DEPARTMENT OF HEALTH & HUMAN SERVICES

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December 15, 2004

John R. Sladek, Jr., Ph.D.
Vice Chancellor for Research
University of Colorado Health Sciences Center
Office of the Chancellor
4200 East Ninth Avenue
Campus Box A095
Denver, Colorado 80262

RE: Human Research Subject Protections Under Federalwide Assurance (FWA) 5070

Research Project:	**The Joint Outcomes Study**
Principal Investigator:	**Marilyn Manco-Johnson, M.D.**
Protocol #:	**95-011**
Research Project:	**Myocardial Energy Substrate Utilization in Patients with Dilated Cardiomyopathy**
Principal Investigator:	**Eugene E. Wolfel, M.D.**
Protocol #:	**01-017**

Dear Dr. Sladek:

As you know, the Office for Human Research Protections (OHRP) conducted an on-site evaluation of the human subject protections system at the University of Colorado Health Sciences Center (UCHSC) from November 30 to December 2, 2004. The evaluation, conducted by five OHRP staff and with the assistance of three expert consultants, included meetings with senior institutional officials, the chairpersons of the Institutional Review Boards (IRBs), approximately 16 IRB members, IRB administrative staff, and approximately 14 research investigators. The evaluation involved the review of IRB files for more than 40 protocols, as well as the minutes of numerous IRB meetings since 2000.

In the course of the OHRP review, the IRB chairpersons, IRB members, and IRB administrative

staff displayed a sincere commitment to the protection of human subjects. Furthermore, the volume of research reviewed and the amount of time and effort devoted to IRB activities by the IRB chairpersons and staff indicate great dedication to the mission of the IRB. Investigators demonstrated a culture of respect for the IRB process. The IRB administrator and staff were very helpful and accommodating to OHRP during the site visit.

Findings

Based on the review of UCHSC's December 17, 2003, September 2, 2004, and November 11, 2004 letters, as well as interviews and materials reviewed during its site visit, OHRP makes the following determinations:

(1) Department of Health and Human Services (HHS) regulations at 45 CFR 46.101(b) delineate six specific categories of exempt human subjects research activities. OHRP finds that UCHSC applied exempt status to the following research activities that exceeded these categories: Protocol # 03-592; 04-0680; 04-0416; 04-0519; and 04-0498. OHRP recommends that documentation for all exemptions include citation of the specific category justifying the exemption.

Required Action: By January 15, 2005, please provide OHRP with a corrective action plan to address this finding, including a plan (i) to ensure that all studies determined to be exempt within the last year meet the exemption criteria and (ii) to obtain IRB review of studies which may have been exempted inappropriately.

(2) HHS regulations at 45 CFR 46.115(a) require that the institution prepare and maintain adequate documentation of IRB activities. In certain instances among the UCHSC IRB files examined by OHRP, it was difficult to reconstruct a complete history of all IRB actions related to the review and approval of the protocol. In some cases, OHRP could not determine what the IRB actually approved. For example, the IRB approved Protocol #03-225 with the assumption that the investigator would only enroll subjects who had previously failed conventional therapy, but the protocol file did not contain any documentation to confirm this inclusion criterion requirement. In addition, Protocol #03-649 was suspended by the IRB based on a concern that the treatment arm might now be inferior to standard treatment; however, the protocol was restarted without any documentation of how the IRB's concern was resolved.

Required Action: By January 15, 2005, please provide OHRP with a corrective action plan to address this finding.

(3) HHS regulations at 45 CFR 46.111(a)(1) require, in part, that risks to subjects be minimized. OHRP notes that UCHSC's September 2, 2004 report regarding Protocol #01-017 states the following:

(a) "It is clear that the subject did experience harm from the research, and the

> extent of the harm was not fully realized until a substantial amount of time had elapsed."
>
> (b) "The work/peer relationship that existed between the investigator and the subject may have inhibited the subject from communicating directly with the investigator about her discomfort."
>
> (c) "COMIRB [Colorado Multiple Institutional Review Board] finds that the investigator did not adequately address the subject's concerns when he failed to provide adequate follow-up to the adverse event."

OHRP finds that the principal investigator for Protocol # 01-017 failed to minimize risks to subjects.

