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June 11, 2001

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**

Dear Drs. Loop and Lichtin:

The Office for Human Research Protections (OHRP) has reviewed Dr. Lichtin's September 27, 2000 report responding to questions and concerns raised in OHRP's August 25, 2000 letter concerning the human subject protection program at the Cleveland Clinic Foundation (CCF).

OHRP acknowledges the significant operational improvements in CCF's Office of the Institutional Review Board (IRB), including increased membership and staff for the IRB and the establishment of an ongoing audit program for continuing review.

OHRP makes the following findings and recommendations regarding CCF's human subject protection program:

(1) OHRP finds that the IRB Policies and Procedures Manual now requires researchers submitting protocols for IRB review to provide sufficient information for the IRB to make

the determinations required under Department of Health and Human Services (HHS) regulations at 45 CFR 46.111. Furthermore, your September 27, 2000 letter, in accordance with OHRP guidance, states that each IRB member receives a copy of the protocol, informed consent documentation, and advertising materials.

(2) OHRP acknowledges CCF's statement that the IRB has adopted the practice recommended by OHRP of determining, with respect to each protocol reviewed, whether revisions requested by the IRB are substantive, and therefore require re-review by the fully convened IRB.

The IRB appears not to have a formal policy with respect to the re-review of revised protocols where the modifications requested were determined by the IRB to be nonsubstantive. OHRP recommends that when the IRB requests specific revisions requiring simple concurrence by the investigator, the IRB Chair or an IRB member designated by the Chair subsequently approve the protocol under an expedited review procedure.

(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 recent CCF IRB meetings comply with these requirements.

(4) OHRP finds that CCF has modified its continuing review procedures to ensure that protocols undergoing continuing review at convened meetings are discussed and voted upon individually.

Your September 27, 2000 letter states that protocol summaries pertaining to studies undergoing continuing review are available to each IRB member at the meeting. Please note that OHRP recommends that IRB members should receive and review such protocol summaries, together with a status report on the progress of the research, prior to the meeting, to facilitate substantive and meaningful discussion of the protocols when the convened IRB meets.

(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. OHRP acknowledges CCF's statement that (i) CCF conducted a self-audit of IRB meetings to confirm the presence of a quorum and identified two meetings at which a quorum was lacking; and (ii) the IRB re-reviewed all matters previously reviewed at these two meetings.

The IRB minutes reflect that current practice is to confirm the presence of a quorum prior to each IRB meeting. The minutes provided to OHRP for three IRB meetings (July 14, 2000, August 4, 2000, and September 1, 2000) do not appear to note any departures or abstentions of IRB members that might affect the quorum count. OHRP emphasizes that

should the quorum fail during a meeting (e.g., those with conflicts being excused, early departures, loss of a non-scientist), the meeting is terminated from further votes unless the quorum can be restored.

(6) OHRP acknowledges that the CCF IRB has adopted the practice of identifying in the IRB minutes a risk level for pediatric research protocols using the categories of risk delineated at 45 CFR 46.404-407, the HHS regulations governing research on children. However, OHRP notes that these regulations set forth additional required findings. OHRP strongly recommends that the IRB fully document these required findings in the meeting minutes, including protocol-specific information justifying each IRB finding. Other areas where HHS regulations require specific findings on the part of the IRB which the IRB should document with protocol-specific information are: (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)]; and (c) approving research involving prisoners [see 45 CFR 46.305-306].

(7) OHRP finds that the CCF IRB changed its meeting schedule from bi-weekly to weekly, and expanded its membership, in order to ensure adequate opportunity for review of the large number of protocols over which it has oversight responsibility.

(8) OHRP finds that CCF, as requested by OHRP, has developed written IRB Policies and Procedures that adequately describe the IRB's process for conducting continuing review and for ensuring prompt reporting of noncompliance with the HHS regulations or any restriction of IRB approval, as required by 45 CFR 46.103(b)(4) and (b)(5).

(9) OHRP acknowledges CCF's statement that CCF has developed a comprehensive and detailed handbook of IRB guidelines for investigators, as recommended by OHRP.

Based upon its review, OHRP has determined that CCF's corrective actions adequately address OHRP's findings and concerns, and there is no need for further involvement of OHRP at this time. Please note that OHRP is considering conducting a compliance oversight visit at CCF within the next 12-24 months.

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.
Division of Compliance Oversight

cc: Dr. Angelo Licata, CCF
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