DEPARTMENT OF HEALTH & HUMAN SERVICES

Office of the Secretary
Office of Public Health and Science

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February 19, 2009

John C. Elkas, M.D., J.D.
Partner
Northern Virginia Pelvic Surgery Associates
3289 Woodburn Road Suite 320
Annandale, VA 22003

RE: Human Research Protections Under Federalwide Assurance FWA-13356

Research Project: A Phase III Trial of Carboplatin and Paclitaxel Plus Placebo vs. Carboplatin and Paclitaxel Plus Concurrent Bevacizumab, Followed by Placebo, vs. Carboplatin and Paclitazel Plus Concurrent and Extended Bevacizumab, in Women with Newly Diagnosed, Previously Untreated, Stage III (Suboptimal) and All Stage IV, Epithelial Ovarian or Primary Peritoneal Cancer
Principal Investigator: Dr. John C. Elkas
HHS Protocol Number: Gynecology Oncology Group (GOG) -0218

Dear Dr. Elkas:

Thank you for your September 25, 2008 report in response to our August 28, 2008 request that Northern Virginia Pelvic Surgery Associates (NVPSA) evaluate allegations of noncompliance with Department of Health and Human Services (HHS) regulations for the protection of human research subjects (45 CFR part 46). Based on our review of your response, we make the following determinations:

A. Determinations regarding the above-referenced research

(1) The complainant alleged that the informed consent documents reviewed and approved by the institutional review board (IRB) that approved this study on behalf of NVPSA did not include an accurate description of any additional costs to the subject that may result from participation in the research, as required by HHS regulations at 45 CFR 46.116(b)(3). In specific, the complainant alleged that she is now being asked to pay the co-pay for the visits to infuse Bevacizumab/placebo, even though the informed consent document states "In the case that the costs of administering Bevacizumab/placebo are not covered by your health plan or insurance company, you will not be held personally responsible for covering these costs" and she had been previously told the costs of those visits in which she received an infusion were "written off and you will not be charged a co-pay for these types of visits

going forward." We determine that the informed consent documents reviewed and approved by the IRB for this study failed to include an accurate description of any additional costs to the subject that may result from participation in the research, as required by HHS regulations at 45 CFR 46.116(b)(3).

Corrective Action: We acknowledge that all co-payments remaining on the complainant's account have been written off.

Required Action: By March 27, 2009 please provide additional corrective actions to ensure that other subjects are not charged co-payments for study visits in which Bevacizumab/placebo are administered, or that the informed consent document is changed to reflect such required payments.

(2) The complainant alleged that changes to the protocol were implemented without informed consent or IRB review and approval, in contravention of HHS regulations at 45 CFR 46.116(a)(1), 46.103(b) and 46.109(a). In specific, the complainant alleged that additional office visits and tests were performed without informed consent or IRB review and approval. After the 6th cycle, the end of standard treatment, there were to be blood tests every other cycle, or every six weeks. However, the complainant underwent several more tests. It appears there were two tests done, 10/2/07 and 10/5/07, just preceding the 10/9/07 treatment, another test on 10/9/07, the day of treatment, and two tests done on 10/16/07 and 10/23/07, just after the 10/9/07 treatment. This appears to exceed the protocol of one test every six weeks when all these tests were done over a period of approximately three weeks.

We note the statement in your September 25, 2008 response that, although these tests were outside of the protocol parameters, they were permissible and consistent with the standard of care for oncology patients. Dr. Bicher had concerns regarding the complainant's white blood and platelet counts and weekly labs were obtained during October 2007 because of the need to monitor the patient's condition. On October 30, 2007, the complainant's counts were within the acceptable range and therefore weekly monitoring was discontinued. We therefore determine that the allegation is unproven.

(3) The complainant alleged that the informed consent document for this study included exculpatory language through which the subject was made to waive, or appeared to waive, her legal rights, in contravention of HHS regulations at 45 CFR 46.116. In specific, the complainant alleged that language was added to the informed consent document in August 2007 stating that subjects will not be able to find out whether they received Bevacizumab or placebo and that such language was exculpatory. We acknowledge the statement of the Chairperson of the Inova Health System IRB that the IRB does not interpet this statement as a waiver of the subject's legal rights. We are not aware of any state or local law that would allow subjects to have access to their research records. In the absence of any laws on point, it is not clear that any legal rights are being waived or appear to be waived. We therefore make no determination regarding this allegation.