Corrective Action: OHRP acknowledges that the principal investigator will hire a qualified research coordinator to assist with protocol management. The principal investigator has added an unaffiliated cardiologist to the Data Safety Monitoring Board (DSMB) to improve the objectivity of the safety monitoring. The principal investigator will no longer recruit subjects into high-risk protocols where a working relationship exists with him or another co-investigator. UCHSC has also required that the principal investigator conduct a self-audit of his open studies for any unreported adverse events, and that Protocol #01-017 be placed on a six-month continuing review cycle. Furthermore, the UCHSC General Clinical Research Center has created an audit plan to ensure that all studies utilizing femoral artery catheterization include the appropriate risks in the informed consent documents. OHRP finds that these corrective actions adequately address the above finding and are appropriate under the UCHSC FWA.

(4) HHS regulations at 45 CFR 46.116(a)(2) require that informed consent include a description of the reasonably foreseeable risks and discomforts of the research. OHRP notes that UCHSC's September 2, 2004 report regarding Protocol # 01-017 states, "UCHSC agrees that the consent form failed to provide information about the risk of peripheral nerve damage in the consent form." Accordingly, OHRP finds that the informed consent document for Protocol #01-017 failed to provide an adequate description of the reasonably foreseeable risks and discomforts of the research.

Corrective Action: OHRP notes that UCHSC Protocol #01-017 was suspended and the informed consent document for this protocol and all others utilizing femoral artery catheterization were modified to include the risk of permanent nerve damage. OHRP finds that these corrective actions adequately address the above finding and are appropriate under the UCHSC FWA.

(5) HHS regulations at 45 CFR 46.111(a)(6) require that, when appropriate, the research plan makes adequate provision for monitoring the data collected to ensure the safety of subjects. OHRP notes that an investigative report dated June 23, 2004 by UCHSC

regarding Protocol # 95-011 stated the following:

> (a) "In her November 13, 2003, written response to the complainant's allegations, the respondent admitted that she did review the 2002 and 2003 DSMB reports because she believed the reports prepared by the complainant were incomplete."
>
> (b) "In her November 13, 2003, written response to the complainant's allegations, the respondent admitted that she did ask [name omitted] to exclude certain data analyses from the 2002 report to the DSMB. She wrote that her reason for doing so was that she believed that only analyses that the DSMB had requested should be included in the report to the DSMB and that the DSMB was primarily concerned with data completeness and quality rather than statistical analysis of the data."

OHRP also notes that UCHSC's November 11, 2004 letter states:

> (a) "The CRE [Committee for Research Ethics] found that [the principal investigator] reviewed statistical reports before they were to be submitted to the DSMB."
>
> (b) "The CRE was advised by witnesses that [the principal investigator] had received instruction that she was not to view the data and was to be blinded."
>
> (c) "UCHSC agrees that the principal investigator failed to ensure that the research had adequate provision for monitoring the data collection to ensure the safety of subjects."

OHRP finds that the principal investigator failed to ensure that the research had adequate provisions for monitoring the data collection to ensure the safety of subjects.

(6) It was alleged that the principal investigator for Protocol # 95-011 failed to ensure that risks to subjects were minimized by using procedures which are consistent with sound research design, in accordance with HHS regulations at 45 CFR 46.111(a)(1). In specific, it was alleged that the principal investigator discussed outcomes of enrolled subjects with the reviewing radiologist, thereby biasing the judgment of this independent evaluator. OHRP finds that this allegation could not be substantiated.

(7) HHS regulations at 45 CFR 46.103(b) and 46.109(a) and the UCHSC FWA require that the UCHSC IRB review and approve all nonexempt human subject research covered by the UCHSC FWA. OHRP notes the following:

> (a) Regarding an abstract presented to the American Society for Pediatric Hematology/Oncology, a November 3, 2004 letter from COMIRB Panel C to the principal investigator states, "[The principal investigator] admitted she conducted

a retrospective study without COMIRB approval which is a violation of 45 CFR 46.103(b)."

