DEPARTMENT OF HEALTH & HUMAN SERVICES

Office of the Secretary
Office of Public Health and Science

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Eli L. Capilouto, M.D.
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RE: Human Research Subject Protections Under Federalwide Assurance (FWA) 5960

Dear Drs. Garrison and Capilouto:

As you know, the Office for Human Research Protections (OHRP) conducted an on-site evaluation of human subject protection procedures at the University of Alabama, Birmingham (UAB) on February 3-5, 2004. The evaluation was conducted by three OHRP staff members with the assistance of an expert consultant, and included meetings with institutional officials, the Chair and Vice Chair, members and administrative staff of the UAB Institutional Review Boards (IRB) #1 and #2, the members of the Human Studies Advisory Committee, and a limited number of principal investigators who submit protocols to the IRBs. OHRP reviewed IRB files for approximately 20 open protocols, and the minutes of IRB meetings held during 2003-2004.

In the course of the OHRP review, the IRB Chair and Vice Chair, IRB members, and IRB administrative staff displayed an enthusiastic and sincere concern for, and commitment to, the protection of human subjects, and stated that they view themselves as providing a valuable service to subjects and the research community. IRB procedures for review of research appear to be substantive and meaningful, and IRB

records appear to be complete and well organized. The IRB administrative staff were helpful and accommodating to OHRP during the site visit.
After its site visit, OHRP received a letter from UAB's Office of Counsel dated February 17, 2004, requesting reconsideration of preliminary concerns expressed by OHRP during the site visit regarding certain actions of the Acting Vice President for Research that may have undermined the ability of the IRB to exercise its authority in accordance with HHS regulations for the protection of human subjects and the UAB FWA. On February 19, 2004, OHRP met with both of you and two members of UAB's Office of Counsel by video conference to hear your oral presentation of issues presented in the February 17, 2004 letter.

OHRP Findings and Concerns Relative to Systemic Protections for Human Subjects

Based on its evaluation, OHRP makes the following determinations:

(1) HHS regulations at 45 CFR 46.103(a) and 46.103(b)(5) and the UAB FWA require that (i) any unanticipated problems involving risks to subjects or others, or any serious or continuing noncompliance with this policy or the requirements or determinations of the IRB; and (ii) any suspension or termination of IRB approval be promptly reported to the IRB, appropriate institutional officials, the department or agency head, and OHRP. Section 8(j) of the UAB IRB Policies and Procedures (Procedures) revised as of January 8, 2004 states: "The Acting Vice President for Research will assess all reports, IRB determinations, actions, and requests for assistance and provide for any institutional intervention necessary to facilitate the action of the IRBs." OHRP notes that section 8(k) of the UAB IRB Procedures also states: "the Acting Vice President for Research shall report the decision and actions of the IRB discussed in this section, to OHRP, other appropriate federal officials, the IRB, pertinent research personnel, the Provost, and other appropriate officials of UAB, keeping all aware of the importance of these matters."

OHRP finds that during the last 12 months, the UAB IRB suspended research studies entitled *Diagnosis and Treatment of Sleep Apnea in Treating High Thoracic and Cervical Spinal Cord Injury* (S981123006), *Nuclear Magnetic Resonance Spectroscopy in Epilepsy* (F910927011), and *GABA Concentrations in Healthy Adults Receiving Benzodiazepines* (F970501019) due to serious or continuing noncompliance with the requirements of the HHS regulations for the protection of human subjects and the UAB FWA. OHRP finds that with regard to these three research studies, the Acting Vice President for Research failed to promptly report these suspensions and serious or continued noncompliance in accordance with the above requirements, and specifically, failed to promptly report to OHRP.

(2) HHS regulations at 45 CFR 46.115(a) require that an institution, or when appropriate, an IRB, shall prepare and maintain documentation of IRB activities, including minutes of IRB meetings. Furthermore, HHS regulations at 45 CFR 46.115(a)(2) require that such minutes be in sufficient detail to show attendance at the meetings; actions taken by the IRB; the vote on these actions, including the number of members voting for, against, and abstaining; the basis for requiring changes in or disapproving research; and a written summary of the discussion of controverted issues and their resolution. OHRP finds that written minutes of UAB IRB meetings do not yet exist for a number of meetings held since the Spring of 2003.

