DEPARTMENT OF HEALTH & HUMAN SERVICES

Office of the Secretary
Office of Public Health and Science

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May 13, 2003

Richard J. Sohn, Ph.D.
Associate Vice President and Associate
Dean for Research Administration
Columbia University Health Sciences
630 West 168th St, 2-421
New York, NY 10032

RE: Human Research Subject Protections Under Multiple Project Assurance (MPA) M-1356 and Federalwide Assurance FWA-2636

Research Project: Evaluation of Intensive Pancreatic Proteolytic Enzyme Therapy with Ancillary Nutritional Support in the Treatment of Inoperable Pancreatic Adenocarcinoma
Columbia Presbyterian Medical Center (CPMC) IRB Number: 8544
Principal Investigator: John Chabot, M.D.

Dear Dr. Sohn:

The Office for Human Research Protections (OHRP) has reviewed the Columbia University Health Sciences (CUHS) April 18, 2003 report regarding the above-referenced research that was submitted in response to OHRP's December 3, 2002 letter to CUHS.

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

(1) Department of Health and Human Services (HHS) regulations at 45 CFR 46.110(b)(2) permit use of expedited procedures for review of minor changes to previously approved research during the period for which approval is authorized. OHRP finds that the CUHS institutional review board (IRB) employed expedited procedures to review changes that exceed this limitation. On January 20, 2000, the CUHS IRB received a request from the principal investigator to approve an amendment to the protocol that included eliminating the randomization and adding a patient questionnaire. It appears that approval of this amendment was done in an expedited manner.

Corrective Action: OHRP acknowledges that CUHS agrees that such changes should have been brought to the convened IRB for review. A revised protocol reflecting these and other necessary changes identified as a result of OHRP's evaluation will be re-submitted to the convened IRB for review. In addition, the informed consent document is being revised and the enrolled subjects will be re-consented. Enrollment of new subjects has been suspended pending revision and IRB approval of the informed consent document. In addition, CUHS has instituted a comprehensive evaluation and reorganization of its human subject review process. Improvements include: (1) addition of a third IRB; (2) improving the IRB's computer capability; (3) improving and enhancing training and education programs for IRB members, IRB staff, and clinical research personnel; (4) creating an Office for Responsible Conduct of Research; and (5) plans to apply for accreditation of CUHS's human subjects protection program. OHRP finds that these corrective actions adequately address the above finding and are appropriate under the CUHS FWA.

(2) OHRP finds that when reviewing protocol applications, the IRB appeared to lack the sufficient information to make the following determinations required for approval of the above-referenced research under HHS regulations at 45 CFR 46.111:

(a) Section 46.111(a)(1) and (2): The 5-12-1998 version of the protocol did not state the sample size for the study.

(b) Section 46.111(a)(3) and (4): Several documents indicated that there would be some form of advertising for the study. OHRP can find no evidence that the CUHS IRB approved any such advertisements.

Corrective Action: OHRP acknowledges that the above-referenced information will be provided to the CUHS IRB and that the revised protocol will be re-submitted to the IRB for review. In addition, the investigators will be instructed as to the need to obtain such review for any future proposed advertisements. OHRP finds that these corrective actions adequately address the above finding and are appropriate under the CUHS FWA.

(3) OHRP finds that the informed consent documents reviewed and approved by the CUHS IRB for this study failed to adequately address the following elements required by HHS regulations at 45 CFR 46.116(a)(1):

(a) An explanation of the purposes of the research. The IRB-approved protocol stated that "primary endpoint is survival...." However, the informed consent document stated that "the purpose of this research study is to determine whether enzyme-nutritional therapy is as effective as a drug called gemcitabine for treating pancreatic adenocarcinoma."

(b) A complete description of the procedures to be followed, and identification of any procedures which are experimental.

(i) The protocol included an evaluation of nutritional status by a "subjective global assessment" questionnaire and a questionnaire regarding quality of life. These assessments were not mentioned in the informed consent document.

(ii) The informed consent document referred to the alternative regimen as "pancreatic proteolytic enzyme therapy" or "enzyme-nutritional therapy" and throughout referred to the study as involving "treatment" and "therapy." The only treatment or therapy available on the protocol was gemcitabine; therefore it appears that the experimental procedures were not accurately described in the informed consent document.

Corrective Action: OHRP acknowledges that the informed consent document will be revised to state the purpose of the study more directly, to refer specifically to the questionnaires and assessments noted above, and replace the words "treatment" and "therapy" with the term "experimental regimen" or similar. OHRP finds that these corrective actions adequately address the above finding and are appropriate under the CUHS FWA.

(4) 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 CUHS IRB for this study appeared to include complex language that would not be understandable to all subjects, such as alleviating, persist, emesis, anorexia, myalgias, arthralgias, transient intolerance, abdomen and pelvis.

Corrective Action: OHRP acknowledges that the revised informed consent document currently being prepared will ensure that all language is understandable to prospective subjects. OHRP finds that this corrective action adequately addresses the above finding and is appropriate under the CUHS FWA.

(5) OHRP finds that CUHS has adequately responded to the additional concerns presented in OHRP's December 3, 2002 letter.

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

Sincerely,

Kristina C. Borror, Ph.D.
Director, Division of Compliance Oversight

cc: Ms. Patricia Seymour, Acting CUHS IRB Director
Dr. Adrew Wit, Chair, CUHS IRB #1
Dr. James Garvin, Chair, CUHS IRB #2
Dr. John Chabot, CUHS
Dr. David LePay, FDA
Commissioner, FDA
Dr. Bernard Schwetz, OHRP
Dr. Melody Lin, OHRP
Dr. Michael Carome, OHRP
Ms. Shirley Hicks, OHRP
Mr. George Gasparis, OHRP
Ms. Yvonne Higgins, OHRP
Ms. Patricia El-Hinnawy, OHRP
Ms. Melinda Hill, OHRP