(b) Regarding an abstract presented in *Pediatric Research* in 2001, a November 3, 2004 letter from COMIRB Panel C to the principal investigator states, "[The principal investigator] admits that this was a retrospective study conducted without COMIRB approval at the time the abstract was published. [The principal investigator] states she recognized that error and submitted protocol 02-257 for approval prior to additional data analysis and approval. That protocol was approved by COMIRB on May 27, 2002."

OHRP finds that the investigator conducted human subjects research without IRB review and approval. OHRP acknowledges that UCHSC has suspended or designated a new principal investigator for all of this investigator's protocols.

Required Action: By January 15, 2004, please provide OHRP with a corrective action plan to address findings (5) and (7). The corrective action plan should include systemic steps that will be taken to ensure that all nonexempt human subjects research conducted under the UCHSC FWA is prospectively reviewed and approved by an IRB designated under the UCHSC FWA.

(8) OHRP finds that the UCHSC IRB occasionally approves research contingent upon substantive modifications or clarifications without requiring additional review by the convened IRB. 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.

For example, the UCHSC IRB appears to have approved Protocols # 04-0410 and 04-0307 without having (i) information regarding the provisions to protect the privacy of subjects and maintain the confidentiality of data; (ii) information regarding data and power analysis, although the IRB requested this information; and (iii) additional safeguards to protect the rights and welfare of subjects who are likely to be vulnerable. In addition, the UCHSC IRB approved Protocol # 00-221 contingent upon clarification of how consent would be obtained, how comprehension would be assessed, and how confidentiality would be maintained.

(9) HHS regulations at 45 CFR 46.103(a) and (b)(5) require prompt reporting to the IRB,

appropriate institutional officials, the Department or Agency head and OHRP of (i) any unanticipated problems involving risks to subjects or any serious or continuing noncompliance and (ii) any suspension or termination of IRB approval. OHRP finds that femoral nerve damage noted in a healthy subject enrolled in Protocol # 01-017 represented an unanticipated problem involving risks to subjects, and that this problem was not promptly reported to the UCHSC IRB or OHRP. Furthermore, the unanticipated death of a subject enrolled in a gene-transfer trial was not reported to OHRP. In addition, OHRP finds that Protocols # 01-017 and # 03-649 were suspended by the UCHSC IRB, and these suspensions were not reported to OHRP.

(10) OHRP finds that certain informed consent documents reviewed and approved by the UCHSC IRB failed to include an adequate description of the reasonably foreseeable risks and discomforts, as required by HHS regulations at 45 CFR 46.116 (a). For example:

(a) The informed consent document for Protocol #00-153 failed to adequately describe which risks resulted from the research, as opposed to those resulting from clinical care.

(b) The informed consent document for Protocol #03-225 failed to describe the risks associated with being assigned to the placebo arm of the trial.

(c) The informed consent document for Protocol #04-0494 failed to describe the risks associated with the combined administration of the test agents in populations with seizure disorders and hypertension.

Required Action: By January 15, 2004, please provide OHRP with a corrective action plan to address findings (8) through (10).

Questions and Concerns

At this time, OHRP has the following additional questions and concerns:

(11) [Redacted]

(12) [Redacted]

(13) [Redacted]

(14) [Redacted]

(15) [Redacted]

(16) [Redacted]

Please submit your response to the above questions and concerns by January 15, 2005.

Guidance

At this time, OHRP offers the following additional guidance:

(1) HHS 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 dated November 9, 1995 at http://ohrp.osophs.dhhs.gov/humansubjects/guidance/ic-non-e.htm). OHRP strongly 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.

(2) OHRP recommends that the IRB develop policies that address how the IRB will address allegations of noncompliance with the requirements of 45 CFR part 46.

(3) OHRP recommends that documentation for initial and continuing reviews conducted under an expedited review procedure include (a) the specific permissible categories (see 63 FR 60364-60367 at http://ohrp.osophs.dhhs.gov/humansubjects/guidance/expedited98.htm) justifying the expedited review and (b) documentation of the review and action taken by the IRB chairperson or designated reviewer, and any findings required under the HHS regulations.

(4) OHRP recommends that UCHSC develop a program to educate investigators that any requests for determination of exemptions from the regulations should be reviewed and approved prior to initiation of the research. OHRP notes that the protocol entitled “Chiari Networks are a Common Finding in Patients Referred for Percutaneous Closure of Patent Foramen Ovale” was completed prior to a request for an IRB exemption determination.