(4) The complainant alleged that her contacts to the National Cancer Institute (NCI) Central institutional review board (CIRB) were not responded to, in contravention of HHS

regulations at 45 CFR 46.116(a)(7) which require that informed consent include an explanation of whom to contact for answers to pertinent questions about the research and research subjects' rights. In specific, the complainant alleged that multiple phone calls were made to the phone number listed in the consent document for the NCI CIRB beginning in January 2007, and at the request of the NCI CIRB phone operator, concerns were sent to the NCI CIRB in writing. The complainant alleged she never received a response to these concerns. The NCI CIRB indicated that in response to the telephone call to the CIRB regarding payment issues, the caller was referred back to the local IRB on March 5, 2008. The CIRB has no record of any further phone calls. We therefore make no determination regarding this allegation.

(5) We determine that NVPSA designated an additional IRB under their Assurance without prior OHRP approval. In specific, we note that correspondence from the IRB chairperson indicates that the NCI CIRB is the IRB of record for this study; however the NCI CIRB was not designated under the NVPSA FWA at the time we opened our evaluation into this matter in August 2008.

Corrective Action: We acknowledge that from October 2006 to July 2008 this protocol was covered under the Inova Health System FWA 573. In July 2008 NVPSA acquired their own FWA, but the NCI CIRB was not included due to an oversight. This was corrected September 5, 2008.

B. Additional Concerns

[Redacted]

C. Recommendations

We make the following recommendations regarding NVPSA's human subject protection program:

(1) Page 16 of the informed consent document for the above-referenced research approved by the Inova Health System IRB on January 11, 2008 has the following phrase which appears to be boilerplate language: "For industry-sponsored studies:" We recommend that the boilerplate language be deleted.

(1) Inova Health System Policy #5.07 section 4.c. describes what should happen if a subject becomes a prisoner after enrollment in research. We recommend that the policy be revised to note that when a previously enrolled research subject becomes a prisoner and the relevant research protocol was NOT reviewed and approved by the IRB in accordance with the requirements of HHS regulations at 45 CFR part 46, subpart C, all research interactions and interventions with, and obtaining identifiable private information about, the now-incarcerated prisoner-subject must cease until the requirements of subpart C have been satisfied with respect to the relevant protocol, unless it is in the best interests of the now incarcerated subject to continue participating in the research.

(2) Policy #5.08 outlines the requirements for research involving fetuses, pregnant women and in vitro fertilization. The policy includes the requirements of HHS regulations at 45 CFR part 46, subpart B; however we note that the language is from the previous version of subpart B. Please note that subpart B was modified in 2001. We recommend that the policy be updated accordingly.

(3) Policy #5.17 states that a "research protocol for which no new subjects will be enrolled must be periodically reviewed until such time that: a. analysis of the data has concluded that no new information needs to be provided to enrolled subjects; and/or b. there is no need to re-contact enrolled subjects to obtain additional research information." Please note that continuing review must occur at least annually as long as identifiable private information is being analyzed for research purposes. We recommend that the policy be revised accordingly.

(4) Policy #7.09 states regarding when a subject who is participating in a research study at one institution is admitted to an Inova Health System facility:

> When the involvement of Inova is reasonably foreseen and is an anticipated part of the research, e.g., the need for inpatient care is anticipated for the condition under study, or the need for subjects to return home and receive medical follow-up: …..c. Even though the test article is being given at Inova, only routine medical monitoring [sic] conducted by the local health provider with little or no reporting to the PI, who remains responsible for the test drug administration and collects research data when the subject returns to initial institution; d. The involvement of Inova is incidental to the study (i.e. research data are not collected or reviewed) and thus, [Inova] is not participating in the study;….

We note that if the above situation occurred in an HHS-supported research study, we would consider Inova Health System to be engaged in the research, because the test article would be given at Inova and therefore the study would need to have review and approval by an IRB designated under the Inova Health System FWA. Please see

http://hhs.gov/ohrp/humansubjects/guidance/engage08.html for OHRP's guidance on engagement.

Please provide us with responses to the above required action for determination (1) and the above concern by March 27, 2009, including a corrective action plan for the determination. Feel free to contact me if you would like guidance in developing a corrective action plan.

We appreciate the continued commitment of your institution to the protection of human research subjects. Please do not hesitate to contact me should you have any questions.

Sincerely,

Kristina C. Borror, Ph.D.
Director
Division of Compliance Oversight

cc:

Ms. Sheila D. Whitt, Research Coordinator, Northern Virginia Pelvic Surgery Associates
Dr. Michael Sheridan, IRB Chair, Inova Health System
Dr. Annette Bicher, Northern Virginia Pelvic Surgery Associates
Commissioner, FDA
Dr. Joanne Less, FDA
Dr. John E. Niederhuber, Director, National Cancer Institute
Dr. Maureen Kavanah, Chair, Adult NCI Central IRB
Ms. Jacquelyn Goldberg, IRB Administrator, NCI Central IRB
Dr. Sherry Mills, NIH
Mr. Joseph Ellis, NIH