



DEPARTMENT OF HEALTH & HUMAN SERVICES

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August 14, 2012

Stephen R. Forrest, Ph.D.  
Vice President of Research  
University of Michigan  
Office of Vice President of Research  
4080 Fleming Building  
Ann Arbor, MI 48109-1340

**RE: Human Research Subject Protections Under Federalwide Assurance (FWA)- 4969**

Dear Dr. Forrest:

Thank you for your July 10, 2012 report in response to our May 31, 2012 request for information related to our evaluation of the University of Michigan (UM) system for protecting human research subjects as part of our program to evaluate human subjects protection programs of institutions that receive Department of Health and Human Services (HHS) support for research.

(A) Based on our review of your response, we make the following determinations:

- 1) We have determined that many of the informed consent documents provided in your response do not appear to include all the pertinent alternatives to participation in the research, as required by HHS regulations at 45 CFR 46.46116(a)(4) which require that when seeking informed consent specific information shall be provided to each subject, including a disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject. Specifically, we note that the informed consent documents for the following protocols did not include appropriate information regarding the option of obtaining the research intervention outside of the research:
  - a. HUM00000392: Micronutrient prevention of noise-induced hearing loss at the Spanish (NATO) Air Force Base and cutlery stamping factories of Albacete.
  - b. HUM00000408: The Effect of Chronic Macrolide Administration on the Frequency and Severity of COPD Exacerbations.
  - c. HUM00001093: Sublobar resection versus Sublobar resection plus brachytherapy.

- d. HUM00004369: A Multi-center Study of the Safety and Efficacy of N-acetylcysteine in the Treatment of Acute Liver Failure Not Caused by Acetaminophen in Children.
- e. HUM00004684: Does EPA or DHA prevent depressive symptoms in pregnancy and postpartum?.
- f. HUM00007923: A tailored behavioral intervention to improve neuropathy and mobility in older adults with early diabetes.
- g. HUM00012280: Oral Insulin for Prevention of Diabetes in Relatives at Risk for Type 1 Diabetes Mellitus.
- h. HUM00033520: Pilot Study of the Safety, Feasibility, and Potential Efficacy of Continuous Glucose Monitoring and Insulin Pump Therapy in Diabetic Gastroparesis (GLUMIT-DG).
- i. HUM00015709: UMCC 2007.123 Using FDG-PET Acquired During the Course of Radiation Therapy to Individualize Adaptive Radiation Dose Escalation in Patients with Non-Small Cell Lung Cancer.
- j. HUM10107-- Brain and Behavior Depending on Timing of Iron Deficiency in Human Infants.
- k. 1998-0210 (HUM00041883): Phase III Trial of Radiation Therapy With or Without Casodex in Patients With PSA Elevation Following Radical Prostatectomy For Pt3n0 Carcinoma Of The Prostate.

Your response stated that some of the studies were conducted under an FDA IND, and it would be inappropriate to offer this experimental therapy outside of the study and that the consent forms for some of these studies did not include the investigational intervention as it is not part of standard of care. HHS regulatory requirements at 45 CFR 46.116(a)(4) do not specify that only information about standard of care interventions must be provided to subjects, but must include a disclosure of appropriate alternative procedures or courses of treatment, if any, that *might* be advantageous to the subject. Your response also stated that offering as an option the use of some over the counter interventions could be viewed as encouraging self-medication without medical supervision, which could potentially be harmful, or that it would be inappropriate to offer an unproven therapy as a treatment option outside of the study. We note that the forms could have advised subjects to obtain such treatments only under medical supervision, if indeed, for the particular treatment in question, such supervision would be appropriate.

- 2) We determine that the consent form provided for a study indicate that subjects may be coerced into participating in open-ended, future research involving their biospecimens, in contravention of the regulatory requirements at 45 CFR 46.116. We note the following in this specific protocol: HUM00033520: Pilot Study of the Safety, Feasibility, and Potential Efficacy of Continuous Glucose Monitoring and Insulin Pump Therapy in Diabetic Gastroparesis (GLUMIT-DG)
  - Page 4: "Your samples and data will be used by the researchers carrying out this study, but they also may be used by other researchers, both during the study and after it ends. Your samples and data will be stored indefinitely."

--Page 12: "If you do not agree to have your samples and data sent to the Repositories, you may not participate in this study." Subjects cannot participate in this research study without agreeing to participate in future, non-specified research studies.

Your response notes that standard of care therapy was not withheld from potential subjects if they did not participate; there were no urgent timelines placed upon potential subjects in which to make a decision; and agreeing to participate in the biobanking portion of the study did not expose the potential subject to any greater risk than the non-biobanking portion of the study since no genetic testing is planned. However, we note that the study did hold out the prospect of direct benefit to the subjects which may be difficult for them to obtain without their agreement to participate in the biobanking portion of the study. Thus, they are being denied the right they have to participate in the study "alone," without participating in the unrelated open-ended future biospecimen research. The level of risks presented by biospecimen research is not relevant to this issue. Even if such research is very low risk, subjects, just because they are enrolling in a particular clinical trial, do not generally give up their autonomy regarding deciding whether their identifiable biospecimens can be used for wholly open-ended and unspecified future research. (See [http://www.hhs.gov/ohrp/detrm\\_lettrs/YR08/apr08b.pdf](http://www.hhs.gov/ohrp/detrm_lettrs/YR08/apr08b.pdf) for a prior determination letter regarding this issue)

(B) [Redacted]

Please provide us with responses to the above determinations, questions and concerns by September 21, 2012, including a corrective action plan for each of our determinations. Feel free to contact me if you would like guidance in developing a corrective action plan.

(C) At this time, we offer the following additional guidance:

- 1) We recommend that when approving consent forms, IRBs ensure that when the study is not expected to provide any direct benefits to subjects that the form clearly state this.” This will help ensure that consent forms accurately describe the benefits to the subject or others that may reasonably be expected from the research, as required by HHS regulatory requirements at 45 CFR 46.116(a)(3).
- 2) We note that the consent form for the study HUM00000392: Micronutrient prevention of noise-induced hearing loss at the Spanish (NATO) Air Force Base and cutlery stamping factories of Albacete contained numerous errors. We recommend that that they be corrected.

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

Sincerely,

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

cc:

Ms. Judith A. Nowack, Associate Vice President for Research, UM  
Dr. Alan Sugar M.D., IRB Chairperson IRBMED B-2 #6  
Dr. Richard Redman, IRB Chairperson IRB #2 & #3, UM  
Dr. Robert W. Hymes, IRB Chairperson Dearborn IRB #4, UM  
Dr. Marianne McGrath, IRB Chairperson Flint IRB #5, UM  
Dr. Michael Geisser, IRB Chairperson IRBMED A-2 #7 & #8 & C-1#9, UM  
  
Dr. Margaret Hamburg, Commissioner, Food and Drug Administration  
Dr. Joanne Less, Food and Drug Administration  
Dr. Sherry Mills, OER, National Institutes of Health  
Dr. Joe Ellis, OER, National Institutes of Health