DEPARTMENT OF HEALTH & HUMAN SERVICES

Office of the Secretary
Office of Public Health and Science

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February 17, 2009

Eugene Z. Oddone, M.D., MHSc
Vice Dean for Research, School of Medicine
Duke University Health System, Inc.
Davison Building, Dean's Suite, room 117A
DUMC Box 2820
Durham, NC 27705

RE: Human Research Protections Under Federalwide Assurance FWA-9025

Research Project: Child Neglect–Psychobiological Consequences (IRB # 4148)
Principal Investigator: Michael D. De Bellis, M.D.
HHS Protocol Number: 5R01MH061744-06

Research Project: PTSD & Childhood Sexual Abuse: Psychobiology (IRB #3928)
Principal Investigator: Michael D. De Bellis, M.D.
HHS Protocol Number: 5R01MH063407-04

Research Project: Adolescent Alcohol Abuse, PTSD and Hippocampal Development (IRB #4197)
Principal Investigator: Michael D. De Bellis, M.D.
HHS Protocol Number: 7R01AA012479

Dear Dr. Oddone:

Thank you for your August 11, 2008 report responding to our July 1, 2008 letter containing questions and concerns about allegations concerning the above research studies at Duke University Health System, Inc. ("Duke").

I. Determinations regarding the above-referenced research

Based on the information submitted, we make the following determinations:

(1) The complainant alleged that investigators initiated changes to the above-referenced research that were not necessary to eliminate apparent immediate hazards to the subjects without seeking the review and approval of the changes

from the Duke institutional review board (IRB), in contravention of the Department of Health and Human Services (HHS) regulations at 45 CFR 46.103(b)(4)(iii). Specifically, the complainant alleged that the following changes were initiated without being reviewed and approved by the Duke IRB:

(a) An investigator frequently changed diagnostic, symptom, and descriptive data on subjects;

(b) Parents were sometimes coerced to medicate their children against their will in order to proceed with neuropsychological testing; and

(c) The instrument upon which symptoms were recorded was modified from its original standardized form and was never validated against the original or any other instrument.

We determine that the above allegations could not be proven based on the following:

(a) Regarding the allegation that an investigator changed subject data, we note that Clinical Trials Quality Assurance (CTQA) auditors in Duke's Compliance Office reviewed a sample of subject files for the above research protocols, including Kiddie Schedule for Affective Disorders and Schizophrenia files which contained data modifications by the investigator that had not been previously reviewed and approved by the IRB. The CTQA auditors found that the investigator's modifications to subject data did not conform with Good Clinical Practice (GCP) standards, and appeared to represent correction of factual errors or updating based upon data acquired from additional evaluations or testing. Duke required that the principal investigator and others involved with the study complete GCP training approved by Duke's Institutional Official, and obtain training from IRB Education staff on IRB policies and procedures. We note that an investigator's correcting or updating information in subjects' medical records in a manner which does not conform to GCP standards does not constitute a violation of 45 CFR 46.103(b)(4)(iii).

(b) Regarding the allegation of parental coercion to medicate children against their will, CTQA auditors reviewed audio tapes of selected subject visits and subjects' clinical records, and interviewed 11 members of the research team. CTQA auditors found no evidence of prescriptions being issued or recommended for the purposes of medicating subjects prior to neuropsychological testing, and no evidence of coercion of parents of subjects.

(c) Regarding the allegation that an instrument was modified and never validated, the CTQA auditors found that the modification was appropriate in order to meet

specific study aims and was submitted to the IRB for review and approval prior to implementation.

(2) The complainant alleged that the investigators for the above-referenced research failed to ensure that the procedures for enrolling subjects minimized the possibility of coercion or undue influence, and failed to ensure that subjects may discontinue participation at any time without penalty or loss of benefits, as required by HHS regulations at 45 CFR 46.116. In specific, the complainant alleged that:

(a) An investigator was observed to spontaneously offer subjects extra money or gifts (not described to or authorized by the IRB) as an inducement to subjects to continue with the study when they expressed the wish to discontinue;

(b) In other instances, an investigator would insist that in order to receive a portion of their compensation, subjects had to engage in all tasks, including a graduate student's add-on project; and

(c) The investigator would force subjects to remain in the exam room to answer all questions about their abuse and their symptoms regardless of their level of distress, even if the subject was crying.

We determine that allegations (a) and (b) could not be proven based on the following:

Based upon a review of research expenditures and discussions with members of the research team, CTQA auditors found no evidence of payments made to subjects beyond those described in study protocols, or that subjects were coerced to complete all elements of interviews or engage in additional tasks for the purposes of a graduate student's project.

We note that under the consent forms approved by the Duke IRB for studies #3928 and #4197, subjects are compensated one amount for completing a full day of research testing, and a proportionately lower amount for partial completion of research tests. Under 45 CFR 46.116, while investigators may remind subjects that their continued participation will result in greater reimbursement under the terms of the research, investigators must minimize the possibility of coercion of subjects if subjects indicate the desire to discontinue research participation.

Regarding allegation (c), we determine, in accordance with findings of the CTQA audit, that an investigator did not permit a 10 year old subject to discontinue participation in the research without penalty or loss of benefits as required by HHS regulations at 45 CFR 46.116. A note in the subject's file stated that "the child was very upset that he

had to spend the day taking tests and stated that his mom told him he would only be there an hour and that she would take him to school afterwards." Clinical notes document that the clinician "did not think the child knew he would be missing school to do this." The CTQA audit found no indication that testing was stopped or postponed for this child. The audit also found that the research team did not have specific standard operating procedures in place for obtaining consent and assent or for discontinuing research participation upon subject request.

Corrective Action: All subject enrollment was suspended until the study team (a) received an off site 3-day course concerning the requirements for obtaining consent and assent and for discontinuing participation in research, and (b) developed study-specific standard operating procedures (SOPs) which were submitted to the IRB for review and approval. An independent subject advocate was required to observe the consent process for at least two subjects. These corrective actions, if implemented as described by Duke, should adequately address the above finding and would be appropriate under the Duke FWA. However, subsequent to Duke's investigation and implementation of the corrective action noted, we received a complaint alleging that these SOPs were never implemented and that research staff were not adequately trained regarding the new SOPs. Please clarify by March 2, 2009 what steps Duke has taken to ensure that investigators have developed and implemented the study-specific-SOPs.

II. Determinations regarding your institution's system for protecting human subjects

In addition to the matter complained about, we make the following determination:

The IRB policies and procedures provided with your August 11, 2008 satisfy the requirements of HHS regulations at 45 CFR 46.103(a) and 46.103(b)(4) and (5).

We appreciate Duke's continued commitment to the protection of human research subjects.

Sincerely,

Carol J. Weil
Division of Compliance Oversight

cc: Ms. Jody F. Power, Executive Director, DUHS IRB, Duke University Health System, Inc.
Dr. Joseph Farmer, Chair, IRBs #1 & #2, Duke University Health System
Dr. John Harrelson, Chair, IRBs #3 & #4, Duke University Health System
Dr. George Parkerson, Chair, IRBs #7 & #8, Duke University Health System
Dr. John Falletta, Chair, IRBs #5, #6 & #10, Duke University Health System
Dr. Michael D. De Bellis, Duke University Health System

Commissioner, FDA
Dr. Joanne Less, FDA
Dr. Sherry Mills, OER, NIH
Dr. Joe Ellis, OER, NIH