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: 301-453-8120
Fax: 301-453-6909
E-mail: Lisa.Rooney@hhs.gov

September 14, 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:

As you know, the Office for Human Research Protections (OHRP) conducted an on-site evaluation of human subject protection procedures at Saint John's Health System (Saint John's), Anderson, Indiana from July 31, 2007 – August 2, 2007. The evaluation, conducted by two OHRP staff with the assistance of two consultants, included meetings with you, as the Saint John's institutional official, institutional review board (IRB) chairs, IRB members, one executive assistant, one research nurse, and two investigators, one of which is supported by the Department of Health and Human Services (HHS). The evaluation involved review of IRB files for over 20 protocols and IRB meetings minutes from 2005 - 2007.

In the course of the OHRP on-site evaluation, the IRB chairs, IRB members, and Saint John's staff displayed an enthusiastic and sincere concern for the protection of human subjects and stated that they view themselves as providing a valuable service to subjects and the research community. Saint John's staff was helpful and accommodating to OHRP during the site visit.

Based on the interviews conducted and the information reviewed, OHRP makes the following determinations regarding Saint John's system for protecting human subjects:

(1) HHS regulations at 45 CFR 46.103(d) require that the adequacy of an IRB be evaluated in light of the anticipated scope of the institution's research activities, the types of subject populations likely to be involved and the size, and complexity of the institution. Moreover, HHS regulations at 45 CFR 46.107(a) provide, among other things, that each IRB shall have at least five members, with varying backgrounds to promote complete and adequate review of research activities commonly conducted by the institution. In addition, the regulations provides that the IRB be sufficiently qualified through the experience and expertise of its members to promote respect for its advice and counsel in safeguarding the rights and welfare of human subjects and be able to ascertain the acceptability of proposed research in terms of institutional commitments and regulations,

applicable law, and standards of professional conduct and practice.

OHRP finds that the Saint John's IRB does 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. For example, the Saint John's IRB does not include an oncologist even though all of the studies currently approved by the IRB are radiation or medical oncology studies. During the site visit, OHRP learned that the IRB routinely relies on the principal investigator of the radiation oncology studies, as its sole IRB consultant for clinical expertise in radiation oncology and/or to answer questions regarding the proposed research risk/benefit ratio.

Required Action: Based on the nature of the research conducted at Saint John's, please provide OHRP with a revised IRB membership roster that includes at least one member with expertise in oncology and/or designate an IRB under Saint John's FWA with appropriate expertise.

(2) HHS regulations at 45 CFR 46.111(a) state that, in order to approve research covered by the regulations, the IRB shall determine that certain requirements are satisfied. OHRP finds that when approving research, the Saint John's IRB routinely fails to obtain sufficient information upon which to make the following determinations required for approval of research under HHS regulations at 45 CFR 46.111:

(a) Risks to subjects are minimized.
(b) Selection of subjects is equitable.
(c) Informed consent will be sought from each prospective subject or the subject's legally authorized representative (informed consent process).
(d) When appropriate, the research plan makes adequate provision for monitoring the data collected to ensure the safety of subjects.
(e) When appropriate, there are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data.

OHRP finds no evidence that these criteria are considered by the IRB prior to approving research. OHRP notes that IRB members did not describe consideration of these requirements. For example, when IRB members were asked to identify what criteria are used to determine whether a study can be approved by the IRB, the IRB members only referred to informed consent requirements; IRB members were unable to refer to other criteria outlined in 45 CFR 46.111. In particular, OHRP was informed that IRB members do not solicit information regarding subject recruitment, enrollment procedures, and provisions to protect the privacy of subjects and maintain confidentiality of data. In addition, the protocols that were reviewed did not mention subject recruitment, enrollment procedures, or provisions to protect the privacy of subjects and maintain confidentiality. Of note, during the on-site evaluation, OHRP learned that a research nurse maintains human subject research records on an open shelf in an office that is not locked. It appears as if this information was never shared with the IRB given that the IRB does not solicit information regarding provisions to protect the privacy of subjects

and to maintain confidentiality of data.
In addition, OHRP notes that IRB records did not document consideration of the 45 CFR 46.111 criteria. This is particularly concerning given that OHRP previously closed a compliance oversight evaluation of Saint John's based on a corrective action plan that included the use of a 3 page IRB application form entitled "Request for Initial Review of a Protocol." See Saint John's September 22, 2004 response letter to OHRP. During the on-site evaluation, OHRP could not locate IRB application forms in the majority of IRB-like files. See item (8) below. As a result, OHRP queried the IRB members about the use of the above-referenced IRB application form. The IRB members informed OHRP that while the IRB utilized the IRB application form initially, the IRB stopped using the form shortly after it was introduced because the IRB members did not believe the form was helpful; and that the IRB had not been using any IRB application form for approximately one year and possibly longer. OHRP notes that this information contradicts information that Saint John's previously provided to OHRP, i.e., in an email dated July 24, 2007 Saint John's informed OHRP that the IRB Application Form entitled "Request for Initial Review of a Protocol" is the "form submitted to the IRB for all requests. No other application materials are used."

