coordinator
Division of Compliance Oversight

cc: Ms. Barbara J. Riter, Research Administrator, Women & Infants Hospital
Dr. Paul A. DiSilvestro, IRB Chair/Gynecologic Oncologist, Women & Infants Hospital
Commissioner, FDA
Dr. David Lepay, FDA
Dr. Sam Shekar, Director, OEP/OER, NIH
Dr. Andrew C. von Eschenbach, Director, NCI, NIH
Ms. Joan Mauer, NCI, NIH
Dr. Bernard Schwetz, OHRP
Dr. Melody H. Lin, OHRP
Dr. Michael Carome, OHRP
Ms. Shirley Hicks, OHRP
Dr. Irene Stith-Coleman, OHRP