DEPARTMENT OF HEALTH & HUMAN SERVICES
Office of the Secretary
Office of Public Health and Science

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March 17, 2009

Arnold W. Strauss, M.D.
Chief Medical Officer
Cincinnati Children's Hospital Medical Center
3333 Burnet Avenue
Cincinnati, OH 45229

RE: Human Research Protections Under Federalwide Assurance FWA-459

Research Project: **A Prospective Randomized Multicenter Trial of Amnioreduction vs Selective Fetoscopic Laser for the Treatment of Severe Twin-Twin Transfusion Syndrome**

Principal Investigator: **Timothy M. Crombleholme, M.D.**

HHS Protocol Number: **R01HD41149**

Dear Dr. Strauss:

Thank you for your February 6, 2008 letter in response to our December 21, 2007 request that the Cincinnati Children's Hospital Medical Center (CCHMC) evaluate allegations of noncompliance with Department of Health and Human Services (HHS) regulations for the protection of human research subjects (45 CFR part 46). Based on the information submitted, we make the following determinations:

A. Determinations Regarding the Above-Referenced Research

The complainant alleged that the risks to subjects who participated in the research were not minimized, and that the risks were not reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that was reasonably expected to result, in contravention of HHS regulations at 45 CFR 46.111(a)(1) and (2). In specific:

(1) The complainant alleged that none of the surgeons performing the selective fetoscopic laser photocoagulation (SFLP) had previously demonstrated competence in this procedure.

We find that this allegation could not be proven. According to CCHMC, the experience of the Children's Hospital of Philadelphia (CHOP) and University of California, San Francisco

(UCSF) investigators were included in the original grant application and reviewed by a National Institutes of Health (NIH) study section in February 2001. CCHMC continued that in December 2003, the principal investigator for the research, Dr. Crombleholme, relocated from CHOP to CCHMC. As a result, on December 23, 2003, Dr. Crombleholme submitted the above-referenced study to the CCHMC institutional review board (IRB) for review and approval. As part of the CCHMC IRB review, Dr. Crombleholme was asked to (i) provide available safety data from the patients already enrolled in the trial at CHOP and UCSF; and (ii) clarify who would perform the study interventions at CCHMC and whether these individuals had the appropriate expertise to perform both aggressive serial amnioreduction (AR) and SFLP. The principal investigator provided a response to the CCHMC IRB on June 15, 2004. This response included, among other things, a description of the personnel performing the procedures and their respective expertise in performing AR and SFLP procedures. Of note, the principal investigator provided the following information regarding the total number of fetal surgical procedures (4) conducted at the Fetal Care Center of Cincinnati as of June 15, 2004: one open fetal surgery to resect a paracardial teratoma; a radio frequency oblation of a cord in twin reversed arterial perfusion sequence pregnancy; and two SFLP for Twin-Twin Transfusion Syndrome (TTTS). In addition, the investigator included a description of a certification process for performing SFLP. According to the investigator, this certification process was proposed by the DSMB and approved on March 18, 2004 by the Director of NICHD as a way to ensure that SFLP was being performed identically at all three laser sites according to the TTTS protocol. According to the investigation, this certification process required two investigators from each laser site (i.e., CHOP, CCHMC, and UCSF) to receive training from a surgeon with the largest experience with SFLP for treatment of TTTS. As of June 15, 2004, two surgeons from CHOP and two surgeons from CCHMC had completed the training. Thus, there is no evidence indicating that the CCHMC surgeons performing SFLP were not competent to perform this procedure.

(2) The complainant alleged that the inclusion criteria in the protocol included a criterion that the deepest vertical pocket (DVP) of fluid in the amniotic cavity of the recipient twin was at least 6 cm; and that if this inclusion criterion was followed, subjects without bona fide TTTS were included in the study.