(3) Continuing review of research must be substantive and meaningful. As stated above, HHS regulations at 45 CFR 46.111 set forth the criteria that must be satisfied in order for the IRB to approve research. The IRB must ensure that these criteria are satisfied at the time of both initial and continuing review.

In conducting continuing review of research not eligible for expedited review, all IRB members should at least receive and review a protocol summary and a status report on the progress of the research, including: (i) the number of subjects accrued; (ii) a summary of adverse events and any unanticipated problems involving risks to subjects or others and any withdrawal of subjects from the research or complaints about the research since the last IRB review; (iii) a summary of any relevant recent literature, interim findings, and amendments or modifications to the research since the last review; (iv) any relevant multi-center trial reports; (v) any other relevant information, especially information about risks associated with the research; and (vi) a copy of the current informed consent document and any newly proposed consent document.

At least one member of the IRB (e.g., a primary reviewer) also should receive a copy of the complete protocol including any protocol modifications previously approved by the IRB. Furthermore, upon request, any IRB member also should have access to the complete IRB protocol file and relevant IRB minutes prior to or during the convened IRB meeting.

OHRP finds that the Saint John's IRB fails to conduct substantive and meaningful continuing review. OHRP found no evidence that the IRB considers 45 CFR 46.111 criteria prior to approving research at continuing review. As stated above, IRB members did not describe, and IRB records did not document, consideration of 45 CFR 46.111 criteria. In addition, OHRP found no evidence that the IRB reviews the complete protocol at the time of continuing review. According to one IRB member, the IRB does

not review the complete protocol (i.e., all documents previously submitted and approved

by the IRB) at the time of continuing review unless a protocol modification has been requested or an issue has been identified. Furthermore, OHRP learned that the IRB routinely engages in "block voting" for continuing reviews of, and amendments to, "closed protocols" (i.e., protocols closed to accrual). OHRP notes that such "block voting" does not allow for substantive and meaningful continuing review. In addition, OHRP notes that the Saint John's IRB has continued to utilize such "block voting" even though Saint John's was previously informed that such voting does not allow for substantive and meaningful continuing review. See OHRP's December 6, 2004 letter to Saint John's.

Required Action: Please provide OHRP with a corrective action plan outlining how Saint John's will ensure that the IRB reviews sufficient information to make the determinations required for IRB approval, both at initial and continuing review, and that human subject research which is approved/re-approved by the Saint John's IRB satisfies the criteria outlined in 45 CFR 46.111. Please also provide a corrective action plan describing how the Saint John's IRB will ensure that each protocol undergoing continuing review or modification is considered and voted on separately.

(4) HHS regulations at 45 CFR 46.103(a) and 46.103(b)(5) require that institutions have procedures for ensuring prompt reporting to the IRB, appropriate institutional officials, any department or agency head, and OHRP of: (a) any unanticipated problems involving risks to subjects or others; (b) any serious or continuing noncompliance with 45 CFR part 46 or the requirements or determinations of the IRB; and (c) any suspension or termination of IRB approval. OHRP finds that the suspension of IRB approval for Radiation Therapy Oncology Group (RTOG) 0615, which is 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).

Required Action: Please report this IRB suspension to OHRP and the supporting HHS agency head (or designee). In addition, 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 the events referenced above.

(5) HHS regulations at 45 CFR 46.103(b) state, in part, that assurances applicable to HHS-supported or -conducted research shall include designation of one or more IRBs established in accordance with the requirements of the regulations. The Saint John's assurance presently designates the Saint John's IRB as the only IRB authorized to review research falling under its assurance. Interviews revealed that Saint John's has designated an additional IRB (the Saint Vincent's IRB) to review and approve certain research covered by the Saint John's assurance without prior OHRP approval. Thus, OHRP finds that Saint John's designated an additional IRB to review research covered by the Saint John's assurance without prior OHRP approval.

Required Action: Please update your FWA with OHRP to designate the Saint Vincent's IRB. In addition, please provide OHRP with a corrective action plan outlining how Saint John's will ensure that it will obtain prior OHRP approval before allowing any other IRB to review research to which the Saint John's FWA applies. In addition, please provide OHRP with a list of all the research studies (to which the Saint John's FWA applies) that were reviewed and approved by the Saint Vincent's IRB or any other IRB.

