DEPARTMENT OF HEALTH & HUMAN SERVICES

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June 2, 2008

Steven Shea, M.D.
Columbia University Medical Center
Columbia University Health Sciences
Vice President & Dean's Office,
630 West 168th Street
New York, NEW YORK 10032

RE: Human Research Subject Protections Under Federalwide Assurance (FWA)-2636

Research Project:	**Gemcitabine Compared With Pancreatic Enzyme Therapy Plus Specialized Diet (Gonzalez Regimen) in Treating Patients Who Have Stage II, Stage III or Stage IV Pancreatic Cancer**
Principal Investigator:	**John Chabot, M.D.**
Project Number:	**P30-CA13696**

Dear Dr. Shea:

Thank you for your April 4, 2008 response to our letter of February 25, 2008 regarding the above-referenced research. Based on the information submitted to us, we make the following additional determination regarding this research:

(1) Subject 129 began enzyme treatment in the study 11 weeks after undergoing biopsy of the pancreatic tumor, which was inconsistent with the inclusion criteria stipulated in the institutional review board (IRB)-approved protocol that subjects begin treatment within 8 weeks of pancreatic tumor biopsy. Department of Health and Human Services (HHS) regulations at 45 CFR 46.103(b)(4)(iii) require that the IRB review and approve all proposed changes in a research activity, during the period for which IRB approval has already been given, prior to initiation of such changes, except when necessary to eliminate apparent immediate hazards to the subjects. We note that we made the same determination for subject 113 in our letter of February 25, 2008. We determine that the enrollment of subjects 113 and 129 did not meet all eligibility criteria and represented a change in the research activity that was implemented without IRB approval.

We would like to summarize and clarify previous determinations that we have made regarding this case:

(2) We noted in our February 25, 2008 letter that Columbia University Medical Center (CUMC) found that for 40 of 62 subjects it appeared that informed consent was not documented with a signed written consent form prior to the initiation of research activities involving human subjects (e.g., receipt and analysis of identifiable private information and pathology tissue specimens, or completion of rating forms or patient diary entries), although it was documented prior to the subjects undergoing other research interventions dictated by the protocol. HHS regulations at 45 CFR 46.117(a) require that informed consent be documented by use of a written consent form approved by the IRB and that is signed by the subject or the subject's legally authorized representative, unless the IRB waives this requirement. We determined that the informed consent for the 40 of 62 subjects referenced by CUMC was not documented prior to the start of research activities, nor was the requirement for documentation waived by the CUMC IRB for subjects in this study. Included in this count of 40 subjects were subjects 131 and 133 for whom there was an allegation that a consent form had never been signed. The complainant alleged that this failure to ever having the subject sign a consent form had been documented in a meeting with the National Cancer Institute (NCI) on March 20, 2006. The NCI minutes for this meeting stated,

> "Number of subjects in the enzyme arm and missing consent forms:
> The Columbia staff investigated this issue. Two consent forms from subjects entered in the enzyme arm are missing. Their follow-up into this issue revealed that there are notes in both subjects' medical charts indicating that they were consented and in at least one of these cases, it is recalled that the patient requested to take the consent form with them and planned to return it. It appears that both of these patients 'walked off' with their forms. The IRB was informed of this and as both charts note that subjects were consented, the IRB left it up to the investigators to decide about inclusion of the data. The investigators conducted statistical analyses both with and without these two subjects and there is no effect on statistical conclusions."

We therefore can not prove the allegation that consent forms were never signed by subjects 131 and 133; however, we maintain our original determination that both of these subjects were among the 40 of 62 subjects engaged in research activities prior to the documentation of their signed informed consent in violation of HHS regulations at 45 CFR 46.117(a).

Corrective Action: We note that the CUMC IRB met with the principal investigator and he has acknowledged the non-compliance with the requirements of 45 CFR part 46 in this case with regard to the timing of the documentation of informed consent for 40 of 62 subjects. We also note that the principal investigator has committed to seeking documented informed consent prior to the initiation of any research activities or IRB review and approval for waiver of the requirements for documenting informed consent as appropriate under 45 CFR 46.117 in the future. We note that CUMC has cooperated fully with our evaluation of this matter.

We acknowledge that CUMC has instituted a comprehensive educational training program for ethical conduct of human-subjects research. We also acknowledge the CUMC IRB collaboration with both OHRP and private resources to further develop content for education training materials.

