DEPARTMENT OF HEALTH & HUMAN SERVICES

Office of the Secretary
Office of Public Health and Science

Office for Human Research Protections
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August 23, 2004

Theodore G. Krontiris, M.D., Ph.D.
Executive Vice President for Medical
and Scientific Affairs
City of Hope National Medical Center
and Beckman Research Institute
Administrative Offices
Needleman Building
1500 East Duarte Road
Duarte, CA 91010-3000

**RE: Human Research Subject Protections Under Federalwide Assurance (FWA) 692**

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|---|---|
| **Research Project:** | **Prostate Cancer Prevention Trial** |
| **Principal Investigator:** | **Timothy Wilson, M.D.** |
| **Protocol Number:** | **93090** |

Dear Dr. Krontiris:

The Office for Human Research Protections (OHRP) has reviewed the City of Hope National Medical Center and Beckman Research Institute's (COH) January 13, 2004 report, which was submitted in response to OHRP's October 23, 2003 letter regarding the above-referenced research.

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

(1) Department of Health and Human Services (HHS) regulations at 45 CFR 46.116(a)(2) require that informed consent include a description of the reasonably foreseeable risks or discomforts to the subject. OHRP finds that the institutional review board (IRB)-approved informed consent document for the research failed to describe adequately the risk of serious infection associated with prostate biopsy, which may require hospitalization and could result in death.

COH's January 13, 2004 letter stated that OHRP's guidance prohibits the alteration of risk language unless specific written justification is provided to and approved by the IRB. OHRP's guidance on this matter states, "Any deletion or substantive modification of information concerning risks or alternative procedures contained in the sample informed consent documents must be justified in writing by the investigator and approved by the IRB." This language was meant to discourage the removal or downplaying of risks in informed consent documents. The addition of appropriate language about reasonably foreseeable risks is not prohibited by OHRP's guidance.

**Required Action:** COH must provide an adequate corrective action plan to ensure that all subjects enrolled in the above-referenced research who will undergo a prostate biopsy are informed of the risk of serious infection, possible hospitalization, and death.

(2) HHS regulations at 45 CFR 46.109(e) require that continuing review of research be conducted by the IRB at intervals appropriate to the degree of risk and not less than once per year. OHRP finds that the COH IRB failed to conduct continuing review of the above-referenced research at least once per year.

**Corrective Action:** OHRP acknowledges that the COH IRB has hired additional staff to address staffing shortages that may have contributed to the above deficiency. In addition, COH is introducing electronic submission of IRB documents to aid in the review of submissions and has developed a centralized e-mail box for communications with the IRB. OHRP finds that these corrective actions adequately address the above finding and are appropriate under the COH FWA.

(3) It was alleged that risks to subjects were not minimized in the above-referenced research, as required by HHS regulations at 45 CFR 46.111(a)(1). In specific, it was alleged that one subject died as a result of a prostate biopsy, but the subject was not told what serious complications to look for and how to respond to such complications. Based upon the information provided in your report, OHRP finds that this allegation is not substantiated.

(4) It was alleged that COH failed to promptly report the death of one subject enrolled in the research to OHRP as an unanticipated problem involving risks to subjects, as required by HHS regulations at 45 CFR 46.103(a) and 46.103(b)(5). OHRP finds that this allegation is not substantiated, as the risk of life-threatening infection from prostate biopsy should have been anticipated.

At this time OHRP has the following additional concern:

[redacted]

Please forward your corrective action plan and response to the above concern so that OHRP receives them no later than October 8, 2004.

OHRP appreciates the continued commitment of your institution to the protection of human research subjects.

Sincerely,

Patrick J. McNeilly, Ph.D.
Compliance Oversight Coordinator
Division of Compliance Oversight

cc: Ms. Gwen Oki, Director, Research Subject Protection, COH
Dr. John Zaia, Chair, COH IRB
Dr. Timothy Wilson, COH
Dr. Lana Skirboll, Director, Office of Science Policy, NIH
Dr. Andrew von Eschenbach, Director, NCI, NIH
Ms. Joan Mauer, NCI, NIH
Commissioner, FDA
Dr. David Lepay, FDA
Dr. Bernard Schwetz, OHRP
Dr. Melody H. Lin, OHRP
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Ms. Jan Walden, OHRP
Ms. Patricia El-Hinnawy, OHRP
Ms. Melinda Hill, OHRP