DEPARTMENT OF HEALTH & HUMAN SERVICES

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October 19, 2000

William W. Destler
Vice President for Research and
Dean, Graduate School
University of Maryland
2133 Lee Building
College Park, Maryland 20742-5121

RE: Human Research Subject Protections Under Multiple Project Assurance (MPA) M-1362

Dear Dr. Destler:

The Office for Human Research Protections (OHRP), formerly the Office for Protection from Research Risks (OPRR), has reviewed your October 15, 1999 report regarding systemic protections for human subjects at the University of Maryland at College Park (UM). OHRP apologizes for the delay in responding to your report.

OHRP finds that UM has developed satisfactory corrective action plans to address the major concerns and questions that were presented in OHRP's July 22, 1999 letter.

As a result of the above determination, there should be no need for further involvement of OHRP's Division of Compliance Oversight in this matter. Of course, OHRP should be notified of any new information which might alter this determination.

At this time, OHRP would like to provide the following additional guidance regarding UM's Institutional Review Board (IRB) policies and procedures:

(1) OHRP notes that UM's IRB policies and procedures are diffusely described in a number of documents provided on the UM web page, as well as within the UM MPA. OHRP strongly recommends that these policies and procedures be presented in a single, unified document, either on the UM web page or in a printed document separate from the MPA. Furthermore, the IRB policies and procedures should be expanded to include additional operational details for each of the following IRB policies and procedures:

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

(b) The procedures which the IRB follows for reporting its findings and actions regarding initial and continuing review to the institution.

(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 the previous IRB review.

(e) The procedures for ensuring prompt reporting to the IRB, appropriate institutional officials, the head of any supporting Federal Department or Agency, and OHRP of each of the following events:

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

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

(iii) Any suspension or termination of IRB approval of research.

In order to assist UM in revising its written IRB policies and procedures, please see the enclosed Guidance for Formulating Written IRB Policies and Procedures.

(2) The description of the IRB Application Process on the UM web page appears to indicate that nonexempt Federally supported research, as well as research involving greater than minimal risk that is not Federally supported, must be reviewed and approved by the IRB designated under the UM MPA, whereas nonexempt research involving minimal risk that is not Federally supported is reviewed by departmental human subjects review (HSR) committees that are not IRBs designated under the UM MPA and do not satisfy the IRB membership requirements stipulated by HHS regulations at 45 CFR 46.107.

In contrast, the UM MPA applies to all nonexempt human subject research, regardless of both sponsorship and the level of risk. Furthermore, the MPA indicates that departmental HSR committees only conduct preliminary reviews prior to IRB review.

UM should revise either its MPA or its IRB policies and procedures to ensure that these documents are uniform and consistent. OHRP strongly recommends that UM have a unified system for protecting human subjects to ensure that all subjects are afforded the same protections, regardless of research sponsorship.

(3) OHRP recommends that UM expand its IRB application form to ensure that the IRB receives sufficient information to make all of the determinations required for approval of research under HHS regulations at 45 CFR 46.111, as well as the additional determination required under 45 CFR Part 46, Subpart B, C, and D. For example, the

IRB application should solicit additional information regarding (a) minimization of research risks; (b) subject recruitment and enrollment procedures; (c) provisions to protect the privacy of subjects and maintain the confidentiality of data; and (d) additional safeguards to protect the rights and welfare of subjects who are likely to be vulnerable. Furthermore, for research proposing involvement of prisoners or children, investigators should be prompted to provide specific information justifying the inclusion of such subjects in order to satisfy the requirements of Subparts C and D, respectively.

(4) The UM Sample Informed Consent Form should be revised to include a description of all required elements of informed consent stipulated by HHS regulations at 45 CFR 46.116(a).

(5) OHRP notes that the prisoner representative on the IRB is a Professor of Criminology, an active researcher, and an expert on criminal and prisoner issues. OHRP strongly recommends that UM assess the background and responsibilities of its current prisoner representative to determine whether she (a) is able to adequately represent the interests and perspective of prisoners; and (b) has no real or apparent conflicts of interest when serving in this capacity. UM should consider whether it would be appropriate to appoint another individual to serve as a prisoner representative on the IRB for review of research involving prisoners as subjects.

OHRP appreciates the commitment of UM to the protection of human subjects. Please feel free to contact me if you have any questions regarding this matter. If you have any questions regarding modification of the UM MPA or IRB membership roster, please feel free to contact Ms. Roslyn Edson (301-402-7565), the Assurance Coordinator for Maryland.

Sincerely,

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

Enclosure

cc: Dr. Robert Dooling, Chair, IRB, UM
Commissioner, FDA
Dr. David Lepay, FDA
Dr. James F. McCormack, FDA
Dr. Greg Koski, OHRP
Dr. Melody H. Lin, OHRP
Dr. J. Thomas Puglisi, OHRP
Ms. Roslyn Edson, OHRP
Dr. Katherine Duncan, OHRP
Dr. Clifford C. Scharke, OHRP
Dr. Jeffrey Cohen, OHRP
Mr. Barry Bowman, OHRP

Documents Provided to the IRB. Written IRB policies and procedures should specify the documents and materials that are provided to primary reviewers (if any) and all other IRB members prior to the IRB meetings for protocols undergoing initial or continuing review.

Review by Convened IRB. Initial and continuing reviews of research must be conducted by the convened IRB, except where expedited review is appropriate under HHS regulations at 45 CFR 46.110(b)(1) and 63 FR 60364.

