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June 3, 2010

Joseph J. Ferretti, Ph.D.  
Senior Vice President and Provost  
Board of Regents of the University of  
Oklahoma Health Sciences Center  
1000 Stanton L. Young Blvd., Rm. 221  
Oklahoma City, OK 73117-1213

**RE: Human Research Protections Under Federalwide Assurance  
FWA-7961**

**Research Project: A Phase III Study for the Treatment of Children and Adolescents  
with Newly Diagnosed Low Risk Hodgkin Disease**  
**Principal Investigator: Rene McNall, M.D.**  
**HHS Protocol Number: COG AHOD0431**

Dear Dr. Ferretti:

Thank you for your July 2, 2009 and March 26, 2010 reports in response to our June 4, 2009 and February 16, 2010 letters, respectively. As we indicated in our February 2010 letter, we are responding to both of your reports in this determination letter. Based on the information submitted in both reports, we make the following determinations:

**A. Determinations Regarding the Above-Referenced Research:**

- (1) In our June 4, 2009 letter we determined that the investigator implemented the following changes without first obtaining University of Oklahoma Health Sciences Center institutional review board (UOHSC IRB) review and approval of these changes in the research in violation of Department of Health and Human Services (HHS) regulations at 45 CFR 46.103(b)(4)(iii).
  - (a) The investigator failed to notify two subjects currently on study of the drug toxicity changes associated with Filgrastim. We noted that during the August 13, 2007 UOHSC IRB meeting, the UOHSC IRB contingently approved protocol amendment #1 to the above-referenced study; the contingency being that the investigator notify the two "patients" currently on study of the drug toxicity changes associated with

- Filgrastim. UOHSC informed our office that the investigator: (a) decided not to notify the two patients of the drug toxicity information because at the time the amendment was approved the subjects had completed the therapy involving the drug Filgrastim; and (b) never notified the UOHSC IRB of the investigator's decision. We appreciate and acknowledge UOHSC's statement that the investigator should have notified the IRB when the investigator decided not to notify the enrolled subjects so that the IRB could determine whether its initial approval was affected by the change.
- (b) The investigator failed to provide the complainant's son with prophylaxis for pneumocysti carinii pneumonia (PCP) as indicated in section 8.2 of the IRB-approved protocol (version date October 19, 2005). The complainant alleged that her son was never informed that he was to receive antibiotics prophylactically, and her son did not receive any further antibiotic treatment once the initial prescription was finished despite continuing chemotherapy. According to the complainant, an antibiotic prescription was dispensed by a UOHSC attending physician on May 10, 2007 prior to her son enrolling into the trial on May 14, 2007. The UOHSC responded that the complainant's son, while initially given Bactrim to treat a cellulitis, was never started on PCP prophylaxis as required by the protocol.

**Corrective Action:** We note that UOHSC IRB will implement the following measures to ensure that investigators are aware of the UOHSC IRB Standard Operating Procedure (SOP) 405 "Amendments" and reinforce adherence to this SOP:

- In July 2009, provided specific mandatory training on this SOP for investigators in the Section of Hematology Oncology, Department of Pediatrics;
- Highlight this SOP during the regular in-house IRB training on UOHSC investigators;
- Distribute information on this SOP to all UOHSC research personnel from UOHSC Institutional Official;
- Provide additional training on this SOP to research coordinators;
- Provide additional training on this SOP to investigators during a brown-bag lunch series that was scheduled for July 22, 2009;
- Include this SOP in the next UOHSC IRB Newsletter;
- Check for potential violations of this SOP during local Quality Improvement Evaluations of UOHSC protocols by IRB staff; and
- Emphasize this SOP during the education portion of local Quality Improvement Evaluations.

We determine that the corrective actions noted above adequately address our determination and are appropriate under the UOHSC FWA.

- (2) In our June 4, 2009 letter we raised a concern that the investigator did not follow the complainant's son in accordance with the UOHSC IRB-approved protocol and that the investigator failed to obtain prospective IRB review and approval of this change in

follow-up. We concluded that this failure to obtain IRB review and approval of this change in follow-up was in violation of HHS regulations at 45 CFR 46.103(b)(4)(iii). Moreover, in that same letter, we noted that UOHSC's responses regarding this matter appeared to be conflicting. In specific, UOHSC stated that the February 28, 2008 visit was not construed as a protocol-mandated follow-up visit, while also indicating that the complainant's son was declared "Lost to Follow-up" and removed from the study sometime after April 4, 2008. We questioned whether it was appropriate for the investigator to treat the February 28, 2008 visit as something other than a protocol-mandated follow-up visit when the visit occurred before the complainant's son was removed from the study, which apparently was sometime after April 4, 2008.

