DEPARTMENT OF HEALTH & HUMAN SERVICES

Office of the Secretary
Office of Public Health and Science

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March 17, 2009

Philip R. Johnson, M.D.
Chief Scientific Officer
Joseph Stokes, Jr. Research Institute
Children's Hospital of Philadelphia
Abramson Research Center
Philadelphia, PA 19104

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. Johnson:

Thank you for your March 4, 2008 letter in response to our December 21, 2007 request that the Children's Hospital of Philadelphia® (CHOP) 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 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 twin-twin transfusion syndrome (TTTS) were included in the study.

We find that this allegation could not be proven. CHOP responded that all of the subjects enrolled into the study had TTTS. In specific, CHOP noted that diagnosis of Stage II TTTS was not based solely on presence of a DVP of > 6 cm; rather, subjects were required to meet other clinical criteria representing progressing hemodynamic changes and more advanced disease. CHOP continued that although the original grant application had a criterion for fetuses presenting before 20 weeks gestation – i.e., to allow study entry if the recipient DVP was > 6cm - the protocol was subsequently amended to reflect a DVP of > 8 cm. According to CHOP, 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.

(2) 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 find that this allegation could not be proven. CHOP responded that

(a) There were no reported complications or adverse events associated with the mini-laparotomy procedure used in this trial;

(b) While the use of the procedure at the University of California, San Francisco (UCSF) did exceed the anticipated frequency as stated in the grant proposal, this was a standard approach used as some United States and Europe centers at the time of the trial;

(c) Neither the Trial Oversight Committee (TOC) nor the Data Safety Monitoring Board (DSMB) raised a concern about the number of mini-laparotomies conduced at UCSF; and

(d) An interim analysis, conducted in February 2004, revealed variation in fetal surgical approach between sites and resulted in a DSMB recommendation that a single standard technique for access to the uterus be adopted, eliminating the use of the mini-laparotomy by using a smaller trochar. The laparotomy procedures were eliminated before our office opened this investigation.

Given the above, there is no evidence indicating that surgeons performed an excessive number of laparotomies.

(3) 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. CHOP responded that at the time of the study, amnioreduction (AR) was the standard of care for treatment of TTTS in the United States. Thus, the use of a single AR prior to assignment to study was prudent. In addition, CHOP noted that the study was designed to test the question of which therapy, selective fetoscopic laser photocoagulation (SFLP) or AR, was superior in the treatment of subjects who did not respond to a single AR; the criterion of no response to a single AR was necessary to obtain a homogenous population of subjects with severe TTTS to address the

study question. Moreover, CHOP provided the following data supporting the safety of AR prior to SLFP:

Literature available at the time of the study documented a paradoxical resolution of oligohydromnio after a single AR in a subset of TTTS patients; occurring in up to 20 – 30% of patients. Thus, 20 – 30% of patients would avoid the potential risks of the more invasive SFLP intervention;

The risk of a single AR that would preclude subsequent SFLP in chorioamniotic separation. At the time of the study protocol, the experience of the investigators was that this risk was less than 5%, compared to the risk of SFLP at 15 – 20%.

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]

C. Recommendations

We recommend that CHOP consider changing the language quoted in its Standard Operating Procedure (SOP) 406 – Categories of Action from "the study should be deferred" to "the study must be deferred."

We acknowledge the seven findings that the CHOP subcommittee uncovered while conducting its investigation into the allegations noted above. The corrective actions outlined in the March 4, 2008 CHOP letter satisfactorily address these findings and are appropriate under the terms of the CHOP 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
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