DEPARTMENT OF HEALTH & HUMAN SERVICES

Office of the Secretary
Office of Public Health and Science

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February 25, 2005

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 and January 17, 2005 reports responding to determinations 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 determination regarding the above-referenced research:

> OHRP finds that the IRB failed to review some protocol changes prior to initiation of such changes, in contravention of HHS regulations at 45 CFR 46.103(b)(4)(iii). In specific, some protocol changes were not reviewed and approved by the IRB until continuing review, although the protocol changes had already been implemented.
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> **Corrective Action:** OHRP acknowledges SJHS's statement that all changes that were greater than minor were reviewed at a convened meeting of the IRB. SJHS plans to increase IRB meetings to at least quarterly and will add additional meetings as necessary if the IRB needs to review proposed changes at a convened meeting.
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> OHRP finds that this corrective action adequately address the above finding. OHRP also

finds that corrective actions outlined in SJHS's September 22, 2004 and January 17, 2005 reports adequately address the findings outlined in OHRP's December 6, 2004 letter, and are appropriate under the SJHS FWA. As a result, OHRP is closing its compliance oversight investigation into this matter.

Please note that OHRP anticipates conducting a compliance oversight site visit at SJHS within the next 12-18 months.

At this time, OHRP offers the following additional guidance:

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(a) and (b)(4) and (5):

(a) A description of any primary reviewer system used for initial review, continuing review, review of protocol changes, and/or review of reports of unanticipated problems involving risks to subjects or others or of serious or continuing noncompliance.

(b) Lists of specific documents distributed to primary reviewers (if applicable) and to all other IRB members for initial review, continuing review, review of protocol changes, and review of reports of unanticipated problems involving risks to subjects or others or of serious or continuing noncompliance.

(c) Details of any process (e.g., a subcommittee procedure) that may be used to supplement the IRB's initial review, continuing review, review of protocol changes, and/or review of reports of unanticipated problems involving risks to subjects or others or of serious or continuing noncompliance.

(d) The timing of document distribution prior to IRB meetings.

(e) The range of possible actions taken by the IRB for protocols undergoing initial or continuing review and protocol changes undergoing review.

(f) A description of how expedited review is conducted and how expedited approval actions are communicated to all IRB members.

(g) A description of the procedures for: (i) communicating to investigators IRB action regarding proposed research and any modifications or clarifications required by the IRB as a condition for IRB approval of proposed research; and (ii) reviewing and acting upon investigators' responses.

(h) A description of which institutional office(s) and official(s) are notified of IRB findings and actions and how notification to each is accomplished.

(i) A description, if applicable, of which institutional office(s) or official(s) is

responsible for further review and approval or disapproval of research that is approved by the IRB. Please note that, in accordance with HHS regulations at 45 CFR 46.112, no other institutional office or official may approve research that has not been approved by the IRB.

(j) A specific procedure for how the IRB determines which protocols require review more often than annually, including specific criteria used to make these determinations (e.g., an IRB may set a shorter approval period for high-risk protocols or protocols with a high risk:potential benefit ratio).

(k) A specific procedure for how the IRB determines which projects need verification from sources other than the investigators that no material changes have occurred since previous IRB review, including specific criteria used to make these determinations (e.g., such criteria could include some or all of the following: (i) randomly selected projects; (ii) complex projects involving unusual levels or types of risk to subjects; (iii) projects conducted by investigators who previously have failed to comply with the requirements of the HHS regulations or the requirements or determinations of the IRB; and (iv) projects where concern about possible material changes occurring without IRB approval have been raised based upon information provided in continuing review reports or from other sources).

(l) A description of what steps are taken to ensure that investigators do not implement any protocol changes without prior IRB review and approval, except when necessary to eliminate apparent immediate hazards to subjects (e.g., this might be addressed through training programs and materials for investigators, specific directives included in approval letters to investigators, and random audits of research records).

(m) A description of which office(s) or institutional official(s) is responsible for promptly reporting to the IRB, appropriate institutional officials, any supporting Agency or Department heads, and OHRP any (i) unanticipated problems involving risks to subjects or others; (ii) any serious or continuing noncompliance with 45 CFR Part 46 or the requirements or determinations of the IRB; and (iii) any suspension or termination of IRB approval.

(n) A description of the required time frame for accomplishing the reporting requirements in the preceding paragraph.

(o) The range of possible actions taken by the IRB in response to reports of unanticipated problems involving risks to subjects or others or of serious or continuing noncompliance.

(p) Institutions may wish to consider including additional pertinent information in their written IRB procedures, such as the following: (a) important definitions

(e.g., the definition of *research*, *human subject*, and *minimal risk)*; (b) a description of procedures for implementing other relevant Federal regulations that apply to human subject research (e.g., FDA and HIPAA regulations); (c) procedures for selecting and appointing the IRB chairperson and members in order to satisfy the requirements of HHS regulations at 45 CFR 46.107; (d) procedures for training and educating IRB members and staff and investigators; (e) a description of the required elements of informed consent and criteria for waiving or altering these requirements; and (f) procedures for ensuring that the IRB possesses sufficient knowledge of the local research context.

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
Ms. Joan Mauer, Acting Chief, Clinical Trials Monitoring Branch, NCI
Dr. Lana Skirboll, Director, OSP, NIH
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Ms. Shirley Hicks, OHRP
Ms Patricia El-Hinnawy, OHRP
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