DEPARTMENT OF HEALTH & HUMAN SERVICES **Office of the Secretary**
Office of Public Health and Science

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July 6, 2004

Leopold G. Selker, Ph.D.
Senior Vice President
Evanston Northwestern Healthcare
Research Institute
2650 Ridge Avenue
Evanston, IL 60201

RE: Human Research Subject Protections Under Multiple Project Assurance (MPA) M-1396 and Federalwide Assurance (FWA) 00003000

Research Project: Intraoperative Sentinel Node Mapping in Non-Small Cell Lung Cancer

Principal Investigator: Dr. Michael Liptay

Dear Dr. Selker:

The Office for Human Research Protections (OHRP) has reviewed Evanston Northwestern Healthcare Research Institute's (ENHRI) May 26, 2004 response to OHRP's letter dated April 20, 2004 regarding the above-referenced research.

In its April 20, 2004 letter, OHRP made the following findings regarding the above-referenced research:

> (1) OHRP found that the informed consent document reviewed and approved by the ENHRI institutional review board (IRB) failed to adequately address the following elements of informed consent as required by Department of Health and Human Services (HHS) regulations at 45 CFR 46.116(a)(1) and (4):
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> (a) An explanation of the purpose(s) of the research;
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> (b) A complete description of the procedures to be followed;

(c) Identification of any procedures which are experimental;

(d) Expected duration of the subject's participation; and

(e) A disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject.

(2) OHRP found that the informed consent document approved by the ENHRI IRB included complex language that would not be understandable to all subjects, in contravention of HHS regulations at 45 CFR 46.116.

Corrective Actions: OHRP has determined that the following corrective actions adequately address the above findings and are appropriate under the ENHRI FWA:

(a) The informed consent document for the above-referenced research study has been revised, incorporating the issues identified in OHRP's April 20, 2004 letter. OHRP finds that the revised informed consent document submitted to OHRP on May 26, 2004 adequately addresses the findings and concerns expressed in OHRP's April 20, 2004 letter.

(b) A special committee of ENHRI IRB members will review and modify the boilerplate consent form used at ENHRI.

(c) The ENHRI IRB will consider the concerns raised in OHRP's April 20, 2004 letter when reviewing each consent form.

(d) One member of the ENHRI IRB or an outside lay person, in addition to the primary and secondary reviewers, will be assigned to review the consent form for each protocol.

Further, OHRP makes the following additional determinations regarding the complainant's allegations concerning the above-referenced research:

(3) It was alleged that the investigator failed to obtain legally informed consent under circumstances that provided the subject sufficient opportunity to consider whether or not to participate, and that minimized the possibility of coercion or undue influence, as required by HHS regulations at 45 CFR 46.116. In specific, the complainant alleged that she was pressured to sign the informed consent document for the above-referenced research immediately prior to undergoing surgery. In addition, the complainant alleged that the research nurse who presented the informed consent document to her prior to surgery told her that she did not need to read past the first page of the document, and that she would not get the full benefits of the surgery unless she participated in the research.

OHRP notes that the complainant signed the consent form on February 13, 2002, the day of her surgery. However, ENHRI indicated in its December 12, 2002 response to OHRP's October 30, 2002 letter, that the complainant was given a copy of the study consent form to review at the presurgery meeting that occurred on Feb. 7, 2002, six days before her surgery. The complainant is reported to have called the research nurse with questions about her surgery and the consent form five days before her surgery. ENHRI stated in its December 12, 2002 response, with regard to the statements allegedly made by the research nurse to the complainant on the day of her surgery, that the research nurse denies making such statements.

After considering the statements of both the complainant and the institution, OHRP finds that it is unable to make a determination of noncompliance with the requirements of HHS regulations at 45 CFR part 46 regarding this allegation.

(4) It was alleged that the investigator failed to provide an adequate description of the benefits to the subject which may reasonably be expected from the research, in accordance with HHS regulations at 45 CFR 46.116 (a)(3). In specific, the complainant alleges that the research nurse told her that she would definitely benefit from the study.

ENHRI indicated the following in its December 12, 2002 response: "The nurse stated that she did not tell the subject she would benefit from the study or that it would help her. The nurse gave the standard explanation that she has used with all subjects."

After considering the statements of both the complainant and the institution, OHRP finds that it is unable to make a determination of noncompliance with the requirements of HHS regulations at 45 CFR part 46 regarding this allegation.

(5) It was alleged that the investigator failed to provide an adequate description of the reasonably foreseeable risks and discomforts to the subject, in accordance with HHS regulations at 45 CFR 46. 116(a)(2). In specific, the complainant alleges that the informed consent document does not include the risks associated with the removal of additional lymph nodes, and the possible additional damage to the lymphatic system that may result from the research.

ENHRI stated the following in its March 30, 2004 response to OHRP's Jan. 15, 2004 letter:

> Because of the rich lymphatic network in the thorax and pleural space other healthy nodes not resected compensate for those that are removed. Should a node(s) with increased radioactivity be found following the standard dissection and lobectomy, the removal of that node(s) adds no additional risk and no additional damage to the lymphatic system.

