DEPARTMENT OF HEALTH & HUMAN SERVICES

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Leopold G. Selker, Ph.D.
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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) response dated March 30, 2004 to OHRP's letter dated January 15, 2004.

Based upon its review, OHRP makes the following determinations regarding the above-referenced research:

(1) OHRP finds that the informed consent document reviewed and approved by the ENHRI

institutional review board (IRB) for the above-referenced research failed to adequately address the following elements of informed consent required by HHS regulations at 45 CFR 46.116(a):

(a) Section 46.116(a)(1):

(i) An explanation of the purposes of the research. OHRP finds that the informed consent document failed to adequately describe the purpose of the research. In specific, OHRP notes the following:

– The following sentence from the section entitled, "Why is this Study Being Done?" purports to explain the purpose of the research:

> "The purpose of this research study is to learn if a radioactive substance, injected around the tumor during surgery, will flow accurately to any malignant (cancerous) lymph nodes."

OHRP notes that in your response dated March 30, 2004, you propose to change the phrase "flow accurately" to "go to." However, the revised paragraph still does not explain <u>why</u> the researchers want to learn if a radioactive substance will flow to the malignant lymph nodes. In particular, it does not explain why a radioactive substance is being used or why this procedure would be important to the care of individuals with lung cancer.

– Although the informed consent form states, "The pattern of how lung cancer spreads from the tumor to the local lymph nodes is poorly understood," it does not offer an explanation of the manner in which cancer is thought to spread to the lymph nodes or why this is important for cancer diagnosis or treatment. The title of the consent document, "Intraoperative Sentinel Node Mapping in Non-small Cell Lung Cancer," but the concept of a sentinel node and the intraoperative sentinel node mapping procedure are not explained in the consent document. It would have been appropriate to note in language understandable to subjects that one purpose of the study is to evaluate the feasibility of using the sentinel node mapping technique using radioactive tracer substances in resectable non-small cell lung cancer. It may be appropriate to explain that the technique is being studied because it may help doctors better assess staging in specific lung cancer patients.

– The sentence, "Similar studies in patients with breast cancer have proven effective," misleadingly implies that this study involves treatment. It also implies

that the subject will benefit from participation in the study. The concept that this sentence is attempting to convey– that the sentinel node technique has been used in breast cancer to help determine whether and how far the cancer has spread in the lymph nodes– is not clearly explicated by the current wording of the sentence.

– The last two sentences in the section entitled, "Why is this Study Being Done?" are as follows:

> "Accuracy of the procedure will be determined by a comparison between any nodes that show increased radioactivity and the pathology examination. Portions of the removed cells will be saved and examined for associations between any radioactive lymph nodes and the tumor."

It is not clear that these two sentences are referring to the sentinel node mapping procedure that is being tested in this study. Also, it would be appropriate to explain that if radioactive lymph nodes are removed, they will be examined for cancer cells and then compared to lymph nodes that were removed as part of the standard surgery for lung cancer. It would also be appropriate to explain why this comparison is part of the research study.

(ii) A complete description of the procedures to be followed. OHRP finds that the informed consent document failed to adequately describe the procedures to be followed in the research. In specific, OHRP notes the following:

The section entitled, "What is Involved with this Study?"contains the following paragraph as the sole description of the procedures of the study:

> "You will be injected by a needle with a radioactive material into the area around the lung tumor after you have had anesthesia for surgery. All injections will be performed under the supervision of nuclear medicine personnel. Measurements of any radioactive material in the nodes will be taken with a handheld counter during surgery. A standard lung resection and nodal dissection will be completed. In addition to a standard removal of lymph nodes, remaining nodes that demonstrate increased radioactivity will be removed. All tissue will be examined for malignant cells by a pathologist (a medical doctor who examines laboratory specimens)."

