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February 16, 2001

Robert G. Brooks, M.D.
Secretary
Florida Department of Health
4052 Bald Cypress Way
Tallahassee, Florida 32399-1701

Judge Kathleen A. Kearney
Secretary
Florida Department of Children and Families
1317 Winewood Boulevard
Building 1, Room 202
Tallahassee, Florida 32399-0700

RE: Human Subject Research Protections Under Multiple Project Assurance (MPA) M-1350

Dear Dr. Brooks and Judge Kearney:

The Office for Human Research Protections (OHRP), formerly the Office for Protection from Research Risks (OPRR), has reviewed Dr. Brooks' July 12, 2000 report which was submitted in response to OPRR's May 23, 2000 letter. OHRP has also reviewed Dr. Richard G. Hunter's September 12, 2000 report which was submitted in response to the August 31, 2000 telephone conference between OHRP staff and officials of the Florida Department of Health (FDH) and the Florida Department of Children and Families (FDCF).

Based upon its review of your July 12 and September 12, 2000 reports, OHRP has made the following determinations regarding protection of human subjects at the FDH/FDCF:

(1) Department of Health and Human Services (HHS) regulations at 45 CFR 46.109(e) require that continuing review of research be conducted by the Institutional Review Board (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. Additionally, where the convened IRB specifies conditions for approval of a protocol that are to be verified as being satisfied by the IRB Chair or another IRB member designated by the Chair, the approval period should begin on the date the protocol was reviewed by the convened IRB, not on the date the IRB Chair or his or her designee verifies that IRB-specified conditions for approval have been satisfied.

OHRP finds that the FDH/FDCF IRB failed to conduct continuing review of research involving human subjects at least once per year as required by HHS regulations at 45 CFR 46.109(e).

In particular, OHRP notes the following:

(a) Attachment 6 of your July 12, 2000 report included a list of all active research projects involving human subjects. This list indicated that of the 124 projects listed, 47 had not undergone continuing review at least annually.

(b) The May 23, 2000 OHRP letter specifically requested immediate suspension of enrollment of new subjects and suspension of research activity for all subjects of federally supported studies that were initially approved by the IRB more than one year ago and have not received substantive continuing review and approval by the IRB subsequent to May 24, 1999, in accordance with HHS regulations at 45 CFR 46.109(e). The July 12, 2000 report states that you have reviewed the records and have found no ongoing federally supported research projects that had not received appropriate substantive continuing review.

Our review of the electronic database that you included as Attachment 6 to your July 12, 2000 report has identified four federally supported studies that were initially approved by the IRB more than one year before July 12, 2000 and had not received substantive continuing review and approval by the IRB during the preceding one year period. These proposals are numbered 742, 743, 744, and 750, and are federally supported by the National Institute for Allergy and Infectious Disease, National Institutes of Health (NIH), NIH and the Centers for Disease Control Drug Service, respectively. Attachment 6 shows these studies received initial approval in February 1999. OHRP acknowledges that per your September 12, 2000 report, these projects underwent continuing review on September 5, 2000.

(c) Minutes of the FDH/FDCF IRB meeting held September 5, 2000 included the following:

(i) Regarding the review of Review Council for Human Subjects (RCHS) # 550, the IRB meeting minutes stated, "550/438 (438R) is federally sponsored by NICHD. There have been no changes to the Protocol (dated

May 16, 1995) or its Informed Consent form since they were initially approved by the Full Council on January 24, 1997."

(ii) Regarding the review of RCHS # 821, The IRB minutes stated, "Dr. Chin stated that this Protocol has been ongoing for several years and that this is the fifth version." and "Two participants are currently enrolled in this study, which is sponsored by NICHD. No one has withdrawn. There have been no changes to the protocol, dated May 29, 1999 or its informed consent, dated June 18, 1999."

Neither of these studies were included in the list of all active research projects involving human subjects which was provided as Attachment 6 of your July 12, 2000 report.

Corrective Action: OHRP acknowledges the activities that the FDH/FDCF IRB has undertaken to address the issues surrounding the lack of adequate continuing review. These activities include (i) an assurance that substantive and meaningful review will be conducted at least annually for all research; (ii) the establishment of a data base to track all ongoing projects; and (iii) limitation of expedited review of protocols to those research categories stipulated by HHS regulations. OHRP also acknowledges that the FDH/FDCF IRB will limit expedited review of research to those categories allowed by HHS regulations.

Although the FDH/FDCF has made these efforts to correct the noncompliance relating to lack of adequate timely continuing review of research, OHRP continues to have serious concerns about the extent to which FDH/FDCF has reviewed the research approved by its IRB.

