DEPARTMENT OF HEALTH & HUMAN SERVICES

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October 11, 2000

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Loretta Jett, B.S., B.S.N, R.N.
Institutional Review Board Coordinator
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RE: Human Research Subject Protections Under Cooperative Project Assurance (CPA) T-4496

Dear Mr. Rigdon, Dr. Ferguson, and Ms. Jett:

The Office for Human Research Protections (OHRP) has reviewed the September 19, 2000 report from Northeast Georgia Health System, Inc., (NGHS) responding to the OHRP's August 4, 2000 letter.

OHRP finds that NGHS has developed adequate corrective action plans to address each of the following areas of apparent noncompliance with Department of Health and Human Services (HHS) regulations for the protection of human subjects that were cited in OHRP's August 4, 2000 letter:

> (1) Failure of the institution to maintain adequate written Institutional Review Board (IRB) policies and procedures as required by HHS regulations at 45 CFR 46.103(b)(4) and (5).

Corrective Action: NGHS has written new, detailed IRB policies and procedures.

(2) Failure of the IRB to conduct adequate and timely continuing review of research involving human subjects, as required by HHS regulations at 4CFR 46.109(e).

Corrective Action: NGHS has developed a continuing review procedure that should ensure timely, substantive, and meaningful continuing review of research.

(3) Failure of the IRB to include at least one member who is not otherwise affiliated with the institution and who is not part of the immediate family of a person who is affiliated with the institution, as required by HHS regulations at 45 CFR 46.107(d).

Corrective Action: The current NGHS IRB membership roster includes members who are not otherwise affiliated with NGHS.

(4) The convened IRB reviewed and approved many research protocols without a majority of members being present, in contravention of the requirements of HHS regulations at 45 CFR 46.108.

Corrective Action: NGHS has implemented IRB procedures for ensuring that a majority of members are present whenever the convened IRB reviews and acts upon research protocols.

(5) Failure of the IRB to notify investigators and the institution in writing of its decisions to approve or disapprove proposed research activities, as required by HHS regulations at 45 CFR 46.109.

Corrective Action: NGHS has implemented IRB procedures for ensuring that the IRB notifies investigators and the institution of its decisions to approve or disapprove proposed research activities.

(6) Failure of NGHS and its IRB to maintain the documents stipulated by HHS regulations at 45 CFR 46.115.

Corrective Action: NGHS has implemented IRB procedures for ensuring that the IRB maintains the documents stipulated by HHS regulations at 45 CFR 46.115.

(7) Minutes of IRB meetings lack the information required by HHS regulations at 45 CFR 46.115(a)(2).

Corrective Action: NGHS has implemented IRB procedures for ensuring that IRB minutes include the information required by HHS regulations at 45 CFR 46.115(a)(2).

OHRP acknowledges that (i) NGHS has only one active HHS-supported research protocol involving human subjects; and (ii) this project is closed to enrollment, only involves long-term follow-up of subjects, and had an appropriate IRB review under an expedited review procedure in August 2000.

As a result, there should be no need for further involvement of OHRP in this matter. Of course, OHRP must be notified should new information be identified which might alter this determination.

Additional OHRP Guidance

At this time, OHRP would like to provide the following additional guidance to NGHS:

(1) On page 14 of the NGHS IRB Operating Procedures, a quorum is defines as "50% of members," including at least one physician and one non-physician. Please note that HHS regulations at 45 CFR 46.108(b) require that, except when an expedited review procedure is used, research must be reviewed at a convened meeting at which a majority of members of the IRB are present, including at least one member whose primary concerns are in nonscientific areas. Fifty percent of members does not constitute a majority, and a non-physician is not necessarily a non-scientist. Please revise the definition of a quorum accordingly.

(2) OHRP notes that IRBs frequently approve research contingent upon substantive modifications or clarifications without requiring additional review by the convened IRB. OHRP recommends the following guidelines in such cases: (a) When the convened IRB requests substantive clarifications, protocol modifications, or informed consent document revisions, IRB approval of the proposed research must 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.

(3) OHRP recommends that the description of the procedures for initial and continuing review of research in the NGHS IRB Operating Procedures be expanded to specify the documents and materials that are provided to IRB members for review.

(4) In conducting the initial review of proposed research, IRBs must obtain information in sufficient detail to make the determinations required under HHS regulations at 45 CFR 46.111. Materials should include the full protocol, a proposed informed consent document, any relevant grant applications, the investigator's brochure (if one exists), and any advertising intended to be seen or heard by potential subjects. Unless a primary reviewer system is used, all members should receive a copy of the complete documentation. These materials should be received by members sufficiently in advance of the meeting date to allow review of this material.

(5) Continuing IRB review of research must 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. Furthermore, the minutes of IRB meetings should document separate deliberations, actions, and votes for each protocol undergoing continuing review by the convened IRB.

When conducting research under an expedited review procedure, the IRB Chair (or designated IRB member(s)) should receive and review all of the above referenced documentation.

(6) The NGHS IRB Operating Procedures should be expanded to include the following:

(a) A description of the IRB procedure for determining which projects need verification from sources other than the investigators that no material changes have occurred since the previous IRB review, as required by HHS regulations at 45 CFR 46.103(b)(4)(ii).

(b) A description of the procedures for ensuring prompt reporting to appropriate institutional officials, the HHS agency head, and OHRP any of the following events related to HHS-supported research, as required by HHS regulations at 45 CFR 46.103(b)(5):

(i) Any unanticipated problems involving risks to subjects or others.

(ii) Any serious or continuing noncompliance with the requirements of HHS regulations at 45 CFR Part 46 or the requirements or determinations of the IRB.

(iii) Any suspension or termination of IRB approval.

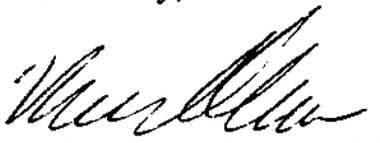
(7) Where HHS regulations require specific findings on the part of the IRB, such as (a) approving a procedure which alters or waives the requirements for informed consent [see 45 CFR 46.116(d)]; (b) approving a procedure which waives the requirement for obtaining a signed consent form [see 45 CFR 46.117(c)]; (c) approving research

involving prisoners (see 45 CFR 46.305-306); or (d) approving research involving children (see 45 CFR 46.404-407), the IRB should document such findings. OHRP strongly recommends that all required findings be fully documented in the IRB minutes, including protocol-specific information justifying each IRB finding.

(8) Where applicable, OHRP requires that each local IRB receive and review a copy of the NIH-approved sample informed consent document and the full NIH-approved protocol as a condition for review and approval of the local informed consent document. Any deletion or substantive modification of information concerning risks or alternative procedures contained in the sample informed consent document must be justified in writing by the investigator, approved by the IRB, and reflected in the IRB minutes.

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,



Michael A. Carome, M.D.
Director, Division of Compliance Oversight

cc: Dr. Frank McDonald, Chairperson, IRB, Northeast Georgia Health Services
Commissioner, FDA
Dr. David Lepay, FDA
Dr. James F. McCormack, FDA
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