DEPARTMENT OF HEALTH & HUMAN SERVICES

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Office of Public Health and Science

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May 19, 2005

Bonnie Phipps, CPA, CMCP
St. Joseph's Hospital Atlanta, Inc.
5665 Peachtree Dunwoody Road, NE
Atlanta, GA 30342-1764

RE: Human Research Subject Protections Under Federalwide Assurance FWA-292

Dear Ms. Phipps:

The Office for Human Research Protections (OHRP) has reviewed St. Joseph's Hospital Atlanta's (SJHA) March 24, 2005 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) involving the above-referenced research as outlined in OHRP's January 28, 2005 letter.

Based upon its review, OHRP makes the following determinations regarding general human subject protections at SJHA:

(1) HHS regulations at 45 CFR 46.109(e) require that continuing review of research be conducted by the IRB at intervals appropriate to the degree of risk, and not less than once per year. OHRP finds that the SJHA IRB failed to conduct continuing review of numerous research protocols at least once per year, and that certain research was conducted during this lapse in approval. In specific, OHRP notes that:

(a) SJHA's August 18, 2004 letter to OHRP stated that, in response to the lapse of approval of protocols, "Sanctions of the IRB have ranged from issuing warning letters ... to principal investigators to the suspension of the enrollment of new subjects in the study or studies at issue of noncompliance until it can be demonstrated that the study is in full compliance." OHRP notes that when approval lapses, all research activity must stop, unless it is determined to be in the best interest of subjects already enrolled.

This appears to be SJHA's written policy (see SOP Number IRB 006, page 1, and

the Notification of Protocol Lapse and Noncompliance), but it is not clear that this policy is followed. For example, SJHA's March 24, 2005 report stated, "Specifically, it has not been clear to the IRB that the collection of data or the follow-up of subjects who are not receiving any study treatment or intervention [emphasis in original] constitutes 'research' that must be stopped during a period of lapse in IRB approval." OHRP notes that, in general, **all** research activities must stop when IRB approval has expired. No interaction or intervention with human subjects for research purposes may be conducted, and no identifiable private information may be obtained or analyzed for research purposes after IRB approval expires, unless it is determined to be in the best interest of subjects already enrolled.

In addition, continuing review must occur as long as human subjects research is being conducted. This means that, as long as interactions or interventions with human subjects for research purposes are being conducted, or identifiable private information is being obtained or analyzed for research purposes, continuing review must occur at least annually.

(b) OHRP finds that continuing review did not occur at least annually for the following protocols:

(i) 007-03 and 038-02 (noted in the minutes of the March 10, 2004 IRB meeting).

(ii) 910-03 (noted in the minutes of the June 10, 2004 IRB meeting; had expired in November 2003.)

(iii) 015-02 (noted in the minutes of the June 16, 2004 IRB meeting; had expired in March 2004 but was not reviewed until May 2004.)

(Iv) Numerous other protocols were not reviewed at least annually as indicated by the spreadsheet of active protocols and review dates provided in SJHA's March 24, 2005 report.

Corrective Action: OHRP acknowledges that the SJHA IRB has conducted a manual audit of files for most recent approval and for cleanup of the electronic tracking system; has ensured that accurate mail logs are kept and cross-checked daily; and is updating the spreadsheet used for tracking protocols on an ongoing basis. Based upon spreadsheet data, IRB staff sends the principal investigator a notice of reminder for continuing review submission about sixty days prior to the expiration of IRB approval. In addition, the reminder notice clearly states that failure to obtain continuing review approval by the expiration date requires that all research stop. The SJHA IRB is also considering the use of a commercial database for tracking protocols. Upon expiration of IRB approval, the IRB will develop and send a form to the principal investigator notifying him or her to stop all research activities, and will include a form that the investigator acknowledges the

termination and assures the IRB that research has stopped. The IRB chair will designate an IRB member to assure that all research activities have stopped. OHRP finds that these corrective actions adequately address the above finding and are appropriate under the SJHA assurance. OHRP recommends that the SJHA IRB adopt written procedures for handling investigator requests to allow research activities to continue for subjects who are already enrolled in protocols for which IRB approval has expired.

