DEPARTMENT OF HEALTH & HUMAN SERVICES

Office of the Secretary
Office of Public Health and Science

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December 6, 2004

D. Kyle DeFur
Vice President, Operations
St. John's Health System
2015 Jackson St
Anderson, IN 46016

RE: Human Research Subject Protections Under Federalwide Assurance FWA- 1780

Research Projects: Radiation Therapy Oncology Group (RTOG) Protocols

Dear Mr. DeFur:

The Office for Human Research Protections (OHRP) has reviewed St. John's Health System's (SJHS) September 22, 2004 report responding to allegations of noncompliance with Department of Health and Human Services (HHS) regulations for the protection of human research subjects (45 CFR part 46).

Based upon its review, OHRP makes the following determinations regarding the above-referenced research:

(1) In accordance with HHS regulations at 45 CFR 46.103(b) and 46.109(a), the institutional review board (IRB) must review and approve all non exempt human subject research covered by an assurance. OHRP found that certain human subjects research was conducted without IRB review at a convened meeting. In specific, the IRB conducted review of protocol RTOG 02-12 via mail, and there was no discussion regarding the individual protocol. In addition, several protocols (RTOG 98-04, 99-02, 99-05, and 99-10) were voted on and approved en bloc at the October 19, 2000 IRB meeting, without any discussion.

Corrective Action: OHRP acknowledges that the SJHS IRB plans to restructure the IRB and that the SJHS IRB will meet monthly or bi-monthly until all protocol revisions are up to date, then will meet at least quarterly. SJHS plans to assign a different IRB member as primary reviewer for each protocol, to present the protocol to the IRB for discussion. In addition, the SJHS IRB has developed Guidelines for Initial Review of Studies and

Consent Forms.

Required Action: By January 19, 2005, please provide OHRP with copies of the minutes of IRB meetings for September, October, and November of 2004. Please also indicate whether or not protocols RTOG 02-12, 98-04, 99-02, 99-05, and 99-10 have been appropriately reviewed by the convened IRB, and provide documentation of that review.

(2) Continuing review of research must be substantive and meaningful. HHS regulations at 45 CFR 46.111 set forth the criteria that must be satisfied in order for the IRB to approve research. These criteria include, among other things, determinations made by the IRB regarding risks, potential benefits, informed consent, and safeguards for human subjects. The IRB must ensure that these criteria are satisfied at the time of both initial and continuing review. The procedures for continuing review by the convened IRB may include a primary reviewer system.

OHRP finds that continuing review of protocols RTOG 02-14, 98-04, 99-03, and 99-10 by the IRB was not substantive and meaningful and did not occur at a convened meeting of the IRB, but instead was conducted by mail. In addition, protocols RTOG 98-01 and 99-02 were sometimes voted on and approved en bloc during continuing review, without any discussion by the convened IRB.

Corrective Action: OHRP acknowledges that the SJHS IRB plans to restructure the IRB, and that the SJHS IRB will meet monthly or bi-monthly until all protocol revisions are up to date, then will meet at least quarterly to reduce the possibility of any lapse in approval of protocols.

Required Action: By January 19, 2005, please provide OHRP with a copy of the IRB's written procedures for conducting continuing review. Please also indicate whether or not protocols RTOG 02-14, 99-03, 99-10, 98-04, 98-01, and 99-02 have received appropriate continuing review by the convened IRB, and provide documentation of that review.

(3) OHRP finds that the institution does not have written IRB procedures that adequately describe the following activities, as required by HHS regulations at 45 CFR 46.103(a) and 46.103(b)(4) and (5):

> (a) The procedures which the IRB will follow for conducting its continuing review of research.
>
> (b) The procedures which the IRB will follow for determining which projects require review more often than annually.
>
> (c) 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.

(d) 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.

(e) 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.

Required Action: By January 19, 2005, please provide OHRP with revised written IRB procedures to address this finding. Written IRB policies and procedures should provide a step-by-step description, with key operational details for each of the procedures required by HHS regulations at 45 CFR 46.103(b)(4) and (5). (See http://www.dhhs.gov/ohrp/humansubjects/guidance/irbgd702.htm for guidance.)

OHRP has the following additional questions:

(4) [Redacted]

Please submit to OHRP corrective actions to address the above findings and responses to the required actions and questions no later than January 19, 2005. If your responses reveal further noncompliance, please provide a description of any corrective actions that have been or will be taken by your institution to prevent such noncompliance from recurring.

At this time, OHRP has the following additional recommendations:

(5) 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, 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 multicenter 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 (i.e., a primary reviewer) also should receive a copy of the complete protocol, including any 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. The minutes of IRB meetings should document separate deliberations, actions, and votes for each protocol undergoing continuing review by the convened IRB.

(6) OHRP has the following recommendations regarding the SJHS written IRB procedures:

(a) The SJHS written IRB procedures state that the purpose of the IRB is to review clinical investigations regulated by the Food and Drug Administration (FDA). as well as clinical investigations that support applications for products regulated by the FDA. The SJHS FWA states that the IRB will review all federally-supported human subjects research, not just clinical investigations. OHRP recommends that the SJHS written IRB procedures be modified to state this.

(b) The SJHS written IRB procedures only reference FDA regulations. OHRP recommends that the SJHS written IRB procedures be modified to reference 45 CFR part 46, as indicated in the SJHS FWA.

(c) The SJHS written IRB procedures state that clinical investigators requesting approval for a protocol will not be present when the IRB committee votes on their protocol or requests. HHS regulations at 45 CFR 46.107(e) stipulate that no IRB member may participate in the IRB's initial or continuing review of a project in which the member has a conflicting interest, except to provide information requested by the IRB. OHRP recommends that except when requested by the IRB to be present to provide information, IRB members absent themselves from the meeting room when the IRB reviews research in which they have a conflicting interest, and such should be noted in the IRB meeting minutes.

(d) The SJHS written IRB procedures note that the minutes of the IRB meetings will reflect several types of actions by the IRB. OHRP recommends that the procedures also reference other requirements of HHS regulations at 45 CFR 46.115(a)(2), such as that minutes of IRB meetings be in sufficient detail to show attendance at the meetings; actions taken by the IRB; the basis for requiring changes in or disapproving research; and a written summary of the discussion of

controverted issues and their resolution.

OHRP appreciates the continued commitment of your institution to the protection of human research subjects. Please do not hesitate to contact me should you have any questions.

Sincerely,

Kristina C. Borror, Ph.D.
Director, Division of Compliance Oversight

cc: Mr. Lawrence M. Tarnow R.Ph., IRB Administrator, St. John's Hlth System
Dr. Thomas P. Bright M.D., Chairman, St. John's Hlth System IRB #1
Dr. Andrew C. von Eschenbach, Director, NCI
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