The above description of the procedures does not adequately convey that the study involves the injection of a radioactive tracer, measurements of radioactivity, and the removal of lymph nodes with measurable radioactivity. This description also does not make clear that the research potentially increases the amount of time the subject is on the surgical table and potentially increases the number of lymph nodes that will be removed. It is also not clear that the surgeon will wave the gamma probe over the surgical site a second time after the lung cancer tumor and some of the surrounding lymph nodes have been removed as part of the standard treatment for lung cancer, and will then remove any of the remaining nodes in which radioactivity is detected by the gamma probe.

(iii) Identification of any procedures which are experimental. OHRP finds that the consent document does not clearly differentiate between the standard treatment for non-small cell lung cancer–in this case, surgical resection of the tumor and removal of lymph nodes–and the experimental procedure to be tested, that is, the sentinel node mapping procedure involving the injection of a radioactive tracer substance and removal of additional nodes that contain radioactivity.

It would be appropriate to include information about the approximate number of lymph nodes that may be removed during the usual surgery for this type of lung cancer, and then the number of additional nodes that may be removed as a result of participation in this research. It would also be appropriate to include an explanation that would be understandable to a layperson of the following sentence offered in your March 30, 2003 response: "Because of the rich lymphatic network in the thorax and pleural space, other healthy nodes not resected compensate for those that are removed."

(iv) Expected duration of the subject's participation. OHRP finds that the informed consent document approved for this research does not describe the duration of participation.

(b) Section 46.116(a)(4): Disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject. OHRP finds that the informed consent document fails to adequately describe alternative procedures or courses of treatment. In specific, OHRP notes that the section entitled, "What Other Options are There?" contains the following sentence:

> "If you decide not to participate in this study, the standard procedures of surgical resection of your lung cancer, a nodal dissection, and a laboratory examination of the removed tissue will take place."

This sentence does not make clear that the patient may instead simply choose to undergo their scheduled surgery to remove their lung cancer, which usually involves removing some of the lymph nodes but does not involve the injection of any radioactive substances.

(2) HHS regulations at 45 CFR 46.116 require that informed consent information be in language understandable to the subject or the subject's legally authorized representative. OHRP finds that the informed consent document approved by the IRB for this study includes complex language that would not be understandable to all subjects, as in the following examples:

(a) The consent document contains the following words and phrases that are complex: "local lymph nodes" and "negligible exposure."

(b) The sentence structure of the following sentence is too complex: "Accuracy of the procedure will be determined by a comparison between any nodes that show increased radioactivity and the pathology examination.

Corrective action: OHRP notes that in your response dated March 30, 2004, you proposed adding parenthetical explanations following certain terms in the section entitled, "What is Involved in This Study?" [see bold text below].

> "You will be injected by a needle with a radioactive material into the edges of the lung tumor after you have had anesthesia for surgery. All injections will be performed under the supervision of nuclear medicine personnel **(trained doctors and technician that are trained to work with radioactive material).** Measurements of any radioactive material in the nodes will be taken with a **device that measures radioactivity (gamma probe) held over your chest during surgery.** A standard lung resection **(removing part or all of the lung with the tumor)** and nodal dissection **(removing the lymph nodes in the middle of the chest and around the part of the lung that is taken out**) will be completed. In addition, remaining nodes that demonstrate radioactivity will be removed. All tissue will be examined for malignant cells by a pathologist (a medical doctor who examines laboratory specimens **under a microscope.)"**

OHRP notes that the parenthetical explanations further explicate the terms and phrases that precede

them. However, as stated in the subcategories of finding (1) above, the consent form does not adequately explain nor provide a context for the individual terms and phrases.

You stated in your March 30, 2004 response, "The consent form is part of a process which involves discussion, questions, and answers as well as reading the informed consent form." While OHRP applauds your institution's recognition of this important concept, HHS regulations at 45 CFR 46.117(a) and (b)(1) require that informed consent shall be documented by the use of a written consent document that embodies the elements of informed consent required by 45 CFR 46.116.

Required action: By May 28, 2004, please submit an informed consent document that has been revised to address the above findings. Please also provide OHRP with a satisfactory corrective action plan to address how the ENHRI IRB will ensure that all consent documents approved by the IRB contain language that would be understandable to the subject or the subject's representative.

OHRP appreciates your institution'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

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