



DEPARTMENT OF HEALTH & HUMAN SERVICES

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November 9, 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-68

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 June 11, 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) The complainant alleged that none of the surgeons performing the 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).

We acknowledge the University of California, San Francisco's (UCSF's) response noted in your letter dated June 11, 2009. Of note, we acknowledge that UCSF directed our office to

the grant application which included the qualifications of the UCSF investigators. Moreover, we acknowledge that the UCSF investigators conducting the SFLP were authorized to conduct fetal surgery and SFLP at UCSF and that the SFLP procedure had been reviewed by the Fetal Surgery Oversight Committee. Given the above, we determine that this allegation could not be proven and thus make no determination of noncompliance.

- (2) HHS regulations at 45 CFR 46.116(a)(1) provide that, when seeking informed consent, a description of the procedures to be followed shall be provided to each subject, unless an institutional review board (IRB) has appropriately waived or altered the requirements to obtain informed consent. HHS regulations at 45 CFR 46.117 require that, unless the “short form” written consent document is used or documentation of consent is waived, the written consent document must contain all of the elements of informed consent required by 45 CFR 46.116. We reviewed the UCSF IRB-approved documents and noted that the UCSF IRB-approved protocol for the above-referenced research stated that “Upon delivery the placenta will be sent fresh packed on ice via overnight delivery by Federal Express for pathologic examination by Dr. G. Machin or Dr. Eduardo Ruchelli at CHOP.” However, neither of the UCSF IRB-approved informed consent forms for this study included information regarding the research procedures involving the placenta. Moreover, we reviewed the IRB file for this study and could not locate evidence demonstrating that the IRB approved a waiver or alteration of any of the required elements of informed consent.

In your response, you acknowledged that the IRB-approved consent forms failed to include a discussion of the research procedures involving the placenta. We note that the “short form” written consent document was not used for this research and the IRB did not waive documentation of consent. Notwithstanding this oversight, you note that subjects were verbally informed about such research procedures. Given this acknowledgement, we determine that, while subjects were provided with information about the research procedures involving the placenta in the informed consent process, the IRB-approved informed consent forms failed to include a complete description of the research procedures to be followed, as required by HHS regulations at 45 CFR 46.117(b)(1).

Corrective Action: We note that beginning in 2005, after the above-referenced research started, UCSF began implementing changes to the UCSF IRB policies and procedures that ensure that IRB-approved informed consent forms will include, among other informed consent elements, descriptions of the procedures to be followed, unless the IRB has appropriately waived or altered the requirements to obtain informed consent. We determine that this corrective action adequately addresses our determination and is appropriate under the UCSF FWA.

- (3) We determine that the UCSF 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: We note that UCSF has implemented changes to the UCSF IRB policies and procedures that ensure that IRB-approved informed consent forms include all of the basic informed consent elements outlined in HHS regulations at 45 CFR 46.116(a). In particular, we acknowledge that IRB members are now provided with checklists which specify all of the informed consent elements noted under 45 CFR 46.116(a). In addition, we note that certain IRB staff members are required to use a similar informed consent checklist when screening new studies. We determine that these corrective actions adequately address our determination and are appropriate under the UCSF FWA.

- (4) HHS regulations at 45 CFR 46.116(a)(2) and (3) provide that when seeking informed consent, a description of the reasonably foreseeable risks or discomforts to the subject, as well a description of any benefits to the subject or others which may reasonably be expected from the research, must be provided unless an IRB appropriately waived or altered the requirements to obtain informed consent. We previously noted that an October 15, 2003 letter from the DSMB to the Chairman of the IRB stated that the study informed consent form must be modified to provide the Eurofetus Trial preliminary results, which found laser treatment more effective than fluid reduction. Moreover, we noted that the Eurofetus Trial results were subsequently published in a *New England Journal of Medicine* article dated July 8, 2004. See NEJM, 2004; 351:136-144. These results included the conclusion that laser treatment was more effective than fluid reduction as well as the additional risks associated with laser treatment versus fluid reduction, i.e., increase in pregnancy loss, premature rupture of membranes and intrauterine fetal demise within seven days of laser treatment.

With this as background, we noted that a modification request regarding the inclusion of the Eurofetus Trial results into the UCSF IRB approved protocol/informed consent form was not submitted to the UCSF IRB until December 31, 2004 and ultimately approved by the UCSF IRB on February 25, 2005. We noted further that three subjects were enrolled into the trial between July 8, 2004 and February 25, 2005 (November 12, 2004; December 18, 2004 and January 31, 2005). Given the above, we expressed concern as to whether or not the subjects that were enrolled between July 8, 2004 and February 25, 2005 were provided with information, e.g., either verbally or with a written document, which accurately described the relative risks and benefits of amnioreduction (AR) and SFLP in light of the published Eurofetus Trial results.

We note that two of the three subjects, who were enrolled by a non-UCSF referral institution, signed an informed consent form that accurately described preliminary Eurofetus Trial results (although not the the final published Eurofetus Trial results). We note further, however, that the third subject did not sign a similar document; instead, the third subject signed an informed consent form that did not accurately describe either the preliminary or final Eurofetus Trial results. Lastly, we note that you could not confirm that the third subject was verbally informed about the Eurofetus trial results, although you stated that in general, the participants in this study were already well informed about the state of the research in the

field at the time of initial consultations. Notwithstanding your response, we determine that for the one subject referenced above, informed consent failed to include a description of the reasonably foreseeable risks or discomforts to the subject (as modified by the Eurofetus Trial results) as well a description of the benefits to the subject or others which may reasonably be expected from the research (as modified by the Eurofetus Trial results) as required by HHS regulations at 45 CFR 46.116(a)(2) and (a)(3) and that the IRB did not approve a waiver or alteration of the requirement to provide this information.

Required Action: The UCSF IRB must develop a plan for contacting the one subject who participated in the above-referenced research who was not provided with the Eurofetus Trial preliminary or final results and informing her that, at the time of enrollment, the institution should have provided her with information regarding the final Eurofetus Trial results. The final Eurofetus Trial results, published July 8, 2004, altered the risks and benefits as initially outlined in the IRB-approved informed consent documents. Thus, the investigator should have sought IRB approval to modify the approved informed consent form to reflect the final Eurofetus Trial results prior to enrolling this subject into the study on December 18, 2004. By December 11, 2009, please subject to OHRP a written report regarding the IRB's plan for this matter, including the proposed text to be provided to the one subject.

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

We appreciate the commitment of your institution to the protection of human subjects.

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,
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