(5) The following criteria (see 48 FR 9266-9270) must be satisfied to invoke the exemption for research and demonstration projects examining "public benefit or service programs" as specified under HHS regulations at 45 CFR 46.101(b)(5): (a) the program under study must deliver a public benefit (e.g., financial or medical benefits as provided under the Social Security Act) or service (e.g., social, supportive, or nutrition services as provided under the Older Americans Act); (b) the research or demonstration project must be conducted pursuant to specific federal statutory authority; (c) there must be no statutory requirement that the project be reviewed by an Institutional Review Board (IRB); (d) the project must not involve significant physical invasions or intrusions upon the privacy of participants (see OPRR Guidance dated December 1997 at http://ohrp.osophs.dhhs.gov/humansubjects/guidance/exmpt-pb.htm). This exemption is

for projects conducted by or subject to the approval of federal agencies, and is most appropriately invoked with the authorization or concurrence of the funding agency.

(6) OHRP recommends that UCHSC make efforts to increase the diversity of the IRB membership, including consideration of race, gender, and cultural backgrounds and sensitivity to such issues as community attitudes, to promote respect for its advice and counsel in safeguarding the rights and welfare of human subjects, as required under HHS regulations at 45 CFR 46.107(a).

(7) HHS regulations at 45 CFR 46.103(d) require that the adequacy of IRBs be evaluated in light of the anticipated scope of the institution's research activities, the types of subject populations likely to be involved, and the size and complexity of the institution. The regulations further require at 45 CFR 46.107(a) that IRBs be (a) sufficiently qualified through the diversity of the members, including consideration of race, gender, and cultural backgrounds and sensitivity to such issues as community attitudes, to promote respect for its advice and counsel; and (b) able to ascertain the acceptability of proposed research in terms of institutional commitments and regulations, applicable law, and standards of professional conduct and practice. Institutions have a profound responsibility to ensure that all IRBs designated under an OHRP-approved Assurance possess sufficient knowledge of the local research context to satisfy these requirements.

For detailed guidance on appropriate mechanisms for ensuring that the IRB has adequate knowledge of the local research context, please see http://ohrp.osophs.dhhs.gov/humansubjects/guidance/local.htm.

(8) HHS regulations at 45 CFR 46.116(d) require that the IRB make and document four findings when approving a consent procedure which does not include, or which alters, some or all of the required elements of informed consent or when waiving the requirement to obtain informed consent. OHRP recommends that when approving such a waiver for research reviewed by the convened IRB, these findings be documented in the minutes of the IRB meeting, including *protocol-specific* information justifying each IRB finding.

Similarly, where HHS regulations require specific findings on the part of the IRB, such as (a) approving a procedure which waives the requirement for obtaining a signed consent form [see 45 CFR 46.117(c)]; (b) approving research involving pregnant women, human fetuses, or neonates (see 45 CFR 46.204-207); (c) approving research involving prisoners (see 45 CFR 46.305-306); the IRB should document such findings. OHRP recommends that for research approved by the convened IRB, all required findings be fully documented in the minutes of the IRB meeting, including *protocol-specific* information justifying each IRB finding.

For research reviewed under an expedited review procedure, these findings should be documented by the IRB chairperson or other designated reviewer elsewhere in the IRB record.

(9) The UCHSC IRB written procedures state, "The COMIRB roster identifies the full members for whom each alternate member may substitute." OHRP recommends that the IRB follow its own written procedures regarding the formal designation of alternate members.

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,

Patrick J. McNeilly, Ph.D.
Compliance Oversight Coordinator
Division of Compliance Oversight

cc: Ms. Lisa Jensen, Director, COMIRB
Mr. Ken Easterday, Chair, IRB Panel A, UCHSC
Dr. Norman Stoller, Chair, IRB Panel B, UCHSC
Dr. Doug Ford, Chair, IRB Panel C, UCHSC
Mr. Stephen Bartlett, Chair, IRB Panel D, UCHSC
Dr. Marilyn Manco-Johnson, UCHSC
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