We acknowledge the following timeline that was provided by UOHSC:

- July 2, 2007: Complainant's child finished therapy;
- October 1, 2007: Complainant's child returned for a 3 month follow-up visit and was scheduled for a 6 month follow-up visit that was to occur on December 27, 2007;
- December 27, 2007: Complainant's son did not keep appointment, reschedule or contact the investigator;
- January/February 2008: Phone calls between the investigator and complainant regarding the complainant's concerns regarding exposure to diagnostic irradiation and return appointments;
- January 31, 2008: An investigator met with complainant to discuss concerns about diagnostic irradiation exposure;
- February 28, 2008: Complainant's son was seen for clinic/interim visit. The visit was out of window for follow-up scans or ESR per protocol. At this visit, the complainant refused further protocol-mandated testes. We note that UOHSC considered this refusal to equate to a withdrawal of consent for any further data submission. (See section 9.2.d of the UOHSC IRB approved protocol.) Moreover, at this visit the complainant was instructed to make the next follow-up appointment in 3 months; the complainant did not do this;
- April 4, 2008: UOHSC notified the Children's Oncology Group (COG) that patient was Lost to Follow-Up and taken off study. See section 9.2.b of the UOHSC IRB approved protocol.

Based on the timeline provided above, UOHSC concluded that the investigator's failure to obtain all of the protocol-mandated interventions during the February 28, 2008 visit and subsequent removal of the complainant's child from the protocol was neither a protocol violation nor an act that conflicted with HHS regulations at 45 CFR 46.103(b)(4)(iii). Based on this information, we determine that this allegation of noncompliance is unproven.

- (3) In our June 4, 2009 letter we raised a concern regarding how the complainant's son was withdrawn from the above-referenced study by UOHSC investigators.

According to the complainant, her son was withdrawn from the study in contradiction to what was stated in the UOHSC IRB-approved informed consent documents and protocol (version date 10/19/2005) without first obtaining IRB review and approval of these changes in the research in violation of HHS regulations at 45 CFR 46.103(b)(4)(iii). The complainant stated that her son had not voluntarily withdrawn from the study, and also alleged that no one has notified her or her son that her son has been excluded from further participation. Given the above, we asked UOHSC whether the IRB-approved protocol or informed consent form required the investigator to notify the complainant or her son that her son had been excluded from further research participation.

UOHSC responded that section 9.0 of the UOHSC IRB-approved protocol permitted investigators to remove from the study those subjects who were considered lost to follow-up. UOHSC stated that, at the time the complainant's son completed therapy, nothing, i.e., the protocol, federal regulations, informed consent form or UOHSC SOPs, required the investigator to notify subjects in writing of their off-study status. Based on this information, we determine that this allegation of noncompliance is unproven.

We further note that UOHSC acknowledged that in order to avoid possible misunderstanding, the investigator should have provided the complainant written notification that her son was removed from the study due to Lost to Follow-Up. We understand that the UOHSC IRB will instruct investigators that when research subjects are removed from study due to lack of compliance, the decision should be documented and the subject should receive notification in writing that they are being removed from study, if contact information for that subject is available, and will accordingly amend standard operating procedure (SOP) 801 – Investigator Qualifications and Responsibilities and the informed consent form template. The UOHSC IRB will inform investigators of the revised SOP and informed consent form template via

- A future issue of the UOHSC IRB Newsletter;
- Training for research coordinators at the next local chapter meeting;
- Training for investigators during a brown-bag lunch educational series; and
- During regular in-house IRB training program of UOHSC investigators.

We commend UOHSC for its voluntary actions regarding this matter.

- (4) The complainant alleged that investigators failed to minimize risks of harm to the complainant's son (through exposure to excessive levels of ionizing radiation without expected or derived benefit) in accordance with HHS regulations at 45 CFR 46.111(a)(1) by failing to use procedures which are consistent with sound research design and which do not unnecessarily expose subjects to risks when:

- (a) Researchers allegedly performed a July 10, 2007 PET/PET/CT on the complainant's son even though two prior imaging tests, a May 30, 2007 PET/PET/CT and a June 4, 2007 Gallium scan both revealed that the complainant's son was in remission.