Initial Review Materials. 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.

Primary Reviewer Systems. If the IRB uses a primary reviewer system, the primary reviewer(s) should do an 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.

IRB Review in Emergency Situations. 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 a research activity. When emergency care involves investigational drugs, devices, or biologics, U.S. Food and Drug Administration (FDA) requirements must be satisfied.

"Conditional" Approvals. Convened IRBs often set conditions under which a protocol can be approved (OPRR discourages use of the term "Conditional Approvals"). The following guidelines apply 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 Chairperson or designated reviewer subsequently approve the research on behalf of the IRB.

Continuing Review Materials. 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.

Approval and Expiration Dates. OPRR recommends that IRBs affix the approval and expiration dates to all approved informed consent documents and stipulate that copies of these dated documents must be used in obtaining consent. This procedure helps ensure that only the current, IRB-approved informed consent documents are presented to subjects and serves as a reminder to the investigators of the need for continuing review.

The approval date should be the most recent of the following: (i) date the protocol and informed consent document were initially reviewed and approved by the IRB; (ii) date of the most recent IRB continuing review and approval of the protocol and informed consent document; or (iii) date that the IRB approved the most recent modification to the informed consent document. In all three circumstances, the approval date which appears on the consent document is the date of approval of the most recent version of the consent document. The expiration date should correspond to the end of the current IRB approval period.

NIH-Supported Multicenter Clinical Trials. OPRR 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 (see OPRR Reports 93-01).

Documentation of Informed Consent for Non-English Speakers. The regulations require that informed consent information be presented "in language understandable to the subject" and, in most situations, that informed consent be documented in writing (45 CFR §46.116 and §46.117). Where informed consent is documented in accordance with §46.117(b)(1), the written consent document should embody, in language understandable to the subject, all the elements necessary for legally effective informed consent. Subjects who do not speak English should be presented with a consent document written in a language understandable to them. OPRR strongly

encourages the use of this procedure whenever possible. Alternatively, §46.117(b)(2) permits oral presentation of informed consent information in conjunction with a short form written consent document (stating that the elements of consent have been presented orally) and a written summary of what is presented orally. A witness to the oral presentation is required, and the subject must be given copies of the short form document and the summary. When this procedure is used with subjects who do not speak English, (i) the oral presentation and the short form written document should be in a language understandable to the subject; (ii) the IRB-approved English language informed consent document may serve as the summary; and (iii) the witness should be fluent in both English and the language of the subject.

Exemptions. OPRR recommends that institutions adopt clear procedures under which the IRB (or some authority other than the investigator) determines whether proposed research is exempt from the human subjects regulations [see 45 CFR 46.101(b)]. Documentation should include the specific category justifying the exemption.

IRB Records. IRB protocol records must include all the information stipulated at 45 CFR 46.115(a)(1),(3),(4),(7). The minutes of IRB meetings must include all the information stipulated at 45 CFR 46.115(a)(2).

Initial and Continuing Expedited Review. OPRR recommends that documentation for initial and continuing reviews conducted utilizing expedited review procedures include the specific permissible categories (see 63 FR 60364) justifying the expedited review.

Expedited Review of Minor Changes. OPRR recommends that institutions adopt policies describing the types of minor changes in previously approved research which can be approved by expedited review in accordance with HHS regulations at 45 CFR 46.110(b)(2).

Quorum Requirements. A quorum for IRB meetings is a majority of the IRB's voting members (see 45 CFR 46.108). Approval of research is by majority vote of those present (i.e., of a valid quorum). 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.

Conflicting Interest. OPRR strongly recommends that IRB members absent themselves from the meeting room when the IRB votes on research in which they have a conflicting interest [see 45 CFR 46.107(e)], and such should be noted in the IRB meeting minutes.

Recording of Votes. 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. OPRR 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).

Documentation of Findings. 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), OPRR strongly recommends that these findings be fully documented in the IRB minutes, including protocol-specific information justifying each IRB finding.

Documentation of Risk and Approval Period. IRBs must determine which protocols require continuing review more often than annually, as appropriate to the degree of risk [see 45 CFR 46.103(b)(4) and 46.109(e)]. OPRR recommends that the minutes of IRB meetings clearly reflect these determinations regarding risk and approval period (review interval).

Protocol Revisions. OPRR recommends that each revision to a research protocol be incorporated into the written protocol. This practice ensures that there is only one complete protocol with the revision dates noted on each revised page and the first page of the protocol itself. This procedure is consistent with the procedure used for revised and approved informed consent documents which then supersede the previous one.

Applicability of State and Local Laws to HHS-Supported Research. The HHS regulations do not affect any applicable State or local laws or regulations which provide additional protections for human subjects [see 45 CFR 46.101(f)].

Inclusion of Women and Minorities in Research. Institutions have an responsibility to create an environment in which equitable selection of research participants is fostered. IRBs should specify that NIH-supported investigators provide details of the proposed involvement of humans in the research, including the characteristics of the subject population, anticipated numbers, age ranges, and health statuses. The proposed research should specify the gender and racial/ethnic composition of the subject population, as well as criteria for inclusion or exclusion of any subpopulation. If ethnic, racial, and gender estimates and continuing review numbers are not included in the background data for a protocol, the investigators must provide a clear rationale for exclusion of this information (see OPRR Reports 94-01).

NOTE: OPRR Reports referenced above can be found at http://ohrp.osophs.dhhs.gov/dearcoll.htm.