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August 7, 2000

Walter W. Sullivan, Ph.D.
Vice President for Operations and Planning
Morehouse School of Medicine
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Dear Dr. Sullivan:

The Office for Human Research Protections (OHRP), formerly the Office for Protection from Research Risks (OPRR), has reviewed the documents that were submitted with your letter of November 11, 1998, in response to the September 18, 1998 letter from Ms. Diane Aiken of this office. OHRP apologizes for the delay in responding to your report.

OHRP acknowledges the following responses to the list of discrepancies that was issued by the Food and Drug Administration (FDA) at the conclusion of the inspection on March 12, 1998. The numbers correspond to the numbered items on the form FDA 483 that was issued to Dr. Gene McGrady.

1. The written procedures for the institutional review board (IRB) were to be rewritten, with the final version expected on January 10, 1999. The revised procedures were to address the frequency of continuing reviews, handling of adverse events (AEs), expedited reviews, prompt reporting of AEs, and prompt reporting of changes in ongoing research.

2. The IRB had 13 members, not 15, therefore seven voting members did meet the quorum requirements.

3 and 4. The IRB roster did not include non-institutional members. The roster was to be revised to include all members.

5. A new procedure for formal IRB action on studies closed by the principal investigator was to be initiated. When a study is closed by the principal investigator, the IRB was to take a formal action closing the study and send a letter to the principal investigator.

6. The revised procedures were to require IRB review of the investigator's brochure, when one exists.

7. The revised procedures were to require documentation of AEs in the meeting minutes and filing the AE reports with the IRB's study records.

8. The minutes of the September 17, 1997 meeting are missing. Both the IRB chair and the IRB administrator were to maintain paper and disc copies of minutes in separate files to preclude this from happening again.

In addition to the above specific responses, OHRP notes your statement that operational changes were in process at the time of the 1998 FDA inspection. These changes were to include appointment of an IRB administrator and relocation of the IRB office to the Office of Research Development, Office of the Dean.

OHRP findings regarding the draft IRB guidelines.

OHRP has also reviewed the copy of the draft IRB guidelines that was included with your November 11, 1998 response. OHRP finds that the institution does not have written IRB policies and procedures that adequately describe the following activities, as required by the Department of Health and Human Services (HHS) regulations at 45 CFR 46.103(b)(4) and (5):

(1) The IRB's initial review of research projects.

(2) The IRB's continuing review of ongoing research projects.

(3) Reporting the IRB's findings and actions to the investigator and the institution.

(4) Determining which projects require continuing review more often than annually.

(5) Determining which projects need verification from sources other than the investigators that no material changes have occurred since the previous IRB review.

(6) Ensuring that changes in approved, ongoing research are not initiated without IRB review and approval, except when necessary to eliminate apparent immediate hazards to the subjects.

(7) Ensuring prompt reporting to 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.

The IRB guidelines include template copies of documents that principal investigators are to submit to the IRB, but fail to adequately describe the operational details of the process the IRB follows to review research projects and do not include template copies of forms the IRB subsequently issues to the principal investigators and to the institution.

Required Action: By September 30, 2000, Morehouse School of Medicine must submit to OHRP revised written IRB policies and procedures that adequately describe the operational details of all activities stipulated by HHS regulations at 45 CFR 46.103(b)(4) and (5).

OHRP has the following additional concerns and guidance about specific items in the draft IRB guidelines.

(1) Item 1.a on page 3 states that the submission to the IRB should be limited to 10 pages, not including amendments. It is not clear from reviewing appendices A and B whether the study protocol is regarded to be an amendment or whether it is under the 10 page restriction. Further, item XVII of Section 5, Appendix A, and item XVI of Section 5, Appendix B, indicate the detailed protocol need not be submitted to the IRB. The regulations at 45 CFR 46.109(a) require submission and review by the IRB of ". . . all research activities . . . ," including the complete study protocol as prepared by the study sponsor. 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 a in-depth review of all pertinent documentation. 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.

(2) Item D, page 21, indicates that "element 9" of informed consent (alternatives to participation) only applies to "therapeutic research." Please note that the element of informed consent required by HHS regulations at 45 CFR 46.116(a)(4) applies to all nonexempt research, unless waived by the IRB in accordance with HHS regulations at 45 CFR 46.116(c) or (d).

(3) Regarding item E, page 11, please note that the list of categories of research that may be reviewed by an IRB through expedited procedures, was updated by OPRR and FDA on November 9, 1998 at 63 FR 60364.

(4) Regarding item I, Reporting Proposed Changes in a Research Protocol, page 15, OHRP notes the statement that proposed changes "which affect the human subjects" must be reported and reviewed by the IRB prior to implementation. HHS regulations at 45 CFR 46.103(b)(4)(iii) require **all** changes in a research activity to be promptly reported to the IRB and for the changes not to be initiated until IRB review and approval has been accomplished. The regulations do not contain a provision for exempting from IRB review changes which "do not affect the human subjects."

(5) Regarding item 3, Style, page 20, OHRP notes the description of consent forms for "innovative therapy." OHRP is concerned about the substitution of "innovative therapy" for "research," "patient" for "subject," and "physician" for "investigator," because the substituted terms may lead the prospective subjects to believe they are receiving "standard" treatment rather than participating in a research project. The HHS regulations do not provide for a lesser standard of informed consent for "innovative therapy" research.

