



DEPARTMENT OF HEALTH & HUMAN SERVICES

Office of the Secretary
Office of Public Health and Science

Office for Human Research Protections
The Tower Building
1101 Wootton Parkway, Suite 200
Rockville, Maryland 20852

Telephone: 240-453-8120
FAX: 240-453-6909
E-mail: Lisa.Rooney@hhs.gov

November 9, 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 April 24, 2009 letter in response to our March 17, 2009 letter that included determinations, questions, and concerns. Based on the information submitted, we make the following determinations:

Determinations Regarding the Above-Referenced Research

- (1) A complainant alleged that none of the surgeons performing selective fetoscopic laser photocoagulation (SFLP) had previously demonstrated competence in this procedure, resulting in both a failure to minimize risks to the subjects and risks that 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 Department of Health and Human Services (HHS) regulations at 45 CFR 46.116(a)(1) and (2). In our March 17, 2009 letter we indicated that we were concerned as to whether or not the Children's Hospital of Philadelphia (CHOP) institutional review board (IRB) ensured, prior to IRB approval, that the CHOP investigators performing SFLP had previously demonstrated competence in this procedure and thereby ensured that risks to subjects were minimized and reasonable. As a result of our concern, we asked that CHOP explain what criteria the CHOP IRB considered in determining

that the CHOP investigators conducting SFLP were qualified to conduct this highly complex procedure. In addition, we asked CHOP to indicate whether the CHOP investigators conducting SFLP were credentialed to conduct such a procedure at CHOP.

We find that this allegation could not be proven and thus make no determination of noncompliance. CHOP responded that the CHOP investigators had previously demonstrated competence in this procedure based on the privileges granted to them by the Medical Staff, approval of their Department Chair, and the IRB’s knowledge of these individuals and of Medical Staff standards. In this case, at the time of initial IRB review and approval of this study, each surgeon performing SFLP had demonstrated their training, experience and competence by having performed a total of 22 fetoscopic laser coagulations. Thus, at the time of initial IRB approval of this study, each study investigator was granted privileges for fetal surgery: the highest of 5 categories of privileges within the CHOP Department of Surgery.

- (2) We determine that the CHOP IRB-approved informed consent documents for the treatment arm of the above-referenced study failed to: (i) explain that the echocardiograms and neuroradiologic evaluations conducted after one and four weeks of life to check for the subsequent development of brain abnormalities and the progression or regression of abnormal cardiac function were experimental, as required by HHS regulations at 45 CFR 46.116(a)(1); and (ii) describe the reasonably foreseeable risks or discomforts associated with these echocardiograms and neuroradiologic evaluations, as required by HHS regulations at 45 CFR 46.116(a)(2).

Corrective Action: CHOP responded that the IRB-approved informed consent document(s) for the study lacked sufficient clarity on whether test evaluations were being done solely for research purposes or for standard of care and did not describe the reasonably foreseeable risks or discomforts associated with these evaluations. CHOP indicated that current IRB policies and procedures provide various means to ensure that informed consent documents meet the requirements of HHS regulations at 45 CFR 46.116(a)(1) and (a)(2). For example, the current electronic submission forms require the investigator to list each procedure and intervention in the study, and for each, provide an answer to the question: “What is the purpose of the study intervention/procedure? Research or Standard of Care?” Moreover, the CHOP standard operating procedure 701 entitled “Required Elements of Consent and Documentation of Consent” assigns the investigator the responsibility to ensure that the informed consent contains all required elements and assigns to the IRB the responsibility to review the proposed consent and ensure that it contains all required elements. Having already listed each procedure in the electronic submission, the investigator can better ensure that this requirement is met, and the IRB can better review compliance with this requirement. CHOP believes that these revised policies/procedures will prevent this situation from recurring in the future. We determined that this corrective action adequately addresses our determination and is appropriate under the CHOP FWA.

The remaining questions and concerns from our March 17, 2009 letter have been adequately addressed.

At this time, there should be no need for further involvement by our office in this matter. Please notify us if you identify new information which might alter this determination.

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. Deborah Barnard, Director of Research Compliance and Regulatory Affairs, 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
Dr. Victor I. Reus, Chair, Parnusus IRB #1, University of California, San Francisco
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, National Institutes of Health (NIH)
Dr. Sherry Mills, Office of Extramural Research, NIH
Dr. Duane Alexander, Director, National Institute of Child Health and Human Development,
NIH