DEPARTMENT OF HEALTH & HUMAN SERVICES

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August 25, 2000

Floyd D. Loop, M.D.
Executive Vice President and Chairman, Board of Governors
The Cleveland Clinic Foundation
Office of the Institutional Review Board/Wb2
9500 Euclid Avenue
Cleveland, Ohio 44195

Alan Lichtin, M.D.
Chair, Institutional Review Board
The Cleveland Clinic Foundation
Office of the Institutional Review Board/Wb2
9500 Euclid Avenue
Cleveland, Ohio 44195

RE: Human Research Subject Protections Under Multiple Project Assurance (MPA) M-1388
Research Projects: Gynecologic Oncology Group (GOG) Protocols
Principal Investigator: Kenneth D. Webster, M.D.

Dear Dr. Lichtin:

The Office for Human Research Protections (OHRP), formerly the Office for Protection from Research Risks (OPRR), has reviewed Dr. Lichtin's September 18, 1998 report responding to the information you submitted in reply to OPRR's letter of August 25, 1998 (copy enclosed). OHRP apologizes for the delay in its response.

OHRP acknowledges the following findings made by the Cleveland Clinic Foundation (CCF) during its investigation of the above referenced research projects, as well as the corresponding corrective actions taken by the CCF in response:

(1) Department of Health and Human Services (HHS) regulations at 45 CFR 46.109(e) require that continuing review of research by conducted by the institutional review board (IRB) at intervals appropriate to the degree of risk and not less than once per year. The CCF has found that the IRB failed to conduct continuing review at least annually for GOG

protocol 149. Furthermore, the CCF found that this failure to provide timely continuing review for GOG protocol 149 was an aberration in the IRB's otherwise timely continuing review practice, and apparently resulted from a malfunctioning of the internal mail system.

Corrective Action: The CCF has implemented the following procedures to prevent recurrence of similar noncompliance: (1) renewal applications sent from the GOG office to the CCF will simultaneously be faxed to the IRB office; (ii) the CCF GOG representative will keep a log of a communication (e-mail or phone call) confirming that the IRB office has been notified of renewals; (iii) the IRB office will keep track of renewal dates of the GOG studies and confirm with GOG personnel at the CCF that all documentation necessary for continuing review is received and that continuing review has been conducted in accordance with HHS requirements at 45 CFR 46.109.

(2) The CCF has found that the CCF IRB requires GOG investigators to use standardized chemotherapy risk language developed by the IRB, which differs from risk statements suggested by GOG for cisplatin, Taxol and carboplatin.

Corrective Action: In order to ensure that human subjects in GOG protocols at CCF are appropriately informed of all risks in accordance with HHS requirements at 45 CFR 46.116, CCF will include GOG investigators in the process of updating standard risk statements for cisplatin, Taxol and carboplatin.

OHRP finds that the above referenced corrective actions should adequately address the findings of noncompliance cited in the April 28, 1998 GOG Clinical Trials Monitoring Site Visit Report.

OHRP has the following additional findings, concerns, and questions regarding the CCF's overall system for protecting human subjects:

(1) 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.

If the IRB uses a primary reviewer system, the primary reviewer(s) should do an in-depth review of all pertinent documentation described in the preceding paragraph. All other IRB members should at least receive and review a protocol summary (of sufficient detail to make the determinations required under HHS regulations at 45 CFR 46.111), the proposed informed consent document, and any advertising material. In addition, the complete documentation should be available to all members for review.

On pages 3-4 of the Procedure Manual for the IRB, OHRP notes the following statement regarding Initial IRB Review:

> "The primary reviewer receives a copy of the protocol, the consent document, the investigational drug brochure and/or device brochure, if applicable, and any other pertinent documents. *All other members receive the consent document and the first 4 pages of our IRB application which provides a summary of the proposed research.*" [italics added for emphasis; copy of pages 1 to 4 of the CCF IRB application enclosed]

Given the content of pages 1-4 of the CCF IRB application, OHRP is concerned that when reviewing protocol applications, the full IRB appears to lack sufficient information to make the determinations required for approval of research under HHS regulations at 45 CFR 46.111. For example, pages 1-4 of the CCF IRB application appears to contain minimal or no information regarding (i) research design and procedures; (ii) risks of harm or discomfort associated with the research; (iii) subject recruitment and enrollment procedures; (iv) the equitable selection of subjects; (v) provisions to protect the privacy of subjects and maintain the confidentiality of data; and (vi) additional safeguards to protect the rights and welfare of subjects who are likely to be vulnerable.

Please respond.

(2) OHRP is concerned that the IRB frequently approves research contingent upon substantive modifications or clarifications without requiring additional review by the convened IRB. OHRP recommends the following guidelines in such cases: (i) 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. (ii) 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.

Please respond.

(3) HHS regulations at 45 CFR 46.115(a)(2) require that the minutes of IRB meetings document the vote on all IRB actions including the number of members voting for, against, and abstaining. OHRP finds that the minutes of IRB meetings provided with your report fail to comply with this HHS regulatory requirement. Please submit a corrective action plan to address this deficiency.