(3) HHS regulations at 45 CFR 46.103(c) require that an institution's assurance of compliance with the regulations for the protection of human subjects shall be executed by an individual authorized to act for the institution and to assume on behalf of the institution the obligations imposed by the regulations.

Regarding Dr. Sadis Matalon, the acting Vice President for Research and the authorized Institutional Official who endorses the UAB FWA, OHRP notes the following:

(a) The UAB IRB (02) minutes of July 31, 2002 state the following:

(i) "In a memorandum from Ms. Moore (IRB Director), dated September 28, 2001, Dr. Matelon [*sic*] was informed that the protocol would expire on October 28, 2001, and if he did not receive IRB approval by October 28, 2001, all work on the protocol must cease. Today, Ms. Moore informed the Board that study activities for the protocol continued after October 28, 2001without IRB approval.... In addition, Dr. Matelon [*sic*] did not call the IRB Office in early October after receiving the renewal notice to clarify the situation. Also, Dr. Matelon [*sic*] did not promptly respond to repeated requests from the IRB for additional information. Based on the information described above, the IRB made the determination that Dr. Matelon [*sic*] was non-compliant with the IRB requests."

(ii) "The Board requested the Dr. Matelon [*sic*] be informed that non-compliance is a matter of concern for the IRB. Any further instances of non-compliance will be considered 'serious non-compliance.' Serious non-compliance will result in suspension from human subjects research for a period of time determined by the Board and will be reported to the appropriate University and Federal regulatory agencies as well as to the sponsor(s) for the research. (VOTE: For - 9, Against - 0, Abstain - 0)

"Ms. Moore also informed the Board that Dr. Matalon would be taking over the role of Dr. Joan Lorden, Associate Provost for Research, while she is serving as Dean-in-Residence at the National Science Foundation. *The Board was concerned about Dr. Matalon's placement in this position, considering his noncompliance and the tone and content of his communication with Ms. Moore* [emphasis added]. The Board expressed an interest in discussing this concern with Dr. Lorden. This item will also be discussed next week at the Board-01 meeting."

(b) As stated in item (1) above, the acting Vice President for Research failed to ensure that procedures were followed for prompt reporting of suspensions of IRB approval of research in accordance with HHS regulations at 45 CFR 46.103(a) and 46.103(b)(5), including prompt reporting to OHRP. Furthermore, as the authorized Institutional Official who endorses the UAB FWA, the acting Vice President for Research knew, or should have known, that failure to promptly

report such suspensions of IRB approval to OHRP represented noncompliance with the requirements of the HHS regulations for the protection of human subjects and the UAB FWA.

(c) The UAB IRB (02) minutes of April 23, 2003 state the following:

(i) "Dr. Sadis Matalon and Dr. Sam Tilden, for presentation of request from Dr. Guay-Woodford."

(ii) "Dr. Matalon, accompanied by Dr. Sam Tilden [UAB Compliance Officer], presented a request from Dr. Lisa Guay-Woodford to audit her protocols from July 1, 2002, which was the date of her last approval on the one deferred protocol ... in question. After considerable discussion, the Board decided that 1) it was important to assure that a precedent was not set where audits would be limited in scope; 2) the process of auditing was obstructed by the request from Dr. Matalon. The decision of the Board was to audit all three Guay-Woodford protocols back to their origin. This decision was approved by a vote of 7 for, 1 against and 2 abstentions. *In addition, the Board made a motion to express concern to Dr. Matalon that the request to the Board had in fact delayed the audit process and that intervention by the office of the provost had undermined the effectiveness of the Board* [emphasis added]. This motion passed with 8 votes for the motion, and 2 abstentions."

(d) Based on review of documents contained in the IRB files and discussions with the Acting Vice President for Research, the IRB Chair and Vice Chair, IRB members and IRB staff, OHRP notes that the Institutional Official (the Acting Vice President for Research) has interacted with the UAB IRBs on behalf of investigators who were suspended by the IRB from conducting human subjects research due to serious noncompliance. Indeed, the Institutional Official stated explicitly in an interview with the site-visit team that he felt that his role was to act as an advocate for investigators when disagreements arose between the IRB and investigators. OHRP notes that these interactions included (i) attending IRB meetings specifically as an advocate for investigators; (ii) negotiating alternative sanctions for investigators; and (iii) requesting limitations on the scope of an investigator audit by the IRB. In interviews with IRB members, OHRP noted that the presence of the Institutional Official at IRB meetings to personally appeal IRB administrative sanctions imposed for serious or continuing noncompliance was perceived as inappropriate, intimidating, and undermining the effectiveness of the IRB.