UOHSC responded that the PET/CT imaging performed on July 10, 2007 was the End of Therapy evaluation and was mandated by section 7.2 of the protocol. Given that the results of the July 10, 2007 PET/CT were negative, the investigator elected to rely on the PET/CT results and not expose the subject to gallium scanning and additional diagnostic imaging radiation for this End of Therapy assessment. According to UOHSC, this decision was consistent with the study requirements and the general goal of limited exposure to diagnostic radiation. Based on the documentation provided, we have determined that this allegation of noncompliance is unproven.

- (b) Researchers allegedly scheduled a December 27, 2007 FDG-PET/CT as part of a 6 month review (even though two prior imaging studies, the May 30, 2007 PET/PET/CT and the June 4, 2007 Gallium scan, revealed remission), but failed to schedule protocol-mandated CT scans of the neck and chest.

UOHSC stated that an October 1, 2007 clinic note clearly indicated the correct imaging for the 6 month visit ("Imaging –[CT of chest/neck])," and that a 3-month return to clinic visit (RTC) would include CT of chest/neck. Conversely, a November 5, 2007 phone note documents that a staff member called the complainant confirming an appointment for PET/CT on December 27, 2007. UOHSC responded that it is not possible to discern why a PET/CT and not a CT of neck and chest appointment was confirmed by a call to the complainant when a clinic note indicated that a 3-month RTC would include CT of chest/neck. UOHSC highlighted that the subject did not keep the appointment and had neither additional PET/CTs nor CT scans and was not exposed to any additional diagnostic radiation. Based on the documentation provided, we have determined that this allegation of noncompliance is unproven.

- (c) Researchers allegedly gave the complainant's son a 6.8 mCi of FDG (.12 mCi/kg) during his July 10, 2007 FDG-PET/CT, which was lower than the protocol-recommended radiopharmaceutical dosage.

In responding to this concern UOHSC highlighted that there was a .015 mCi/kg discrepancy between section 17.0 of the protocol entitled "Imaging Studies Required and Radiology Guidelines" which refers to Appendix II: Radiology Guidelines, Imaging Techniques and section 17.2.2 of the protocol. Of note, Appendix II of the protocol states FDG is to be administered intravenously at a dose of 0.125-2.00 mCi/kg, with a minimum total dose of 2 mCi and a maximum does of 20 mCi; equating to a dose of between 6.8 to 11 mCi for a 55 kg patient. Conversely, section 17.2.2 of the protocol recommended a dosage of FDG between 0.140-0.200 mCi/kg, which for a 55kg patient is 7.7 to 11 mCi.

With this discrepancy noted, UOHSC stated that while the injected dose of 6.8 mCi/kg was slightly below the section 17.2.2 protocol-recommended dose (but within the section 17.0 recommended dose), the treating nuclear medicine specialist asserted that because the PET/CT was relatively new, it functioned very well at the lower dose ranges and all scans were of good diagnostic quality. Thus, this slightly below the protocol-recommended dose did not affect the diagnostic quality of the scan and allowed research team members to reduce subject radiation exposure without reducing the good diagnostic quality scans. Based on the documentation provided, we have determined that this allegation of noncompliance is unproven.

- (d) Researchers allegedly did not follow a standardized protocol for patient preparation and administration of radiopharmaceuticals during the complainant's son's imaging studies. The complainant asserted that this lack of standardization for patient preparation prior to PET imaging contributes to false-positive findings, which upstages diagnosis. The complainant further asserted that inconsistencies in the patient preparation and radiopharmaceutical administration can lead to additional PET scans through misinterpretation, which occurred in the case of the complainant's son.

UOHSC responded that researchers did follow a standardized protocol for preparation and administration of radiopharmaceuticals during the complainant's son's imaging studies and that the FDG dosage was within an acceptable range that took into account all of the specific facts and circumstances. Based on the documentation provided, we have determined that this allegation of noncompliance is unproven.

