DEPARTMENT OF HEALTH & HUMAN SERVICES

Office of the Secretary
Office of Public Health and Science

Office for Human Research Protections
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March 30, 2005

Michael M. Gottesman, M.D.
Deputy Director for Intramural Research
National Institutes of Health
Building 1, Room 114
Bethesda, MD 20892

RE: Human Research Subject Protections Under Federalwide Assurance (FWA) 5897

Research Project:	**A Phase I Study of an Oral Histone Deacetylase Inhibitor, MS-275, in Refractory Solid Tumors and Lymphomas**
NIH Project #:	**01-C-0124**
Intramural Institute:	**National Cancer Institute (NCI)**
PI:	**Edward Sausville, M.D.**
Research Project:	**A Phase I Study of an Oral Perifosine with Different Loading Schedules in Patients with Refractory Neoplasms**
NIH Project #:	**99-C-0043**
Intramural Institute:	**National Cancer Institute (NCI)**
PI:	**Edward Sausville, M.D.**
Research Project:	**Amifostine as a Rectal Protector During Beam Radiotherapy for Prostate Cancer: A Phase II Study**
NIH Project #:	**02-C-0215**
Intramural Institute:	**National Cancer Institute (NCI)**
PI:	**C. Norman Coleman, M.D.**
Research Project:	**A Phase II Study of MR-Guided High Dose Rate Brachytherapy Before and After External Beam Radiotherapy in Patients with Prostate Cancer**
NIH Project #:	**02-C-0207**
Intramural Institute:	**National Cancer Institute (NCI)**
PI:	**Kevin A. Camphausen, M.D.**
Research Project:	**A Pilot Study of Pirfenidone for the Treatment of Radiation-Induced Fibrosis**
NIH Project #:	**01-C-0143**

Intramural Institute: **National Cancer Institute (NCI)**
PI: **Rosemary Altemus, M.D.**

Research Project: **Genetic Characterization of Movement Disorders**
Intramural Institute: **National Institute on Aging (NIA)**
NIH Project #: **2003-081**
PI: **John Hardy, Ph.D.**

Dear Dr. Gottesman:

The Office for Human Research Protections (OHRP) has reviewed the National Institute of Health's (NIH) May 14, 2004 report evaluating allegations of noncompliance with Department of Health and Human Services (HHS) regulations for the protection of human research subjects (45 CFR part 46) involving the above- referenced research.

Based upon its review, OHRP makes the following determinations regarding the protection of human subjects in this research:

(1) HHS regulations at 45 CFR 46.103(b)(4)(iii) require investigators to obtain institutional review board (IRB) approval before initiating changes in an approved research activity, except when change is necessary to eliminate apparent immediate hazards to subjects.

(a) Regarding allegations that investigators enrolled subjects who did not meet the inclusion criteria for the respective studies, in violation of 45 CFR 46.103(b)(4)(iii), OHRP finds the following:

(i) NCI determined that all subjects enrolled in study 99-C-0043 met eligibility criteria at the time of enrollment.

(ii) Regarding NIA study 2003-081/WIRB20020788, OHRP notes NIA's finding that six subjects, including five individuals under the age of eighteen who were relatives of probands with movement disorders and whose blood was drawn for genotyping, did not meet eligibility criteria. OHRP finds that the subject population for the study was specified as "all participants over age 18 and their families with confirmed or suspected movement disorder diagnosis."

OHRP acknowledges that NIA investigators destroyed blood samples and records for the six subjects who NIA determined were ineligible for study 2003-081/WIRB20020788. OHRP notes that HHS regulations at 45 CFR 46.115(b) state that records relating to research which is conducted shall be retained for at least three years after completion of the research.

Required Action: By April 10, 2005, please provide OHRP with a corrective

action plan to help ensure that no investigator initiates changes in an approved research activity prior to obtaining IRB approval.

(b) Regarding allegations that amendments to ROB study 01-C-0143 approved by the IRB were deleted without IRB approval, OHRP acknowledges NCI's finding that three additions made by protocol amendment A submitted to the IRB on July 19, 2001, were not incorporated into subsequent versions of the protocol. OHRP also acknowledges NCI's finding that ROB procedures for ensuring that IRB-approved amendments were incorporated into subsequent versions of protocols were not adequate.

Corrective Action: The ROB instituted a computerized Novell computer system on which all investigators are required to maintain updated versions of protocols.

(2) HHS regulations at 45 CFR 46.115(b) require the preparation and maintenance for at least three years of records pertaining to research which is conducted. Regarding allegations that investigators for NCI study 2003-081 maintained inaccurate or incomplete records of subject information, OHRP acknowledges NIA's finding that informed consent documentation for seventeen subjects was deficient in that: (a) six charts did not contain all pages of the consent form; (b) two charts contained a photocopy of the consent form, not the original; and (c) eight charts contained consent forms that were not properly signed.

Corrective Action: OHRP acknowledges that NIA excluded from its study data all information from the records of the seventeen subjects whose charts did not include appropriate consent documentation. OHRP further acknowledges that NIA destroyed the records for these seventeen subjects, and notes that HHS regulations at 45 CFR 46.115(b) state that records relating to research which is conducted shall be retained for at least three years after completion of the research.

OHRP notes that NIA instituted protocol tracking procedures for informed consent review, including central protocol registry in the NIA protocol office and the use of data entry forms to ensure accuracy.

(3) HHS regulations at 45 CFR 46.111(a)(7) require the IRB to determine, in order to approve research, that there are adequate provisions to protect subject privacy and to maintain the confidentiality of data. Regarding allegations that electronic data relating to NCI study 2003-081 were accessible through an unsecured database, OHRP finds that these allegations have not been substantiated.

OHRP appreciates NIH's continued commitment to the protection of human research subjects. Please feel free to contact me if you have any questions.

Sincerely,

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

cc: Dr. Elias Zerhouni, Director, NIH
Dr. Richard Hodes, Director, NIA
Dr. Andrew von Eschenbach, Director, NCI
Dr. Alan L. Sandler, OHSR, NIH
Ms. Joan Mauer, CTEP, NCI
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