(2) 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 the initiation of such changes, except when necessary to eliminate apparent immediate hazards to the subjects. OHRP finds that numerous protocol changes were implemented without IRB approval. In specific, OHRP notes the following:

(a) At the September 5, 2003 IRB meeting, the SJHA IRB noted that protocol #018-00 had a large number of deviations (changes to protocol). In addition, five "protocol exceptions" were approved in advance for this protocol by the sponsor, but were not approved by the IRB.

(b) At the October 3, 2003 meeting, the SJHA IRB accepted the American Cardiovascular Research Institute's (ACRI) action plan to ensure the reporting of deviations in a timely manner. The IRB apparently did not address the number of deviations or the changes that had been made to the protocol without IRB review and approval.

(c) The minutes of the July 15, 2004 SJHA IRB meeting indicate 17 deviations in protocol 009-04, some of them having occurred as long ago as April 2004. There was no discussion in the minutes of the deviations or any plans to prevent them.

Corrective Action: OHRP acknowledges that the SJHA IRB has taken numerous actions to help ensure that the SJHA IRB reviews and approves all proposed changes in a research activity, during the period for which IRB approval has already been given, prior to the initiation of such changes, except when necessary to eliminate apparent immediate hazards to the subjects. The IRB's written procedures indicate that the IRB must approve all changes to a protocol prior to their implementation, and the IRB approval form to investigators will make this clear. The IRB will also offer a mandatory educational opportunity for investigators and research coordinators to ensure their understanding of reporting requirements. OHRP finds that these corrective actions adequately address the above finding and are appropriate under the SJHA assurance.

(3) HHS regulations at 45 CFR 46.115(a) require that the institution prepare and maintain adequate documentation of IRB activities. OHRP finds that the SJHA IRB often failed to maintain records adequately. On the list of active protocols in SJHA's August 18, 2004 report, 46 protocols had as the date of initial approval, "Initial approval letter not on file

at IRB or site." This implies that the SJHA does not have any record of when these studies were first approved.

Corrective Action: OHRP acknowledges that the SJHA IRB has increased its ability to monitor protocol documentation with the expanded database and has increased the number of IRB staff. OHRP finds that these corrective actions adequately address the above finding and are appropriate under the SJHA assurance.

(4) HHS regulations at 45 CFR 46.115(a)(2) require that minutes of IRB meetings 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. OHRP finds that the SJHA IRB minutes sometimes failed to meet these requirements. In specific, OHRP notes the following:

(a) The minutes of the July 11, 2003 meeting had nine members listed as present, but only seven or eight voted on protocols (there is no mention of members leaving the room or abstaining). Most of the protocols for full board review at this meeting have no vote or decision listed.

(b) The minutes of the February 19, 2004 IRB meeting lack a vote or decision on protocol # 008-03, which was up for continuing review by the convened IRB.

(c) The minutes of the April 8, 2004 IRB meeting lack a vote or decision on protocol # 018-02, which had an amendment that required review by the convened IRB.

(d) The minutes of the May 13, 2004 IRB meeting indicate that, in reviewing minutes of previous IRB meetings, it was discovered that members were noted as attending a particular meeting they had not actually attended. This is another indication of problems with recording attendance and with keeping track of votes.

Corrective Action: OHRP acknowledges that the SJHA IRB has introduced a sign-in sheet for IRB members for each meeting, and that at least two IRB staff members are present at each meeting to ensure that votes and discussions are accurately reflected in the minutes. Required follow-up from each meeting will be recorded on an action checklist by the IRB administrator. OHRP finds that these corrective actions adequately address the above finding and are appropriate under the SJHA assurance.

(5) HHS regulations at 45 CFR 46.103(a) and (b)(5) require that institutions promptly report to OHRP: (1) any unanticipated problems involving risks to subjects or others; (2) any serious or continuing noncompliance with this policy or the requirements or determinations of the IRB; and (3) any suspension or termination of IRB approval. OHRP finds that SJHA did not promptly report all such incidents to OHRP. In specific, OHRP notes the following:

(a) At the September 5, 2003 IRB meeting, the IRB voted to suspend enrollment in protocol #005-02. This was not reported to OHRP.

(b) On December 5, 2003, the minutes indicated, "Due to the **repeated** non-compliance issues at ACRI from multiple studies.... [emphasis added]" This continuing noncompliance was not reported to OHRP until March 2004.

(c) At the October 3, 2003 meeting, the IRB voted to consider enrollment of subjects in protocol # 038-02 to be serious noncompliance. This was not reported to OHRP.