Based on all of the above, OHRP is particularly concerned that the acting Vice President for Research, as the authorized Institutional Official for UAB's FWA, has failed (a) to fulfill his obligations imposed by HHS regulations for the protection of human subjects and the UAB FWA, and (b) to support and facilitate the UAB IRBs' federally mandated authority and decisions.

(4) HHS regulations at 45 CFR 46.116(d) require that the IRB find and document four specific criteria when approving waiver or alteration of some or all of the required elements of informed consent. Based upon its review of the research study entitled *Treatment Preferences for Addiction in the Ukraine* (X030313007), OHRP is concerned that the IRB may have inappropriately waived the requirements for informed consent.

Action 1 - Required: By April 9, 2004, UAB must submit to OHRP a revised Part 7 of its FWA signed by a new Authorized Institutional Official. This official should reside at an administrative level above the Acting Vice President for Research.

Action 2 - Required: By April 9, 2004, UAB must submit to OHRP a satisfactory corrective action plan which addresses the findings and concerns stated above.

At this time, OHRP would like to offer the following guidance:

(5) OHRP reminds UAB that should the IRB approve research contingent upon subsequent modifications or clarifications without requiring additional review, OHRP recommends the following guidelines in such cases: (a) When the convened IRB requests substantive clarifications or modifications regarding the protocol or informed consent documents that are directly relevant to the determinations required by the IRB under HHS regulations at 45 CFR 46.111, IRB approval of the proposed research should be deferred, pending subsequent review by the convened IRB of responsive material. (b) Only when the convened IRB stipulates specific revisions requiring simple concurrence by the investigator may the IRB Chair, or another IRB member designated by the Chair, subsequently approve the revised research protocol on behalf of the IRB under an expedited review procedure.

(6) 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 notes that for the research study entitled *A Randomized Open-Label Phase I/II Study to Evaluate the Safety and Pharmacokinetics of Hepatitis C Immune Globulin (Human), Civacir in Liver Transplant Recipients* (F000831007), an informed consent document approved by the IRB appeared to include complex language that would not be understandable to all subjects. OHRP recommends that the informed consent language (especially explanation of the study's purpose, duration, experimental procedures, alternatives, risks, and benefits) be written in "lay language," i.e., language understandable to the people being ask to participate.

(7) The regulations require that informed consent information be presented "in language understandable to the subject" and, in most situations, that informed consent be documented in writing (see 45 CFR 46.116 and 46.117). Where informed consent is documented in accordance with HHS regulations at 45 CFR 46.117(b)(1), the written informed consent document should embody, in language understandable to the subject, all the elements necessary for legally effective informed consent. Subjects who do not speak English should be presented with an informed consent document written in a language

understandable to them (see OPRR Guidance November 9, 1995 at URL http://ohrp.osophs.dhhs.gov/humansubjects/guidance/ic-non-e.htm). OHRP encourages the use of this procedure whenever possible.

Alternatively, HHS regulations at 45 CFR 46.117(b)(2) permit oral presentation of informed consent information in conjunction with a short-form written informed consent document (stating that the elements of consent have been presented orally) and a written summary of what is presented orally. A witness to the oral presentation is required, and the subject must be given copies of the short-form document and the summary. When this procedure is used with subjects who do not speak English, (i) the oral presentation and the short-form written informed consent document should be in a language understandable to the subject; (ii) the IRB-approved English language informed consent document may serve as the summary; and (iii) the witness should be fluent in both English and the language of the subject.

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,

Robert J. Meyer
Compliance Oversight Coordinator
Division of Compliance Oversight

cc: Dr. Sadis Matalon, Acting Vice President for Research, UAB
Dr. Ferdinand Urthaler, IRB Chair, UAB
Dr. Albert Oberman, IRB Vice Chair, UAB
Ms. Sheila Moore, IRB Human Protections Administrator and Director, UAB
Commissioner, FDA
Dr. David Lepay, FDA
Dr. Bernard Schwetz, OHRP
Dr. Melody Lin, OHRP
Dr. Michael Carome, OHRP
Dr. Kristina Borror, OHRP
Ms. Shirley Hicks, OHRP
Dr. Irene Stith-Coleman, OHRP
Ms. Janice Walden, OHRP
Ms. Melinda Hill, OHRP