- (e) Researchers allegedly utilized FDG-PET for surveillance purposes. The complainant alleged that UOHSC physicians utilized FDG-PET/CT as the preferred imaging modality at follow-up even though the use of such a modality was contrary to the IRB-approved protocol as well as ACR Practice Guidelines and the NCCN Task Force Report: PET/CT Scanning in Cancer (2007) (NCCN Report). The complainant stated that the intention of the UOHSC physicians to utilize FDG-PET for monitoring after complete remission was not substantiated by literature, was not clinically indicated and violated the IRB-approved protocol.

UOHSC stated that it did not use PET/CT for surveillance; rather all PET/CT imaging was done solely at times indicated by protocol. UOHSC pointed out that the final PET/CT was done on July 10, 2007 to fulfill the End of Therapy protocol-mandated imaging. Based on the documentation provided, we have determined that this allegation of noncompliance is unproven.

- (f) Researchers allegedly relied on an inexperienced UOHSC physician when interpreting the complainant's son's FDG-PET/CT results. We noted that according to the complainant this physician misread a May 30, 2007 PET/PET/CT and that this misread resulted in the complainant's son undergoing a subsequent (and allegedly unnecessary) PET/PET/CT on July 10, 2007 even though the May 30, 2007

PET/PET/CT (and a “back-up” June 4, 2007 Gallium scan) both revealed that the complainant’s son was in remission. Per the complainant, (i) the Children’s Oncology Group (COG) central review of the May 30, 2007 FDG-PET/CT indicated remission was received; (ii) the complainant’s son’s current oncologist independently reviewed that May 30, 2007 FDG-PET/CT and recognized that remission was received; and (iii) the June 4, 2007 Gallium Scan, conducted to provide a diagnostic “back up,” recognized that remission was received, reporting “no scintigraphic evidence of residual or recurrent Hodgkin lymphoma.” Given the above, the complainant alleged that this physician did not have the appropriate training in the use of FDG-PET/CT at the time that the complainant’s son was treated under the protocol given that this physician was in the midst of developing a competency in FDG-PET/CT at the time that UOHSC was participating in the above-referenced trial.

UOHSC stated that according to the nuclear medicine specialist, review of the May 30, 2007 PET/CT report indicated persistent metabolically active nodes in the neck and mediastinum with SUB values in the 2.1 to 2.7 range. This represents a greater than 50% drop from the scan of May 4, 2007; where SUV values in the neck and mediastinum were 6.0 to 6.3 and is indicative of a good initial response to therapy, but it does not indicate the disease is in remission. However, the update in the involved nodes did drop all the way down to background levels on the scan of July 10, 2007; and this is indicative of metabolic remission.

Moreover, UOHSC noted that the UOHSC physician interpreting the FDG-PET/CT results was board certified by the American Board of Nuclear Medicine in 1994 and recertified in 2003 and currently maintains certification with this group. UOHSC continued that this physician began reading PET/CT scans in June 2003 and since that time has read 5 to 15 PET/CTs per day.

Based on the information provided, we have determined that this allegation of noncompliance is unproven.

- (5) The complainant alleged that the members of the UOHSC IRB present at the March 27, 2006, January 22, 2007, August 13, 2007, October 29, 2007 and December 17, 2007 convened meetings, where the above-referenced protocol was reviewed and approved, did not have the background and expertise necessary to review the research being proposed, as required by HHS regulations at 45 CFR 46.107(a).

UOHSC maintained that the IRB (a) included individuals who were knowledgeable about and experienced in working with vulnerable populations; (b) recognized that pediatric participants require special protection during diagnostic imaging; and (c) had sufficient experience to review the research involving pediatric population. UOHSC provided our office with the background of the IRB members who reviewed that research at the time of initial review as well as the background of IRB members who participated in later

reviews of the above-referenced research. We believe that this information demonstrates that the IRB had sufficient experience to conduct the review. As a result, we have determined that this allegation of noncompliance is unproven.

The remaining questions and concerns from our June 4, 2009 and February 16, 2010 letters 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: Ms. Meg R. Ribaud, Director, Office of Human Research Participant Protection, UOHSC  
Dr. Lynn Devenport, IRB Chairperson, University of Oklahoma-Norman IRB #1,  
Dr. Karen J. Beckman, IRB Chairperson, UOHSC IRB #1, #3, & #5  
Dr. Terry Dunn, IRB Chairperson, UOHSC IRB #2  
Dr. Martina Jelley, IRB Chairperson, UOHSC IRB #4  
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