DEPARTMENT OF HEALTH & HUMAN SERVICES

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Office of Public Health and Science

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October 3, 2001

William S. Minogue, M.D.
Interim President and Chief Executive Officer
Suburban Hospital
8600 Old Georgetown Road
Bethesda, MD 20814

RE: Human Research Subject Protections Under Cooperative Project Assurance (CPA) T-3753

Dear Dr. Minogue:

As you know, the Office for Human Research Protections (OHRP) conducted an on-site not-for-cause evaluation of human subject protection procedures at Suburban Hospital (SH) on September 25-26, 2001. The evaluation involved meetings with senior institutional officials, the Chair and several members of SH's Institutional Review Board (IRB), the IRB administrator, and investigators who conduct research supported by the Department of Health and Human Services (HHS). The evaluation included a review of current IRB files for 15 HHS funded protocols, and the minutes of IRB meetings convened during the past six months, and SH's written IRB policies and procedures..

During the course of the OHRP visit, the IRB Chair, members, and administrator displayed a sincere concern for the protection of human research subjects and appeared to be highly dedicated. In addition, the investigators interviewed demonstrated a culture of respect for the IRB process. Such actions indicate a significant institutional commitment to the protection of human subjects.

OHRP Findings And Concerns Relative to Systemic Protections for Human Subjects

Based on its evaluation, OHRP makes the following determinations and notes the following concerns relative to systemic protections for human subjects at SH:

(1) OHRP finds that the SH application for approval of research does not solicit all of the information necessary to make the determinations required for approval of research under HHS regulations at 45 CFR 46.111, including information concerning (a) the equitable selection of subjects; (c) provisions to protect the privacy of subjects and maintain the confidentiality of data; and (d) additional safeguards to protect the rights and welfare of subjects who are likely to be vulnerable, including those incapable of giving consent, patients in emergency situations or nursing homes, and patients with incurable diseases.

(2) Continuing IRB review of research should be substantive and meaningful. 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 (a) the number of subjects accrued; (b) a description of any adverse events or

unanticipated problems involving risks to subjects or others and of any withdrawal of subjects from the research or complaints about the research; (c) a summary of any recent literature, findings obtained thus far, amendments or modifications to the research since the last review, reports on multi-center trials and any other relevant information, especially information about risks associated with the research; and (d) a copy of the current informed consent document. Primary reviewer systems may be employed, so long as the full IRB receives the above information. Primary reviewers should also receive a copy of the complete protocol including any modifications previously approved by the IRB (see OPRR Reports 95-01 at http://ohrp.osophs.dhhs.gov/humansubjects/guidance/hsdc95-01.htm).

OHRP is concerned that the minutes of SH IRB meetings rarely document any substantive deliberation of issues for protocols undergoing continuing review. In particular, ORHP is concerned about the lack of documented discussion regarding whether protocols and/or informed consent documents require modification based upon the occurrence of noted adverse events.

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

> (a) The procedures which the IRB will follow (i) for conducting its initial and continuing review of research and for reporting its findings and actions to the investigator and the institution; (ii) for determining which projects require review more often than annually and which projects need verification from sources other than the investigators that no material changes have occurred since previous IRB review; and (iii) 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.
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> (b) The procedures for ensuring prompt reporting to the IRB, appropriate institutional officials, and Department or Agency head of (i) any unanticipated problems involving risks to subjects or others or any serious or continuing noncompliance with 45 CFR Part 46 or the requirements or determinations of the IRB; and (ii) any suspension or termination of IRB approval

(4) OHRP is concerned about the adequacy of the IRB's present procedures for ensuring prompt reporting, review, and evaluation of unanticipated problems involving risks to subjects or others. OHRP finds that SH has confounded the requirements of adverse event reporting to other entities, such as the Food and Drug Administration (FDA), the NIH Office of Biotechnology Activities, and study sponsors, with the HHS reporting requirements at 45 CFR 46.103(b)(5). The SH IRB minutes do not identify which adverse events reported by investigators were determined by the IRB to be unanticipated problems involving risks to subjects or others, requiring a report to ORHP. When an adverse event is reported to the IRB, the IRB should analyze whether the adverse event was anticipated by reviewing the description of potential risks in the research protocol, any applicable Investigator's Brochure, and the informed consent document. The IRB should also make an independent determination of whether the informed consent document(s) related to the

relevant research project should be modified to include information related to the unanticipated adverse event.

