DEPARTMENT OF HEALTH & HUMAN SERVICES

Office of the Secretary
Office of Public Health and Science

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November 28, 2007

Mr. Kyle De Fur
President
Saint John's Health System
2015 Jackson Street
Anderson, IN 46016

RE: Human Research Subject Protections Under Federalwide Assurance (FWA) 1780

Dear Mr. De Fur:

The Office for Human Research Protections (OHRP) has reviewed the Saint John's Health System (Saint John's) September 27, 2007 letter, an undated letter and a November 7, 2007 email in response to OHRP's September 14, 2007 letter regarding research conducted under the above-referenced Federalwide Assurance (FWA).

In its September 14, 2007 letter, OHRP made the following findings:

(1) OHRP found that the Saint John's Institutional Review Board (IRB) did not have the background and expertise to review radiation oncology research based on its failure to include members with sufficient understanding of radiation oncology standards of professional conduct and practice, as required by Department of Health and Human Services (HHS) regulations at 45 CFR 46.103(d) and 45 CFR 46.107(a).

Corrective Action: OHRP acknowledges that Saint John's has decided to "dissolve its IRB, de-activate its operating procedures and contract with third-party IRBs for all future review and oversight of its human subjects involved in clinical research." In specific, OHRP notes that Saint John's has updated its FWA to reflect that the Saint Vincent Hospital and Health Care Center, Inc. IRBs, i.e., IRB#1 and IRB#2, will be responsible for reviewing all human subjects research falling under Saint John's FWA.[1] OHRP has reviewed the Saint Vincent Hospital and Health Care Center IRB membership rosters and notes that the IRBs members listed on the rosters appear to have appropriate expertise to review Saint John's radiation oncology research studies. OHRP further acknowledges

[1] OHRP notes that Saint John's is in the process of changing to the New England IRB for the review of at least one study, RTOG 0615. See November 5, 2007 Saint John's Health System Cancer Center incident report. Please note that in accordance with HHS regulations at 45 CFR 46.103(b), Saint John's must obtain prior OHRP approval before any additional IRB(s) can review research falling under the Saint John's FWA. See OHRP finding (4) and the related corrective action, *infra*.

that Saint John's will submit all studies to one of the Saint Vincent IRBs for re-review and approval before restarting such studies. OHRP notes that these corrective actions appear to adequately address this finding and are appropriate under the Saint John's FWA.

Please note that while Saint John's response only mentions that "clinical research" will be reviewed by a third-party IRB, the HHS protection of human subjects regulations require that Saint John's must have **all** of its HHS-supported non-exempt human subjects research (both clinical and non-clinical) reviewed by an IRB designated under the Saint John's assurance.

(2) OHRP found that when approving research, the Saint John's IRB routinely failed to obtain sufficient information upon which to make certain determinations required for approval of research under HHS regulations at 45 CFR 46.111, both at initial and continuing review. See findings (2) and (3) of the September 14, 2007 OHRP letter.

Corrective Action: OHRP notes that the corrective actions outlined in finding (1), above, appear to adequately address this finding and are appropriate under the Saint John's FWA.

(3) OHRP found that the suspension of IRB approval for Radiation Therapy Oncology Group (RTOG) 0615, which was documented in the June 13, 2007 IRB meeting minutes, was not reported to appropriate institutional officials, OHRP, or the head of the sponsoring federal department or agency as required by HHS regulations at 45 CFR 46.103(a) and 46.103(b)(5).

Corrective Action: OHRP acknowledges receipt of an October 23, 2007 incident report and a follow-up November 5, 2007 incident report regarding the above-referenced suspension. Moreover, OHRP notes that Saint John's has implemented a policy/procedure entitled "Adverse Event Reporting" (effective date 10/2006) to ensure prompt reporting of these matters to appropriate individuals and agencies. OHRP finds that the implementation of this policy does not adequately address the finding noted above. In specific, OHRP finds that while the Adverse Event Reporting Policy addresses the reporting of adverse events, it does not address the reporting of any suspension of IRB approval.

Moreover, OHRP notes that HHS regulations at 45 CFR 46.103(b)(5) require that an institution establish written procedures that address the reporting of unanticipated problems involving risks to subjects or others, any serious or continuing noncompliance with 45 CFR part 46 or the requirements or determinations of the IRB, and any suspension or termination of IRB approval. OHRP notes that this policy does not address the reporting of these types of occurrences.

Required Action: By December 27, 2007 please provide OHRP with a corrective action plan outlining how Saint John's will ensure that it will promptly report to the IRB, appropriate institutional officials, any department or agency head, and OHRP any suspension of IRB approval. Moreover, please ensure that the revised policy complements the Saint

Vincent's IRB procedures regarding the reporting of such incidents.

(4) OHRP found that Saint John's designated an additional IRB to review research covered by the Saint John's FWA without prior OHRP approval.

Corrective Action: OHRP acknowledges that Saint John's has updated its FWA with OHRP to reflect that the Saint Vincent Hospital and Health Care Center, Inc. IRBs will be responsible for reviewing all human subjects research falling under Saint John's FWA. In addition, OHRP acknowledges that Saint John's has implemented the policy/procedure entitled "Methods for Submitting an Update or Renewal to an FWA" (effective date 10/07) to ensure that Saint John's will obtain OHRP approval before allowing any other IRB to review research to which the Saint John's FWA applies. OHRP notes that these corrective actions appear to adequately address this finding and are appropriate under the Saint John's FWA.

