DEPARTMENT OF HEALTH & HUMAN SERVICES

Office of the Secretary
Office of Public Health and Science

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January 7, 2003

William A. Peck, M.D.
Executive Vice Chancellor for Medical Affairs and Dean
Washington University School of Medicine
660 South Euclid Avenue, Campus Box 8106
St. Louis, MO 63110-1093

Philip A. Ludbrook, M.D.
Associate Dean and Chair
Washington University School of Medicine
Human Studies Committee (IRB)
660 South Euclid Avenue, Campus Box 8089
St. Louis, MO 63110-1093

RE: Human Research Subject Protections Under Multiple Project Assurance (MPA) M-1189 and FederalWide Assurance (FWA) 00002284

Research Project: Randomized Study of Vincristine, Actinomycin-D, and Cyclophosphamide (VAC) versus VAC alternating with Vincristine, Topotecan and Cyclophosphamide for Patients with Intermediate-Risk Rhabdomyosarcoma [POG D9803]
Principal Investigator: Lori Luchtman-Jones, M.D.
Protocol Number: HSC 99-0723

Dear Drs. Peck and Ludbrook:

The Office for Human Research Protections (OHRP) has reviewed Washington University School of Medicine's (WUSM's) August 1, 2002 report that was submitted in response to OHRP's June 20, 2002 letter to WUSM regarding the allegations of possible noncompliance with the Department of Health and Human Services (HHS) regulations for the protection of human subjects (45 CFR Part 46) involving the above-referenced research.

Based upon review of your August 1, 2002 report, as well as additional documentation submitted by WUSM on December 5, 2002, OHRP makes the following determinations regarding the above-referenced research:

(1) HHS regulations at 45 CFR 46.116(a)(2) require that in seeking informed consent a description of any reasonably foreseeable risks or discomforts of the research shall be provided to each subject. OHRP finds that the informed consent document approved by the WUSM IRB for use prior to July 16, 2002 failed to include an adequate description of the reasonably foreseeable risks of veno-occlusive disease (VOD) of the liver and its potential complications, including liver failure and death, known to be associated with the VAC drug regimen.

Corrective Action: OHRP acknowledges that:

(a) The WUSM IRB has approved a revised informed consent document for the above- referenced research project, which includes the following statement:

"**RISKS:** There are certain risks and discomforts that may be associated with this research. They include:

Both disease and the treatment are associated with potentially life-threatening or fatal complications and side-effects. There is also the risk of very uncommon or previously unknown side effects. Chemotherapy agents are drugs that, in addition to killing tumor cells, can damage normal tissue. These drugs, however, have been in use long enough so that severe problems can be usually avoided. Side effects are usually reversible when medication is stopped but occasionally can persist and cause serious complications or death. In addition, when chemotherapy drugs are combined the side effects can be increased. Therapy with vincristine, actinomycin-D and cyclophosphamide as given on this protocol has been associated with a small risk of the development of a potentially life-threatening condition called veno-occlusive disease of the liver (VOD). VOD is characterized by elevation of liver enzymes, yellow skin

(jaundice), tenderness in the abdomen where the liver is located, and weight gain or swelling. There is not an effective treatment for VOD at this time. If VOD develops, the chemotherapy that you receive may be changed."

(b) The WUSM IRB has required that the investigators present the information described in (a) above to currently enrolled subjects and to obtain signed confirmation of the subjects' willingness to continue participation in the above- referenced research.

OHRP finds that these corrective actions adequately address the above finding and are appropriate under the WUSM FWA.

(2) In its June 20, 2002 letter, OHRP presented the allegation that the research may have failed to minimize the risks to subjects, as required by HHS regulations at 45 CFR 46.111(a)(1). In particular, it was alleged that investigators in the above-referenced research were unaware of previously reported cases of VOD, some of which resulted in subject death in the above-referenced research, and as a result failed to recognize and diagnose in a timely manner the development of VOD in a subject (DR) who subsequently died from complications related to this disorder. Based on its review of information presented in your report, OHRP finds that this allegation was not substantiated.

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.

At this time, OHRP provides the following additional guidance regarding the informed consent document for the above-referenced research:

(3) HHS regulations at 45 CFR 46.116(a)(1) require that when seeking informed consent, each subject be provided with, among other things, an explanation of the expected duration of the subject's participation.

(a) OHRP notes that the above-referenced research project protocol, as amended June 1, 2002, stated the following:

"APPENDIX V: REQUIRED STUDIES FOR THE POST-THERAPY FOLLOW-UP PERIOD OF PATIENTS WITH RHABDOMYOSARCOMA

1. General Studies for All Patients

a. After completion of chemotherapy patients will be seen one to two months during the first year, every three months the second year, every six months in the third year and yearly thereafter for 10 years. Imaging of the primary and metastatic sites should be done every six months for two years, than yearly for two year (sic) during the follow-up phase. The usual follow-up visit will include a physical examination, CBC, platelet count, and chemistry panel. This may be altered if there are no abnormalities found after three to four months."

(b) The informed consent document that the WUSM IRB approved on July 16, 2002 stated the following:

"How long will you (your child) be on this study?

You (Your child) will be treated on this study for about one year. However, patients will continue to have physical exams and blood tests for a few years after treatment so that researchers can continue to observe any effects of treatment."

Based on the statement in (a) above, OHRP recommends that the WUSM IRB-approved informed consent document for the above-referenced research project be revised to provide a more complete description of the expected duration of the subject's participation and the number of required post-therapy clinical visits.

OHRP appreciates the commitment of WUSM to the protection of human research subjects. Please do not hesitate to contact me should you have any questions.

Sincerely,

Robert J. Meyer
Compliance Oversight Coordinator

Division of Compliance Oversight

cc: Ms. Patricia Scannell, IRB Administrator, WUSM
Dr. H. James Wedner, Chair, IRB-01, WUSM
Mr. Lloyd J. Vasquez, Chair, IRB-02, WUSM
Dr. Perry Grigsby, Chair, IRB-03, WUSM
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