(6) HHS regulations at 45 CFR 46.103(b)(2) require, in part, that institutions provide meeting space and sufficient staff to support the IRB's review and recordkeeping duties. During its on-site evaluation, OHRP found that Saint John's does not have sufficient staff to ensure that all IRB review and recordkeeping duties are completed. OHRP found that the only "IRB-like" files maintained by Saint John's consist of "protocol notebooks" which are maintained by an oncology research nurse for the purposes of satisfying protocol recordkeeping requirements.

Required Action: Please provide OHRP with a corrective action plan outlining how Saint John's will ensure that it provides its IRB with sufficient staff to support IRB review and recordkeeping duties. As part of the corrective action plan, please outline what resources will be provided to the IRB administrative staff person to successfully complete his/her assigned tasks. For instance, please outline what IRB professional training/mentoring opportunities will be offered.

(7) HHS regulations at 45 CFR 46.109(d) provides that an IRB shall notify investigators and the institution in writing of its decision to approve or disapprove the proposed research activity, or of modifications required to secure IRB approval of the research activity. During the evaluation, OHRP learned the following regarding the Saint John's IRB:

(a) The IRB provides RTOG investigators with written documentation regarding IRB decisions. This written documentation consists of a RTOG IRB Certification Form, a certification form required by RTOG, not by Saint John's IRB. This form, which is signed and dated by the IRB Chair, only reflects the date that the IRB approved the proposed research; this form does not include any modifications that were required by the IRB to secure IRB approval.
(b) The IRB verbally notifies non-RTOG investigators of its decision to approve or disapprove proposed research activities.
(c) The IRB verbally notifies investigators of modifications required to secure IRB approval.

Based on the above, OHRP finds that the Saint John's IRB fails 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.

Required Action: Please provide OHRP with a corrective action plan outlining how Saint John's will ensure that the IRB will notify all investigators and the institution in

writing of its decision to approve or disapprove proposed research activities, or of modifications required to secure IRB approval of the research activities.

(8) HHS regulations at 45 CFR 46.115(a) provides that an institution, or when appropriate an IRB, shall prepare and maintain adequate documentation of IRB activities, including the following:

(a) Copies of all research proposals reviewed, scientific evaluations, if any, that accompany the proposals, approved sample consent documents, progress reports submitted by investigators, and reports of injuries to subjects.
(b) Minutes of IRB meetings which shall be in sufficient detail to show attendance at the meetings; actions taken by the IRB; the vote on these actions including the number of members voting for, against, and abstaining; the basis for requiring changes in or disapproving research; and a written summary of the discussion of controverted issues and their resolution.
(c) Records of continuing review activities.
(d) Copies of all correspondence between the IRB and the investigators.
(e) A list of IRB members in the same detail as described in 45 CFR 46.103(b)(3).
(f) Written procedures for the IRB in the same detail as described in 45 CFR 46.103(b)(4) and 45 CFR 46.103(b)(5).
(g) Statements of significant new findings provided to subjects, as required by 45 CFR 46.116(b)(5).

OHRP finds that Saint John's does not maintain adequate documentation of IRB activities in accordance with HHS regulations at 45 CFR 46.115(a). For example, the IRB-like records maintained by Saint John's are limited to copies of IRB minutes and "protocol notebooks" containing only the most current copies of IRB approved protocol-related documents. In one instance, the "protocol notebook" for HOG LUN 04-77 failed to contain any IRB-approved sample consent documents. According to the only person who maintains IRB-like records, Saint John's only maintains the most current IRB-approved protocol documents; all previously approved, but superseded IRB-approved protocol documents are discarded. Thus, Saint John's does not maintain copies of ALL research proposals reviewed (both current and old versions); ALL approved sample consent documents (both current and old versions), progress reports; records of continuing review activities; and copies of correspondence between the IRB and the investigators in accordance with HHS regulations at 45 CFR 46.115(a). As a result, it was not possible to reconstruct a complete history of all IRB actions related to the review and approval of the protocol. In most instances, OHRP could not determine what the IRB actually reviewed and approved.

Required Action: Please provide OHRP with a corrective action plan outlining how Saint John's will ensure that it prepares and maintains adequate documentation of IRB activities as required in HHS regulations at 45 CFR 46.115(a).