(d) The minutes of the December 5, 2003 IRB meeting state, regarding protocol #042-03, "There is concern the SAEs submitted need to be included on the consent in the Risks Section. Specifically the possibility of a stroke and weakening heart muscle." It appears that these events represented unanticipated problems involving risks to subjects or others, since they were not previously mentioned in the informed consent document; these events were not reported to OHRP.

(e) The addendum to the minutes of the February 19, 2004 meeting indicate that the IRB voted to suspend enrollment to protocol #008-03; this suspension was not reported to OHRP.

Corrective Action: OHRP acknowledges that the SJHA written IRB procedures indicate that "any action taken by the IRB related to a SAE or unanticipated problem involving risks to subjects or others shall be promptly reported to ... OHRP." Please note that not only actions taken in response to unanticipated problems need to be reported to OHRP but **all** unanticipated problems involving risks to subjects or others. OHRP also acknowledges that required follow-up from each IRB meeting will be recorded by the IRB administrator on an action checklist which the administrator will use to ensure that all such incidents are reported to OHRP. OHRP finds that these corrective actions are adequate to address the above finding, if the written IRB procedures are revised to ensure that **all** unanticipated problems involving risks to subjects or others are reported to OHRP.

(6) HHS regulations at 45 CFR 46.110(b)(1) limit the use of expedited review procedures to specific research categories published in the Federal Register at 63 FR 60364--60367. OHRP finds that the IRB inappropriately applied expedited review to research that involves minimal risk but that does not appear in the categories of research published in the Federal Register. In specific, at the November 7, 2003 IRB meeting, a protocol was listed as expedited for initial review– #032-03, "A Study of the Effect of a Protocol Guided Rocking Chair Intervention on Delirium in Older Hospital Patients." In your March 24, 2005 report to OHRP, you indicated that this protocol involved the collection of data on the use of a rocking chair as an intervention to facilitate a reduction in the severity of delirium episodes. The study consisted of controlled, randomized open

treatment vs. no treatment. This would not meet the criteria for expedited review category 7, as you indicated in your report, nor for any other category appropriate for expedited review.

Required Action: By June 17, 2005, please provide OHRP with a satisfactory corrective action plan to ensure that the SJHA IRB reviews in an expedited manner only those protocols that are eligible for expedited review. In your corrective action plan please provide for the review of protocol #032-03 by the convened IRB.

(7) OHRP finds that SJHA did 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)(5): The procedures for ensuring prompt reporting to the IRB, appropriate institutional officials, any Department or Agency head, and OHRP of any unanticipated problems involving risks to subjects or others. The written IRB procedures focus on adverse events and do not describe the procedures for reporting to OHRP. Please respond. In addition, the written procedures do not indicate which institutional official(s) is to receive relevant reports.

Corrective Action: OHRP acknowledges that the SJHA written IRB procedures indicate that "any action taken by the IRB related to a SAE or unanticipated problem involving risks to subjects or others shall be promptly reported to ... OHRP." Please note that not only actions taken in response to unanticipated problems need to be reported to OHRP, but **all** unanticipated problems involving risks to subjects or others. OHRP finds that these corrective actions are adequate to address the above finding, if the written IRB procedures are revised to ensure that **all** unanticipated problems involving risks to subjects or others are reported to OHRP.

OHRP has the following additional questions and concerns:

(8) [Redacted]

(9) [Redacted]

At this time, OHRP offers the following additional guidance:

(10) HHS regulations make no provision for any grace period extending the conduct of research beyond the expiration date of IRB approval. Additionally, where the convened IRB specifies conditions for approval of a protocol that are to be verified as having been satisfied by the IRB chair or another IRB member designated by the chair, continuing review for research that is not eligible for expedited review must occur no more than one year after the date on which the protocol was reviewed by the convened IRB, not on the anniversary of the date the IRB chair or his or her designee verified that IRB-specified conditions for approval had been satisfied.

The IRB and investigators must plan ahead to meet required continuing review dates. If an investigator has failed to provide continuing review information to the IRB, or if the IRB has not reviewed and approved a research study by the continuing review date specified by the IRB, the research must stop, unless the IRB finds that it is in the best interests of individual subjects to continue participating in the research interventions or interactions. Enrollment of new subjects cannot occur after the expiration of IRB approval.