We find that this allegation could not be proven. According to CCHMC, the initial inclusion criteria of DVP > 6 cm was never utilized to enroll participants into the trial. In fact, all subjects enrolled into the trial met the DVP > 8 cm criteria. Moreover, CCHMC responded that all of the subjects enrolled into the study had TTTS. In specific, CCHMC notes that a DVP of > 6 cm in the recipient twin was never the sole criteria used to diagnose TTTS. Instead, all subjects were required to meet additional criteria for Stage II disease, as described, representing progressing hemodynamic changes and more advanced disease making the recipient DVP a less important clinical factor in the diagnosis of TTTS. CCHMC continued that although the original grant application had a DVP of > 6 cm criterion for fetuses presenting before 20 weeks gestation, the protocol was subsequently amended to reflect a DVP of > 8 cm. According to CCHMC, all subjects enrolled into the trial up to that time met the more commonly accepted DVP > 8cm criteria. Thus, there is no evidence indicating that subjects without bona fide TTTS were included in the study.

(3) The complainant alleged that the surgeons performed an excessive number of laparotomies, which procedure carries more risk than the alternative of percutaneous fetal surgery.

We acknowledge CCHMC's response to this allegation. Given that laparotomies were not performed at CCHMC, we have decided to address this allegation with both the site that performed the procedures, UCSF, as well as the primary awardee institution, CHOP.

(4) The complainant alleged that the protocol included the performance of a "test" amniocentesis, without data to support the safety of this procedure prior to laser therapy.

We find that this allegation could not be proven. CCHMC responded that the grant application and the trial protocol described the use of a qualifying amnioreduction (AR); not the performance of a "test" amniocentesis. According to the protocol, in order to be eligible for randomization, a participant must have failed a previous clinically indicated amnioreduction as first line treatment for TTTS; thus, the qualifying amnioreduction was not considered a research-related procedure. CCHMC continued that the TTTS trial was designed to test the question of which therapy, SFLP or amnioreduction, was superior in the treatment of subjects who did not respond to a single AR. In addition, CCHMC provided data supporting the justification and safety of AR prior to SFLP. Thus, there is no evidence indicating that the protocol included the performance of a "test" amniocentesis, without data to support the safety of the procedure prior to laser therapy.

B. Questions and Concerns Regarding the Above-Referenced Research:

(1) [Redacted]

(2) [Redacted]

(3) [Redacted]

We acknowledge the three findings that CCMHC uncovered while conducting its investigation into the allegations noted above. The corrective actions outlined in the February 6, 2008 CCHMC letter satisfactorily address these findings and are appropriate under the terms of the CCHMC FWA.

Please provide us with responses to the above questions and concerns by April 15, 2009. If you identify any noncompliance during your review of the above questions and concerns, please describe any corrective actions that have been and will be taken to address the noncompliance. Please don't hesitate to contact me if you have any questions or need assistance in developing any corrective action plan.

Sincerely,

Lisa A. Rooney, J.D.
Compliance Oversight Coordinator
Division of Compliance Oversight

cc: Dr. Jennifer Ruocco, Director, Office of Research Compliance and Regulatory Affairs, Cincinnati Children's Hospital Medical Center
Dr. Robert Frenck, Chair, Cincinnati Children's Hospital Medical Center IRB#1 and #2
Ms. Barbara LoDico, Director, Human Subject Research, Children's Hospital of Philadelphia
Dr. Mark Schreiner, Chair, Children's Hospital of Philadelphia IRB #1and #2
Ms. Sharon K. Friend, Director, Human Research Protection Program, University of California, San Francisco
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Dr. Susan H. Sniderman, Chair, San Francisco General Hospital, IRB #2
Dr. Alan P. Venook, University of California San Francisco, IRB #4
Dr. Timothy M. Crombleholme, Cincinnati Children's Hospital Medical Center

Dr. Joe Ellis, Office of Extramural Research, NIH
Dr. Sherry Mills, Office of Extramural Research, NIH
Dr. Duane Alexander, Director, National Institute of Child Health and Human Development, NIH