DEPARTMENT OF HEALTH & HUMAN SERVICES

Office of the Secretary
Office of Public Health and Science

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March 17, 2009

A. Eugene Washington, M.D., MSc
Executive Vice Chancellor
University of California, San Francisco
Office of Executive Vice Chancellor
513 Parnassus, S115
San Francisco, CA 94143-0400

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. Washington:

Thank you for your March 26, 2008 letter in response to our December 21, 2007 request that the University of California, San Francisco (UCSF) 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 risks to subjects who participated in the research were not minimized, and that 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. UCSF responded that, although the initial grant proposal and TTTS Trial protocol did state that fetuses presenting prior to 20 weeks' gestation could be allowed entry if the recipient DVP was > 6 cm, no subject was randomized in the trial using the DVP > 6 cm criteria; rather, all of the subjects randomized into the trial met the DVP > 8 cm criteria. Moreover, UCSF continued that the protocol was subsequently amended to reflect a DVP of > 8 cm. Lastly, UCSF stated that no subject would have been enrolled on the basis of the single finding of a recipient DVP > 6 cm; all subjects would have had to meet all additional clinical criteria for Stage II disease. 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. UCSF responded that:

(a) This was a standard endoscopic approach used by many centers, including some in the Eurofetus Trial, and is still in use today in some centers in the United States;

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

(c) 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) It was 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. UCSF responded that the study was designed to test the question of which therapy, selective fetoscopic laser photocoagulation (SFLP) or amnioreduction (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, UCSF 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]

[Redacted]

(2) [Redacted]

[Redacted]

(3) [Redacted]

(4) [Redacted]

(5) [Redacted]

(6) [Redacted]

(7) [Redacted]

[Redacted]

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, NICHD, NIH