(11) OHRP expressed concern in our January 28, 2005 letter that when reviewing protocol applications, the SJHA IRB often appears to lack sufficient information to make the determinations required for approval of research under HHS regulations at 45 CFR 46.111. In specific, OHRP noted the following:

(a) At the November 7, 2003 meeting, protocol #036-03 was approved pending information about whether the use of the pacemaker will result in any increased risk to the subject. The information the IRB requested was reviewed by the IRB chair and not by the convened IRB.

(b) At the November 7, 2003 meeting, protocol #030-03 was approved pending receipt of information about whether or not the protocol involved children, and pending the provision of a separate consent. The information the IRB requested was reviewed by the IRB chair and not by the convened IRB. It is not clear from the minutes or how SJHA's March 24, 2005 report if the protocol would have been brought back to the convened IRB for review if the protocol had involved children.

(c) At the May 13, 2004 meeting, protocol #004-98 was approved pending information about if and how patient safety had been affected by the lapse in approval of the protocol. The information the IRB requested was reviewed by the IRB chair and not by the convened IRB.

(d) At the May 13, 2004 meeting, protocol #029-00 was approved pending an explanation of an event in which an untrained investigator deployed a stent, and an explanation about why one third of all patients did not have an ultrasound at approved sites. The minutes of the July 11, 2003 meeting indicate that for the CREST #511 protocol, a deviation had also occurred in the past– "[this] implies a systemic problem." The information the IRB requested was reviewed by the IRB chair and not by the convened IRB.

OHRP recommends the following guidelines in such cases: (a) When the convened IRB requests substantive clarifications or modifications regarding the protocol or informed consent documents that are directly relevant to the determinations required by the IRB under HHS regulations at 45 CFR 46.111, IRB approval of the proposed research should be **deferred**, pending subsequent review by the convened IRB of responsive material. (b) Only when the convened IRB stipulates specific revisions requiring simple concurrence by the investigator may the IRB chair or another IRB member designated by the chair subsequently approve the revised research protocol on behalf of the IRB under an expedited review procedure. OHRP also notes that the SJHA does not appear to defer approval of protocols.

(12) HHS regulations at 45 CFR 46.110 allow expedited review for certain categories of research published in the Federal Register (see 63 FR 60364-60367, November 9, 1998). Continuing review of research previously approved by the convened IRB may be reviewed in an expedited manner where (i) the research is permanently closed to the enrollment of new subjects; (ii) all subjects have completed all research-related interventions; and (iii) the research remains active only for long-term follow-up of subjects; and under other circumstances. OHRP notes that "research-related interventions" would include any medical or psychological procedure done for research purposes, including filling out questionnaires for research purposes. Long-term follow-up includes determining mortality of subjects or a medical record review. If the only ongoing interventions/interactions represent activities that would qualify for expedited review under other categories of research activities eligible for expedited review, it would be reasonable to permit the use of an expedited review procedure for such research.

(13) As noted above in finding (1)(a), continuing review must occur as long as human subjects research is being conducted. This means that, as long as interactions or interventions with human subjects for research purposes are being conducted, or identifiable private information is being obtained or analyzed for research purposes, continuing review must occur at least annually. OHRP notes that the memo "Friendly Reminder of Annual Review" states, "If your site has completed this study, please submit a Retirement Report form for our records." OHRP recommends that the memo elaborate on what is meant by "completed" or that the IRB educate investigators about when a study is considered to no longer involve human subjects.

(14) OHRP notes that the IRB rosters for SJHA IRBs #1 and #2 list several alternate members as alternates for more than one IRB member, with varying expertise, such as cardiology and oncology. When approving assurances designating IRBs which include alternate IRB members, OHRP assumes that, in general, with respect to the capacity in which the primary IRB member was intended to serve, each alternate IRB member has experience, expertise, background, professional competence, and knowledge equivalent to that of the primary IRB member whom the alternate would replace. As such, whenever an alternate member substitutes for a primary member of the IRB, the combined requirements of §§ 46.107(a) and 46.108(b) should remain satisfied.

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: Sr. Jane Gerety, IRB Administrator/Senior VP Sponsorship/CCO
Dr. Guy Orangio, Chair, SJHA IRBs
Commissioner, FDA
Dr. David Lepay, FDA
Dr. Bernard Schwetz, OHRP
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Dr. Michael Carome, OHRP
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