Based on this statement and other information contained in the institution's responses, OHRP is unable to substantiate this allegation.

In its April 20, 2004 letter, OHRP required ENHRI to revise the consent form for this study. OHRP notes that the institution included the following statement in the revised version to better explain the institution's assertion that removal of additional lymph nodes for research purposes constitutes no additional risk:

> There is no way to determine how many lymph nodes will be removed during the standard surgery since each person is different. It is possible that an additional node(s) may be removed as a result of this research study. There will be no difference in the way your lymph system works after the nodes are removed, as there are plenty of lymph nodes left in the chest area to filter out infection.

(6) It was alleged that the investigator failed to include a description of the procedures to be followed and the identification of any procedures which are experimental, as required by HHS regulations at 45 CFR 46.116(a)(1). In specific, the complainant alleges that she underwent a positron emission tomography (PET) scan as part of the research, which was not described in the informed consent document.

ENHRI indicated the following in its December 12, 2002 response to OHRP's October 30, 2002 letter: "The subject did not undergo a PET scan. An error was made in the operative record stating that the scan occurred...."

Based on the information provided in ENHRI's December 12, 2002 response, OHRP is unable to substantiate the complainant's allegation.

(7) It was alleged that the investigators failed to ensure that the ENHRI IRB reviewed and approved all proposed changes in a research activity, during the period for which IRB approval had already been given, prior to initiation of such changes, except when necessary to eliminate apparent immediate hazards to the subjects, as required by HHS regulations at 45 CFR 46.103(b)(4)(iii).

> (a) In specific, the complainant alleges that the investigators injected a radioactive tracer directly into her tumor, although the informed consent document stated that the radioactive tracer would be injected around the tumor.
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> ENHRI's December 12, 2002 response to OHRP's October 30, 2002 letter indicated the following:
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> > The protocol requires injection of the tracer into specific quadrants of the tumor. The exact location of the injection is in a four-quadrant peritumoral fashion....The nurse discussed the protocol at length with the subject one week before the surgery and described that the radioactive

substance is injected around the edges of the tumor.

Based upon ENHRI's response, OHRP is unable to substantiate the allegation that the investigators made a change in a research activity prior to obtaining IRB approval by injecting the radioactive tracer directly into the subject's tumor.

In its April 20, 2004 letter, OHRP made the finding that the informed consent document failed to adequately describe the procedures to be followed in the research. ENHRI was required to submit an informed consent document that had been revised to address the findings in OHRP's letter. The revised informed consent document submitted to OHRP on May 26, 2004 states the following in the section entitled "Explanation of Procedures": "During surgery just before your tumor is removed, your doctor will inject the radioactive substance around the tumor and measure the radioactivity..."

OHRP recommends that ENHRI revise the current informed consent document to include the language used in the February 11, 2002 version of the informed consent document, which indicated that the radioactive substance will be injected "into the edges of the lung tumor," instead of stating that it will be injected "around the tumor." The revised consent form should be reviewed and approved by the IRB.

(b) The complainant also alleges that the principal investigator failed to review the protocol with her, as was required in the informed consent document. The informed consent document that the complainant signed included the following statement: "I have read and discussed the explanation of this study with the study doctor. I have had enough time with the study doctor to discuss all of my questions and concerns."

OHRP finds that the consent procedure approved by the IRB, as indicated by the IRB-approved informed consent document, was not followed by the principal investigator.

Corrective Action: OHRP acknowledges that the draft informed consent document submitted with ENHRI's May 26, 2004 response has been revised appropriately to include the phrase "and/or staff" after references to the "study doctor." OHRP finds that this revision adequately addresses OHRP's finding.

As a result of the above determinations, there should be no need for further involvement of OHRP in this matter. Of course, OHRP must be notified should new information be identified which might alter this determination.

OHRP has the following additional comment:

(8) The complainant alleges that she requested additional information from the IRB

office regarding the above-referenced research, and that she was not provided with this information. The complainant alleges that the IRB Coordinator indicated that the only information the subject needed was in the informed consent document, and that the Coordinator would not provide any additional protocol-related information to the subject.

The institution responded that the IRB Coordinator sent a timely letter to the complainant in which she advised the complainant to contact the IRB office for assistance if she had a complaint regarding the treatment she received in a research trial. The letter also directed the complainant to call the principal investigator (whose phone number was provided) if she had questions about the sentinel node mapping procedure. The IRB Coordinator attached to this letter copies of the consent forms signed by the complainant. Such actions by the IRB Coordinator appear to have been appropriate.

OHRP appreciates ENHRI's continued commitment to the protection of human research subjects. Do not hesitate to contact OHRP if you have any questions regarding this matter.

Sincerely,

Karena Cooper, J.D., M.S.W.
Compliance Oversight Coordinator
Office for Human Research Protections

cc: Mr. Robert Stanton, Director, ENHRI
Dr. Bernard Adelson, IRB Chair, ENHRI
Dr. Michael Liptay, ENHRI
Commissioner, FDA
Dr. David Lepay, FDA
Dr. Bernard Schwetz, OHRP
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