(5) OHRP found that Saint John's does not have sufficient staff to ensure that all IRB review and recordkeeping duties are completed as required by HHS regulations at 45 CFR 46.103(b)(2).

Corrective Action: OHRP acknowledges that Saint John's had decided to "dissolve its IRB, de-activate its operating procedures and contract with third-party IRBs for all future review and oversight of its human subjects involved in clinical research." See corrective action related to OHRP finding (1). OHRP finds that these corrective actions appear to adequately address this finding and are appropriate under the Saint John's FWA, assuming that the Saint Vincent IRBs have sufficient staff to support IRB review and recordkeeping duties.

(6) OHRP found that the Saint John's IRB failed to notify all investigators and the institution in writing of its decision to approve or disapprove proposed research activities, and of modifications required to secure IRB approval of the research activities, as required by HHS regulations at 45 CFR 46.109(d).

Corrective Action: OHRP acknowledges Saint John's decision to "dissolve its IRB, de-activate its operating procedures and contract with third-party IRBs for all future review and oversight of its human subjects involved in clinical research." See corrective action related to OHRP finding (1). OHRP finds that these corrective actions appear to adequately address this finding and are appropriate under the Saint John's FWA, assuming that the Saint Vincent IRBs notify all investigators and the institution in writing of decisions to approve or disapprove proposed research activities, and of modifications required to secure IRB approval of the research activities, as required by HHS regulations at 45 CFR 46.109(d).

(7) OHRP found that Saint John's did not maintain adequate documentation of IRB activities in accordance with HHS regulations at 45 CFR 46.115(a). Moreover, OHRP found that Saint John's did not maintain documentation of such activities for at least 3 years, and did not maintain records relating to research which is conducted for at least 3 years after

completion of the research, as required by HHS regulations at 45 CFR 46.115(b).

Corrective Action: OHRP acknowledges Saint John's decision to contract with the Saint Vincent IRBs for future review and oversight of Saint John's human subjects clinical research. OHRP further acknowledges that Saint John's has implemented a policy/procedure entitled "Interactions with the Institutional Review Boards" (effective date 10/07) to address the above-referenced findings. OHRP notes the following in reference to this procedure:

(a) The procedure appears to allow the addition or deletion of a principal investigator or sub-investigator without receiving prior IRB review and approval of such addition/deletion. Please note that HHS regulations at 45 CFR 46.103(b)(4)(iii) require that the IRB review and approve all proposed changes in a research activity, during the period for which IRB approval has already been given, prior to initiation of such changes, except when necessary to eliminate apparent immediate hazards to the subjects.

(b) The procedure does not address how long Saint John's, or the IRB that oversees human subjects research being conducted at Saint John's, must retain IRB records for studies that were reviewed by an IRB, but never conducted. Please note that HHS regulations at 45 CFR 46.115(b) provides that the records required by 45 CFR part 46 shall be retained for at least 3 years, and records relating to research which is conducted shall be retained for at least 3 years after completion of the research.

(c) The procedure only grants authorized representatives of the Food and Drug Administration (FDA) access to such IRB records, and does not indicate that the funding agency or OHRP have such access. Please note that HHS regulations at 45 CFR 46.115(b) require that all such records shall be accessible by authorized representatives of HHS.

OHRP offers the following additional guidance:

(8) OHRP has reviewed Saint John's policy entitled "Obtaining Informed Consent 7177.002" (effective date 10/07). OHRP notes that the scope of the policy is too limited given that it only applies to informed consent and assent documents associated with studies involving the evaluation of drugs, devices, or biologics. HHS regulations at 45 CFR 46.116 state that, except as provided elsewhere in the regulations, no investigator may involve a human being as a subject in research covered by the regulations unless the investigator has obtained the legally effective informed consent of the subject or the subject's legally authorized representative. Please note that research covered by 45 CFR part 46 involves research activities other than just the evaluation of drugs, devices, or biologics, e.g., medical record chart review studies, non-inferiority studies, biological collections studies. Thus, OHRP recommends revising this policy to encompass all human subjects research, as defined by HHS regulations at 45 CFR 46.102, that does not

qualify for exemption under 45 CFR 46.101(b).

In light of the above corrective actions taken by Saint John's in response to OHRP's findings of noncompliance, OHRP hereby reinstates the Federalwide Assurance (FWA-1780) for Saint John's Health System. This reinstatement, effective as of the date of this letter, provides the Assurance required by HHS regulations at 45 CFR 46.103(a) for Federally supported research involving human subjects at the above FWA signatory institution. The FWA will retain its previous expiration date of November 7, 2010.

Furthermore, in order to ensure adequate protections for human subjects at Saint John's Health System, in accordance with HHS regulations at 45 CFR 46.103, effective as of the date of this letter, OHRP hereby restricts FWA-1780 according to the following conditions:

(1) No HHS-supported research that was previously suspended may resume until

(a) such research is reviewed and approved by one of the IRBs designated under Saint John's FWA; and

(b) Saint John's submits to OHRP the required corrective action plan related to OHRP finding (3), *supra*.

OHRP appreciates the commitment of your institution to the protection of human subjects. Please contact me if you have any questions.

Sincerely,

Lisa A. Rooney, J.D.
Compliance Oversight Coordinator

cc: Dr. Gary Brazel, IRB Chair, Saint John's Health System
Dr. Sam Shekar, OER, NIH
Dr. John E. Niederhuber, NCI
Dr. Andrew C. von Eschenbach, Commissioner, FDA
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