In order to document the continued existence of a quorum, OHRP strongly recommends that votes be recorded in the minutes using the following format: Total = 15; Vote: For-14, Opposed-0, Abstained-1 (NAME).

(4) 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 (i) the number of subjects accrued; (ii) 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; (iii) 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 (iv) 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). Furthermore, the minutes of IRB meetings should document separate deliberations, actions, and votes for each protocol undergoing continuing review by the convened IRB.

Based upon the minutes of IRB meetings provided with your report, OHRP is concerned that continuing review of research by the IRB routinely fails to satisfy all of these requirements. In particular, there is no documentation of discussions, separate actions, or separate votes for any protocols undergoing continuing review. Furthermore, it is unclear from the written IRB policies and procedures what documentation, if any, all IRB members received prior to the meetings for protocols undergoing continuing review. Please respond.

(5) HHS regulations at 45 CFR 46.108 require that, except when an expedited review procedure is used, the IRB review proposed research at convened meetings at which a majority of the members of the IRB are present. Based upon the documentation of members present and absent in the minutes of the IRB meetings provided to OHRP with your report, it appears that the IRB failed to meet this requirement for the following IRB meetings: June 26, 1998, 9 members present and 9 members absent; and July 10, 1998, 9 members present and 9 members absent.

Please respond. In preparing your response, please note that any actions taken at a meeting lacking a quorum must be considered invalid. Furthermore, OHRP recommends that you audit the minutes of all IRB meetings for the past year to confirm the presence of a valid quorum throughout each meeting. OHRP emphasizes that should the quorum fail during a meeting (e.g., those with conflicts being excused, early departures, loss of a nonscientist), the meeting is terminated from further votes unless the quorum can be restored.

(6) HHS regulations at 45 CFR 46.404-407 require specific findings on the part of the IRB for approval of research involving children. Based upon its review of the minutes of IRB meetings, OHRP is concerned that the IRB may not be making the required findings when reviewing research involving children. Please respond.

Where HHS regulations require specific findings on the part of the IRB, such as (i) approving a procedure which alters or waives the requirements for informed consent [see 45 CFR 46.116(d)]; (ii) approving a procedure which waives the requirement for obtaining a signed consent form [see 45 CFR 46.117(c)]; (iii) approving research involving prisoners (see 45 CFR 46.305-306); or (iv) approving research involving children (see 45 CFR 46.404-407), the IRB should document such findings. OHRP strongly recommends that these findings be fully documented in the IRB minutes, including protocol-specific information justifying each IRB finding.

(7) OHRP is concerned that the IRB may be overburdened by the large volume of research for which it has oversight responsibility. Please respond.

(8) OHRP finds that the CCF 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 continuing review of research and for reporting its findings to the institution; and (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.
>
> (b) The procedures for ensuring prompt reporting to the IRB, appropriate institutional officials, any Department or Agency head, and OHRP of (i) 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.

The CCF should develop and provide to OHRP revised IRB policies and procedures that include additional operational details for each of the above referenced activities. To assist the CCF in revising its IRB policies and procedures please see the enclosed Guidance for Formulating Written IRB Policies and Procedures.

(9) OHRP strongly recommends that institutions develop and distribute a handbook of IRB guidelines for research investigators. The handbook should include detailed information concerning (i) federal and institutional requirements for the protection of human research subjects; (ii) the IRB's role and responsibilities; (iii) the requirements and procedures for initial and continuing IRB review and approval of research; (iv) the rationale and procedures for proposing that the research may meet the criteria for expedited review; (v) the requirements and procedures for verifying that research is exempt from IRB review; (vi) the responsibilities of investigators during the review and conduct of research; (vii) 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; (viii) an explanation of the distinction between FDA requirements for emergency use of test articles versus HHS regulations for the conduct of human subjects research; (ix) relevant examples and user-friendly forms for providing information to the IRB; and (x) 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.

OHRP requests that you conduct an investigation into the above referenced findings and concerns and submit a written response to OHRP no later than September 29, 2000. In conducting its investigation of this matter, OHRP strongly recommends that, because of potential conflicts of interest, individuals involved in the duties and responsibilities of the IRB not be assigned primary responsibility for conducting CCF's investigation into these matters.

In your response, please provide IRB minutes for the past three months, and a copy of any revised policies and procedures.

OHRP appreciates your continued commitment to the protection of human research subjects. Please feel free to call me if you have any questions.

Sincerely,

Carol J. Weil, J.D.
Compliance Oversight Coordinator
Division of Human Subject Protections

cc: Dr. Angelo Licata, CCF
Dr. Kenneth Webster, CCF
Dr. Melody Lin, OHRP
Dr. Michael Carome, OHRP
Dr. J. Thomas Puglisi, OHRP
Dr. Katherine Duncan, OHRP
Ms. Roslyn Edson, OHRP
Commissioner, FDA
Dr. David Lepay, FDA
Dr. James F. McCormack, FDA
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