(6) Regarding item 14, Assurance of Confidentiality, page 29, OHRP is concerned that the statement "any information obtained during this study which could identify you will be kept strictly confidential," may lead the subjects to believe their identity will never be released to anyone. The statement should be changed to reflect the anticipated circumstances under which research records identifying the subjects may be disclosed, such as to study sponsors or when required by law.

(7) Regarding item 17, Documentation of Informed Consent, page 31, OHRP is concerned that while the subjects may be able to certify that they understand the content of the informed consent document, they may not be in a position to know whether the meaning of the information has been fully or accurately explained to them.

(8) Regarding the Signature of Witness on the informed consent templates, pages 31, 41, 47, 52 and 80, the statement "My signature as a witness certifies that the subject signed this consent form in my presence . . ." indicates that the witness is present only for the signing of the informed consent form. It appears that Morehouse requires witnessing of all informed consent forms. However, please be advised that when the witness is present to meet the requirements of 45 CFR 46.117(b)(2), the purpose of the witness is to certify that the oral explanation of the information contained in the narrative accompanying the short form has been accurate. Therefore, when this is the case, the witness should be present during the entire consent interview, not just when the consent document is signed.

(9) Regarding item G, Procedures for a Medical Emergency, page 34, please note that there is no provision in the HHS regulations for emergency approval of research by the IRB chairman. The institution may require notification of the IRB chair, but this process should not be documented as IRB approval. The HHS regulations do not permit research activities to be started, even in an emergency, without prior IRB review and approval (see 45 CFR 46.103(b), 46.116(f) and OPRR Reports 91-01). When emergency medical care is initiated without prior IRB review and approval, the patient may not be considered a research subject. Such emergency care may not be claimed as research, nor may any data regarding

such care be included in any report of research activity. When emergency care involves investigational drugs, devices, or biologics, U.S. Food and Drug Administration (FDA) requirements must be satisfied. There is a provision in the FDA regulations for exemption from IRB approval for one use or one course of treatment of an investigational drug or device, see 21 CFR 56.104(c).

(10) Regarding the Sample Consent Form, Explanation of Procedures, page 38, the IRB may wish to consider inclusion of a time versus event chart to supplement the written explanation. A chart may be useful to explain complex studies, such as those involving several visits or multiple procedures.

(11) Regarding the Sample Consent Form, Alternatives to Participation, on page 40, OHRP strongly recommends that the classes of drugs that are routinely used to manage a medical condition be listed (for example, other calcium channel blockers, beta blockers for angina). It would be helpful to subjects to provide at least one generic or brand name as an example of each class of drugs that is available as a treatment alternative to participation in the study.

(12) Regarding the Sample Consent Form, Alternatives to Participation, page 45, please note that the regulations at 45 CFR 46.116(a)(4) require disclosure of appropriate alternative procedures or courses of treatment that might be advantageous to the subject. Simply stating that the alternative to participation in the study is to receive "standard supportive care," does not appear to be an adequate description of the alternatives to participation. For example, would another drug be administered to prevent or treat infection? If so, this use should be explained.

(13) Regarding the Sample Consent Form, Voluntary Participation and Withdrawal, page 51, OHRP notes that this paragraph does not contain an example of an explanation of the consequences of withdrawal and the procedures for orderly withdrawal, as outlined in the HHS regulations at 45 CFR 46.116(b)(4). Including wording that is acceptable to the IRB might be helpful to investigators who are preparing informed consent forms.

Regarding the minutes of IRB meetings, OHRP has the following questions, concerns and guidance.

(14) 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.

(a) OHRP notes that the votes recorded in the minutes of IRB meetings provided with your report are recorded as "unanimous." This does not satisfy the requirement to record the number of members voting for, against, and abstaining.

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)

(b) OHRP notes that the minutes frequently indicated that protocols were approved with "minor revisions" without listing the required revisions. Please note that **all** required changes, and the basis for requiring the changes, should be documented in the minutes.

(15) OHRP notes that the minutes of the July and August 1998 IRB meetings indicated that one member of the IRB "reported" on each protocol to the convened IRB. OHRP presumes that the IRB was using a primary reviewer system. Please describe in detail the procedures used by the IRB for conducting initial and continuing review of research protocols. This description should indicate what protocol materials the primary reviewer receives and what materials all other IRB members receive.

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.

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.

(16) OHRP is concerned that the minutes of IRB meetings appear to provide 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, there appears to be little evidence that the IRB considers systematically and rigorously such issues as equitable selection of subjects and subject recruitment, privacy and confidentiality protections, and special protections required for vulnerable subjects.

(17) 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.

Finally, OHRP has the following concern regarding the IRB membership roster that was provided with your report.

(18) OHRP notes that for the academic year July 1, 1998 - June 30, 1999 Margaret Weber-Levine, Ph.D. was listed as a non-affiliated member even though she is a professor of behavioral science at Morehouse College. Please explain this discrepancy.

Please submit to OHRP a written response to the above concerns and questions no later than September 30, 2000. In your response please indicate whether additional revisions were made to the IRB policies and procedures. Also, please submit a copy of the minutes of IRB meetings for the last three months. OHRP appreciates the commitment of your institution to the protection of human subjects of research. Please contact me if you have any questions regarding this matter.

Sincerely,

Paul W. Goebel, Jr.
Division of Human Subject Protections

cc: John C. Smith, M.S.W., IRB Administrator, Morehouse
Ralph W. Trottier, Jr., Ph.D., J.D., Chairman, IRB, Morehouse
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