(5) 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 IRB minutes often failed to meet these requirements. OHRP notes that SH's stated intention (in its March 7, 2001 letter to the FDA) to tape record meetings would not satisfy the written documentation requirements of HHS regulations at 45 CFR 46.115(a)(2).

(6) OHRP is concerned that the volume of research reviewed by the SH IRB at each convened meeting may be excessive. In particular, OHRP is concerned that adherence to a strict one hour time limit may provide insufficient opportunity for substantive dialogue and may inhibit IRB members from raising important issues. For example, at its meeting on September 11, 2000, the IRB reviewed five new protocols, eleven protocols undergoing continuing review, six adverse event reports, and two protocol updates within the one hour time frame. Given the anticipated expansion of SH's research programs and collaborations with the National Institutes of Health, the volume of research overseen by the SH IRB is likely to increase in the future.

Required Corrective Actions and Recommendations

In order to address the problems and concerns noted above, OHRP requires the following corrective actions and makes the following recommendations:

Action 1 - Required: By November 2, 2001, SH must submit to OHRP a satisfactory corrective plan to address the above findings and concerns. The plan should include: (i) revised IRB Policies and Procedures and (ii) a revised version of the IRB Application for Approval of Research that solicits all of the information necessary for the IRB to make the required determinations under 45 CFR 46.111.

Action 2 - Required: By January 1, 2002, SH must provide to OHRP a copy of its minutes of IRB meetings convened between October 1, 2001, and December 31, 2001, so that OHRP can assess SH's compliance with the HHS regulatory requirements regarding (i) continuing review of research involving human subjects; (ii) assessing and reporting unanticipated problems involving risks to subjects or others; and, (iii) the requirements for documentation of IRB minutes set forth in HHS regulations at 45 CFR 46.115(a)(2).

Action 3- Recommended: In order to document the continued existence of a quorum, votes at convened meetings of the IRB should be recorded in the minutes using the following format: Total = 11; Vote: For-11, Opposed-0, Abstained-0 (NAME OF ANY ABSTAINING MEMBERS).

Action 4 - Recommended: OHRP recommends that SH develop and distribute a handbook of IRB guidelines for research investigators. The handbook should include detailed information concerning (a) HHS and institutional requirements for the protection of human research subjects; (b) the IRB's role and responsibilities; (c) the requirements and procedures for initial and continuing IRB review and approval of research; (d) the rationale and procedures for proposing that the research may meet the criteria for expedited review; (e) the requirements and procedures for verifying that research is exempt from IRB review; (f) the responsibilities of investigators during the review and conduct of research; (g) requirements and procedures for notifying the IRB of unanticipated problems or events involving risks to the subjects, as well as any other expected or unexpected adverse events; (h) an explanation of the distinction between FDA requirements

for emergency use of test articles versus HHS regulations for the conduct of human subjects research; (i) relevant examples and user-friendly forms for providing information to the IRB; and (j) a copy of the institution's MPA, the HHS humans subjects regulations (45 CFR Part 46), and *The Belmont Report*. Where appropriate, OHRP also recommends that IRBs develop written operating procedures to supplement its guidelines for investigators.

Action 5 - Recommended: OHRP recommends that SH consider whether its IRB workload at this point, or in the foreseeable future given the expected increase in volume of research protocols at SH, requires either more than one fully functional IRB, longer IRB meetings, or more frequent meetings.

OHRP appreciates the commitment of SH to the protection of human subjects, and is available to assist SH in implementing the above corrective actions.

Sincerely,

Carol J. Weil, J.D.
Division of Compliance Oversight

cc: Dr. Michael Carome, OHRP
Dr. Jeffrey Cohen, OHRP
Mr. George Gasparis, OHRP
Dr. Melody H. Lin, OHRP
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