DEPARTMENT OF HEALTH & HUMAN SERVICES

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September 4, 2001

David Dunlap
Chief Executive Officer
Memorial Medical Center
Tenet Louisiana HealthSystem
Baptist Campus
2700 Napoleon Avenue
New Orleans, Louisiana 70115

RE: Human Subject Protections Under Cooperative Project Assurance (CPA) T-3744

Dear Mr. Dunlap:

The Office for Human Research Protections (OHRP), formerly the Office for Protection from Research Risks (OPRR), has reviewed Memorial Medical Center's (MMC's) January 13 and 18 2000 reports which were submitted in response to OPRR's November 16, 1999 letter regarding allegations of noncompliance with Department of Health and Human Services (HHS) regulations for the protection of human subjects.

Based upon its review of MMC's reports, OHRP makes the following determinations:

(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. The regulations make no provision for any grace period extending the conduct of the research beyond the expiration date of IRB approval.

OHRP finds that on occasion, the MMC IRB failed to conduct continuing review of research at least once per year.

If the IRB does not re-approve the research by the specified expiration date, subject accrual should be suspended pending re-approval of the research by the IRB. Enrollment of new subjects cannot ordinarily occur after the expiration of IRB approval. Continuation of research interventions or interactions in already enrolled subjects should only continue when the IRB finds that it is in the best interests of individual subjects to do so. OHRP and IRBs must address on a case-by-case basis those rare instances where failure to enroll would seriously jeopardize the safety or well-being of an individual **prospective** subject.

Corrective Action: OHRP acknowledges that MMC has implemented a revised IRB policy to ensure that the MMC IRB conducts continuing review of research at least once per year.

(2) HHS regulations at 45 CFR 46.115(a)(2) require that minutes of IRB meetings be in sufficient detail to show, among other things, the vote on each IRB action, 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 provided with MMC's reports routinely failed to satisfy these requirements.

With respect to votes, please note that recording votes as "unanimous" is not sufficient. In order to document the continued existence of a quorum, OHRP strongly recommends that votes be recorded in the minutes of IRB meetings using the following format: Total = 15; Vote: For-14, Opposed-0, Abstained-1 (NAME).

(3) OHRP is concerned that the minutes of IRB meetings and other IRB records submitted with MMC's reports indicated that little substantive review takes place at convened meetings of the IRB. Furthermore, OHRP finds little evidence that IRB approval of research is consistently based on consideration of the determinations required under HHS regulations at 45 CFR 46.111. In specific, the IRB appears not to consider systematically and rigorously such issues as equitable selection of subjects and subject recruitment, privacy and confidentiality protections, and special protections required for vulnerable subjects.

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

OHRP finds that continuing review of research by the MMC IRB is not substantive and meaningful. In particular, the continuing review progress report utilized at MMC fails to solicit sufficient information for the IRB to perform a substantive and meaningful continuing review.

(5) OHRP finds that the written IRB policies and procedures submitted with MMC's reports failed to 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 follows for conducting its initial review of research.

(b) The procedures which the IRB follows for conducting its continuing review of research.

(c) The procedures which the IRB follows for determining which projects require review more often than annually.

(d) The procedures which the IRB follows for determining which projects need verification from sources other than the investigators that no material changes have occurred since previous IRB review.

(e) The procedure which the IRB follows 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.

(f) The procedures for ensuring prompt reporting to the IRB, appropriate institutional officials, and Department or Agency head of each of the following

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

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

(iii) Any suspension or termination of IRB approval.

Required Action: By October 31, 2001, MMC must submit to OHRP a satisfactory corrective action plan to address findings (2)-(5) above. The corrective action plan should include revised written IRB policies and procedures for each of the activities referenced in finding (5) above. To assist MMC in revising its written IRB policies and procedures, please refer to the enclosed document entitled "Guidance for Formulating Written IRB Policies and Procedures."

OHRP has the following additional concerns and questions regarding the documents provided with MMC's reports:

(6) Regarding the NSABP B28 protocol, OHRP is concerned that the MMC IRB discontinued continuing review and oversight of the research before the research was completed. In particular, OHRP notes that (i) the research protocol involved a five-year follow-up period following completion of the chemotherapy intervention; (ii) the 6/24/98 continuing review form for the protocol indicated that three subjects had been enrolled in the preceding year; and (iii) the study was considered completed on 08/25/1999. Please respond. In your response, please include a description of the status of this research with respect to all subjects enrolled at MMC prior to closure of the IRB protocol file in August 1999.

Please note that continuing review by the IRB is required as long as individually identifiable follow-up data are collected on subjects enrolled in HHS-supported Cooperative Protocol Research Program protocols. This remains the case even after a protocol has been closed at all sites and protocol-related interventions have been completed for all subjects.

(7) Regarding the NSABP B28 protocol, OHRP is concerned that the informed consent document approved by the MMC IRB failed to include an adequate description of the following elements required by HHS regulations at 45 CFR 46.116(a):

(a) Section 46.116(a)(5): A description of how confidentiality and privacy will be maintained.

(b) Section 46.116(a)(7): An explanation of whom to contact for answers to questions about research subjects' rights, and whom to contact in the event of a research-related injury to the subject.

Please respond.

(8) Regarding the NSABP B28 protocol, it appears that it may have been appropriate for the informed consent documents to include the following additional elements, in accordance with HHS regulations at 45 CFR 46.116(b):

(a) Section 46.116(b)(2): The anticipated circumstances under which the subject's participation may be terminated by the investigator without regard to the subject's consent.

(b) Section 46.116(b)(4): The consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject.

(c) Section 46.116(b)(5): A statement that significant new findings developed during the course of the research which may relate to the subject's willingness to continue participation will be provided to the subject.

Please respond.

Please submit to OHRP your response to the above concerns by October 31, 2001. If in formulating its response to the above concerns MMC identifies additional areas of noncompliance, please provide a description of the corrective actions MMC has or will take to address the noncompliance.

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. Barry F. Faust, Chair, IRB, MMC
Ms. Joan Mauer, NCI, CTEP
Commissioner, FDA
Dr. David Lepay, FDA
Dr. James F. McCormack, FDA
Dr. Greg Koski, OHRP
Dr. Melody H. Lin, OHRP
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Mr. George Gasparis, OHRP
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Mr. Barry Bowman, OHRP