(9) HHS regulations at 45 CFR 46.115(b) require that IRB records be retained for at least 3 years, and records relating to research which is conducted be retained for at least 3 years

after completion of the research. All records must be accessible for inspection and copying by authorized representatives of HHS at reasonable times and in a reasonable manner. OHRP finds that Saint John's fails to retain IRB records for at least 3 years as required by HHS regulations at 45 CFR 46.115(b). OHRP reviewed the only IRB-like records that are maintained by Saint John's for all currently active studies and found that these records contain only the most current copies of IRB approved protocol-related documents; all previously IRB-approved documents are discarded when the documents are superseded by more current IRB- approved documents. OHRP discovered that a research nurse routinely shreds signed informed consent forms when the investigator determines that a potential subject can not be randomized into a study because the subject does not satisfy the study inclusion criteria.

Required Action: Please provide OHRP with a corrective action plan outlining how Saint John's will ensure that it retains documentation of IRB activities in accordance with HHS regulations at 45 CFR 46.115(b).

OHRP Action

In view of the above determinations and Saint John's failure to implement previously identified corrective actions, and in order to ensure adequate protections for human subjects, OHRP hereby suspends the Saint John's Health System Assurance (FWA-1780) in accordance with HHS regulations at 45 CFR 46.103(e), pending satisfactory completion of the required actions described below.

This suspension of FWA-1780, effective immediately, removes the Assurance required by HHS regulations at 45 CFR 46.103(a) for all U.S. federally supported research involving human subjects at Saint John's Health System covered by the FWA, including those research studies (covered by the Saint John's FWA) reviewed and approved by the Saint Vincent's IRB.

As a result, all U.S. federally supported human subjects research projects to which the FWA applies must be suspended. For any project affected by this suspension, enrollment of new subjects must cease immediately except in extraordinary cases approved in advance by OHRP. OHRP would expect approval requests for such cases to be rare. Furthermore, research activities involving previously enrolled subjects may continue only where it is in the best interests of such subjects. For each affected protocol this suspension must remain in effect until OHRP approval of the FWA is reinstated.

Required Actions Necessary for Reinstatement of FWA-1780:

(1) Saint John's must develop a satisfactory corrective action plan to address all deficiencies noted above.

(2) No later than September 28, 2007, Saint John's must provide a complete list of all U.S. federally supported research protocols that were suspended. Include the project title, principal investigator, IRB project number, and the federal department or agency project number. Saint John's should identify those projects which Saint John's determines that

research activities involving previously enrolled subjects may continue because it is in the best interests of the individual subjects. Please describe the procedures used to make such determinations.

(3) Saint John's must provide a satisfactory response to the following additional questions and concerns regarding Saint John's system for protecting human subjects:

[Redacted]

[Redacted]

Guidance to Assist Saint John's in Developing an Adequate Corrective Action Plan:

(1) OHRP strongly recommends that Saint John's revise it written IRB procedures so that the procedures include operational details for all of the following activities:

(a) The procedures which the IRB will follow for conducting its initial review of research.
(b) The procedures which the IRB will follow for conducting its continuing review of research.
(c) The procedures which the IRB will follow for reporting its findings and actions to investigators and the institution.
(d) The procedures for ensuring prompt reporting to the IRB, appropriate institutional officials, any department or agency head, and OHRP of: (a) any unanticipated problems involving risks to subjects or others; (b) any serious or continuing noncompliance with 45 CFR part 46 or the requirements or determinations of the IRB; and (c) any suspension or termination of IRB approval.
(e) The procedures which the IRB will follow for determining which projects require review more often than annually.
(f) The procedures which the IRB will follow for determining which projects need verification from sources other than the investigators that no material changes have occurred since previous IRB review.
(g) The procedures which the IRB will follow for ensuring prompt reporting to the IRB of proposed changes in a research activity, and for ensuring that such changes in approved research, during the period for which IRB approval has already been given, may not be initiated without IRB review and approval except when necessary to eliminate apparent immediate hazards to the subject.

Please refer to OHRP's Guidance on Written IRB Procedures, available at http://www.hhs.gov/ohrp/humansubjects/guidance/irbgd107.htm, when revising the

procedures. OHRP notes that Saint John's has not revised its written procedures even though OHRP previously recommended that Saint John's undertake such revisions.

OHRP encourages Saint John's to develop its corrective action plan expeditiously and forward it to OHRP for review as soon as possible. OHRP is available to assist Saint John's in the development and implementation of the corrective action plan. Do not hesitate to contact me should 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
Dr. Joanne Less, FDA
Dr. Bernard Schwetz, OHRP
Dr. Melody H. Lin, OHRP
Dr. Michael Carome, OHRP
Ms. Shirley Hicks, OHRP
Dr. Irene Stith-Coleman, OHRP
Dr. Kristina Borror, OHRP
Dr. Kevin Prohaska, OHRP
Ms. Kelley Booher, OHRP
Mr. Barry Bowman, OHRP