DEPARTMENT OF HEALTH & HUMAN SERVICES

Office of the Secretary
Office of Public Health and Science

Office for Human Research Protections
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January 13, 2003

Regis Kelly, Ph.D.
Vice Chancellor for Research
University of California, San Francisco
513 Parnassus Avenue, S-101
Box 0407
San Francisco, CA 94143

RE: Human Research Subject Protections Under Multiple Project Assurance (MPA) M-1169 and Federalwide Assurance (FWA) #000068
Research Project: A Feasibility Study of Neoadjuvant Vinorelbine and Cisplatinum for Patients with Early Stage, Resectable Non Small Cell Lung Cancer
Principal Investigator: Thierry M. Jahan, MD

Dear Dr. Kelly,

The Office for Human Research Protections (OHRP) has reviewed the University of California, San Francisco's (UCSF's) November 27, 2002 report regarding the above-referenced protocol, including findings of the Ad Hoc Committee you appointed in September 2002 to investigate allegations that six individuals were prospectively enrolled in research without institutional review board (IRB) review and approval as required by Department of Health and Human Services (HHS) regulations at 45 CFR 46.109(a).

OHRP Findings

OHRP has determined that the corrective actions developed by UCSF adequately address the following OHRP findings and are appropriate under the UCSF FWA:

(1) OHRP concurs with UCSF's finding that between October 2, 1996 and August 1, 1997, Dr. Jahan and colleagues at UCSF performed an experimental intervention (induction therapy using a combination of cisplatinum and vinorelbine, followed by resection) upon six individuals with early stage non small cell lung cancer, to determine the feasibility, safety and efficacy of the

combined modalities. OHRP further finds that this prospective, non-exempt research was conducted without review or approval by the UCSF IRB, as required by HHS regulations at 45 CFR 46.109, and without obtaining the legally effective informed consent of the subjects, as required by HHS regulations at 45 CFR 46.116.

Corrective Action: UCSF is requiring Dr. Jahan to write to the four surviving subjects who received experimental treatment before the research was reviewed and approved by the IRB, and to the relatives of the two subjects who are now deceased, to inform them that they (or their relatives) were enrolled in a research study without consent and without IRB approval.

UCSF has informed Dr. Jahan that if he wishes to use data from these six subjects in any additional publications, he must request permission from surviving subjects or relatives.

In order to determine whether the violations pertaining to the above-referenced protocol are isolated and not ongoing, the UCSF IRB requested (a) institutional review of all human subject research studies published by Dr. Jahan or his co-principal investigator, Dr. David Jablons, from 1997 to the present, and (b) special monitoring of all ongoing IRB studies for which either Dr. Jahan or Dr. Jablons is listed as principal investigator. As a condition of future IRB approval of submitted studies, the IRB required Drs. Jahan and Jablons to cooperate fully with such investigation/monitoring. If a satisfactory plan for investigation and monitoring is not in place by January 31, 2003, or if the results of the investigation and monitoring indicate any additional violations of HHS regulatory requirements or of human subject protection ethical standards, the IRB will consider suspending approval of Drs. Jahan's and Jablons' other research involving human subjects.

(2) OHRP concurs with UCSF's finding that the UCSF IRB was not provided with sufficient information necessary to ensure that risks to subjects were minimized, and that risks were reasonable in relation to anticipated benefits, as required by HHS regulations at 45 CFR 46.111(a)(1) and (a)(2). Specifically, when the UCSF IRB initially reviewed and approved the above study, it was not informed about the death of an individual discussed in Dr. Jahan's published study who received itraconazole concurrently with vinorelbine before the protocol was submitted to the IRB. Moreover, despite the recommendation on March 29, 2000 of an institutional investigative committee that consent forms for any new research subjects be revised to disclose the potentially fatal risk of itraconazole interacting with vinorelbine, the IRB failed to ensure compliance with that recommendation.

Corrective Action: UCSF's human subject protection program is revising its procedures for handling reports of problems in the conduct of research and for tracking the resolution of these problems to ensure that there is adequate and more timely follow-through and communication. A Compliance Unit has been established to investigate alleged violations and will coordinate with the IRB.

As a result of the above corrective actions, 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 requests that UCSF provide OHRP with a photocopy of one of the letters sent by Dr. Jahan to one of the 4 surviving subjects, with subject identification redacted.

OHRP Guidance

At this time, OHRP provides the following guidance to UCSF concerning continuing review:

> (3) HHS regulations at 45 CFR 46.111 set forth the criteria that must be satisfied in order for the IRB to approve research initially and upon continuing review. These criteria include, among other things, determinations by the IRB regarding risks, potential benefits, informed consent, and safeguards for human subjects. The IRB must ensure that these criteria are satisfied at the time of both initial and continuing review. The procedures for continuing review by the convened IRB may include a primary reviewer system.
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> In conducting continuing review of research not eligible for expedited review, all IRB members should at least receive and review a protocol summary and a status report on the progress of the research, including: (i) the number of subjects accrued; (ii) a summary of adverse events and any unanticipated problems involving risks to subjects or others and any withdrawal of subjects from the research or complaints about the research since the last IRB review; (iii) a summary of any relevant recent literature, interim findings, and amendments or modifications to the research since the last review; (iv) any relevant multi-center trial reports; (v) any other relevant information, especially information about risks associated with the research; and (vi) a copy of the current informed consent document and any newly proposed consent document.
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> At least one member of the IRB (i.e., a primary reviewer) also should receive a copy of the complete protocol including any modifications previously approved by the IRB. Furthermore, upon request, any IRB member also should have access to the complete IRB protocol file and relevant IRB minutes prior to or during the convened IRB meeting. The minutes of IRB meetings should document separate deliberations, actions, and votes for each protocol undergoing continuing review by the convened IRB.
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> When reviewing research under an expedited review procedure, the IRB Chair (or designated IRB member(s)) should receive and review all of the above-referenced documentation, including the complete protocol.
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> For additional OHRP guidance on continuing review see http://ohrp.osophs.dhhs.gov/humansubjects/guidance/contrev2002.htm.

OHRP appreciates the continued commitment of your institution to the protection of human research subjects. Feel free to contact me if you have any questions.

Sincerely,

Carol J. Weil, J.D.
Division of Compliance Oversight

cc: Ms. Sharon K. Friend, IRB Administrator, UCSF
Dr. Thierry Jahan, UCSF
Dr. David M. Jablons, UCSF
Dr. Reese Jones, IRB (A) Chair, UCSF
Dr. Susan Sniderman, IRB (1) Chair, UCSF
Dr. Melody Lin, OHRP
Dr. Michael Carome, OHRP
Dr. Kamal Mittal, OHRP
Dr. Kristina Borror, OHRP
Dr. John Mather, ORCA, Department of Veterans Affairs