We find that the education programs described in your April 4, 2008 response adequately address the above determinations and are appropriate under the CUMC FWA.

(3) The complainant alleged that subject 133 was enrolled in the enzyme arm of the study beyond the allowable 8-week post-biopsy period stipulated in the IRB-approved protocol, in violation of HHS regulations at 45 CFR 46.103(b)(4)(iii). The information submitted to us indicates that subject 133 was classified as not enrolled. It appears that the principal investigator did obtain identifiable private information about subject 133 prior to providing documented informed consent as stated in (2) above; however, we found no evidence proving that subject 133 was improperly enrolled in the enzyme treatment research arm of the protocol beyond the 8-week period following the subject's diagnostic biopsy as was alleged. We therefore determine that there is no proven violation of HHS regulations at 45 CFR 46.103(b)(4)(iii) regarding this allegation.

(4) The complainant alleged that a minimum of 72 subjects were to be enrolled under the IRB-approved protocol, but that the study was terminated with only 62 enrolled subjects, in violation of HHS regulations at 45 CFR 46.103(b)(4)(iii). CUMC reported that the Data Safety and Monitoring Committee (DSMC) for this protocol recommended that the study be terminated before it reached its full enrollment of 72 subjects. At its September 30, 2005 meeting, the DSMC recommended that the study be terminated due to predetermined stopping criteria. This information was submitted to the CUMC IRB on October 17, 2005, and the study termination was approved by the IRB. Termination of the study in response to the DSMC recommendation was appropriate. We therefore determine that there is no proven violation of HHS regulations at 45 CFR 46.103(b)(4)(iii) regarding this allegation.

(5) The complainant alleged that while patients who could not eat adequately at the time of enrollment were to be excluded under the IRB-approved protocol, study subjects 103, 114, 118, 121, 127, 131, 132, and 147 were enrolled even though they could not eat adequately at the time of enrollment, in violation of HHS regulations at 45 CFR 46.103(b)(4)(iii). CUMC provided excerpts and copies from research medical records that stated that "appetite" or "eating" was adequate for these subjects at the time of enrollment. We therefore determine that there is no proven violation of HHS regulations at 45 CFR 46. 103(b)(4)(iii) regarding this allegation.

(6) The complainant alleged that while patients who lived alone were to be excluded under the IRB-approved protocol, subject 111 was enrolled even though she lived alone, in violation of HHS regulations at 45 CFR 46.103(b)(4)(iii). Review of the study record found that the subject disclosed that she lived with her son at study entry. Subject 111's self-assessment (Functional Assessment of Chronic Illness Therapy for Pancreatic Cancer) questionnaire rated her perception of emotional support from her family with the highest mark. Ten days prior to her death a research chart note stated that her social support had not been what she had indicated at the time of her entry into the study. At the same time period however, there were other records of conversations with the subject's son and daughter regarding the subject's medications and preparation for hospice care. We therefore determine that there is no proven violation of HHS regulations at 45 CFR 46.103(b)(4)(iii) regarding this allegation.

(7) The complainant alleged that while patients with significant histories of psychiatric illness were to be excluded under the IRB-approved protocol, subjects with significant histories of psychiatric illnesses were included in the study, in violation of HHS regulations at 45 CFR 46.103(b)(4)(iii). We note that the protocol exclusion criteria stated that a subject may be included if they have "No serious medical or psychiatric illness preventing informed consent

or intensive treatment (e.g. serious infection)." Based on our review of the provided material, it appeared that subjects with previous histories of psychiatric illnesses were properly evaluated for their ability to cooperate with the protocol and provide informed consent. We therefore determine that there is no proven violation of HHS regulations at 45 CFR 46.103(b)(4)(iii) regarding this allegation.

As a result, there should be no need for further involvement of OHRP in this matter. Of course, we must be notified should new information be identified which might alter this determination.

We appreciate 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,

Paul J. Andreason, M.D.
CAPT, USPHS
Compliance Oversight Coordinator
Division of Compliance Oversight

cc: Mr. George Gasparis, Executive Director, Human Subjects Protections Program, CUMC
Dr. Andrew Wit, Chair IRB #1, CUMC
Dr. Neil Schluger, Chair IRB #3, CUMC
Dr. John Chabot, CUMC
Dr. Sherry Mills, NIH
Mr. Joseph Ellis, NIH