Action 1 - Required: The FDH/FDCF must conduct an adequate audit of all its ongoing research projects to ensure that they have undergone appropriate continuing review as required by HHS regulations at 45 CFR 46.109(e). FDH/FDCF must suspend immediately any Federally sponsored research involving human subjects that has not undergone appropriate continuing review by the FDH/FDCF IRB subsequent to February 16, 2000. For any project affected by this suspension, enrollment of new subjects must cease immediately except in extraordinary cases approved in advance by OHRP (OHRP would expect requests for approval of such cases to be rare). Furthermore, research activities involving previously enrolled subjects should continue only where the IRB finds that it is in the best interests of individual subjects to do so. For each affected protocol this suspension must remain in effect until the protocol has undergone appropriate continuing review by the IRB. Additionally, DFH/FDCF must provide OHRP with a report on the results of this audit and a list of any research activities that have been suspended as a result of this audit.

OHRP recommends that the FDH/FDCF IRB consult with an outside entity, experienced in reviewing research involving human subjects, prior performing the audit described above.

(2) OHRP finds that FDH and FDCF do not have adequate written IRB policies and procedures that 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 initial and continuing review of research and for reporting its findings and actions to the investigator and the institution; (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; and (iii) 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.
>
> (b) The procedures for ensuring prompt reporting to the IRB, 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 FDH/FDCF policies and procedures include template copies of face sheets 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 documents the IRB subsequently issues to the principal investigators and to the institution.

Action 2 - Required: The FDH/FDCF 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). In order to assist FDH/FDCF in this matter, please refer to the enclosed Guidance for Formulating Written IRB Policies and Procedures.

(3) 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. OHRP finds that IRB minutes often failed to meet these requirements.

Corrective Action: OHRP acknowledges the efforts of the FDH/FDCF IRB in improving its meeting minutes, as noted in the copy of the June 21, 2000 IRB meeting.

Please note that, 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). Your September 12, 2000 report includes a copy of the minutes of the IRB meeting held on September 5, 2000. The minutes still failed to document the votes of the IRB members.

Action 3 - Required: The FDH/FDCF must submit to OHRP a satisfactory corrective action plan to ensure that the IRB minutes adequately document the vote on all actions including the number of members voting for, against, and abstaining.

(4) HHS regulations at 45 CFR 46.112 stipulate that research approved by an IRB may be subject to further appropriate review and approval or disapproval by officials of the institution. However, those officials may not approve research if it has not been approved by an IRB.

OHRP notes that the FDH/FDCF IRB policies and procedures included a policy where the Secretary of the FDH or the Secretary of the FDCF may approve research that has been disapproved by an IRB. OHRP acknowledges the changes made to the FDH/FDCF IRB policies and procedures which allow for further review of research by the Secretary of the FDH but which do not allow approval of research which was disapproved by the IRB. Furthermore, OHRP acknowledges that no research protocols which were disapproved by the FDH/FDCF IRB were subsequently approved by the Secretary of FDH or the Secretary of FDCF.

OHRP has the following additional concerns, questions and guidance:

(5) HHS regulations at 45 CFR 46.115(a) stipulate that an institution, or when appropriate an IRB, shall prepare and maintain adequate documentation of IRB activities including, among other things, (a) copies of all research proposals reviewed, approved sample consent documents, progress reports submitted by investigators, and reports of injuries to subjects, (b) records of continuing review activities, (c) copies of all correspondence between the IRB and the investigators, and (d) statements of significant new findings provided to subjects, as required by 45 CFR 46.116(b)(5). OHRP is concerned that the FDH/FDCF IRB protocol records fail to include all the information stipulated at 45 CFR 46.115(a)(1),(3),(4), and (7). Please respond.

(6) HHS regulations at 45 CFR 46.404-407 require specific findings on the part of the IRB for approval of research involving children. OHRP's review of IRB documents provided with your reports reveal no evidence that the IRB consistently makes the required findings when reviewing research involving children. For example, the minutes of the June 21, 2000 IRB meeting include discussion of protocol RCHS # 952, "A

Multicenter Trial of Pediatric Aids Clinical Trials Group," but does not provide the specific findings required. As a result, OHRP is concerned that the review of protocols involving children by the FDH/FDCF IRB fails to meet the requirements at 45 CFR 46.404-407. Please respond.

(7) HHS regulations at 45 CFR 46.305-306 require specific findings on the part of the IRB for approval of research involving prisoners. OHRP notes that FDH/FDCF is conducting at least two ongoing studies that involve prisoners as research subjects, # 733 "Evaluation Prison Environ/HIV/AIDS," and #943, "Behavioral determinant of HIV seropositive recidivists." OHRP's review of IRB documents provided with your reports reveal no evidence that the IRB makes the required findings when reviewing such research. Please respond.

(8) HHS regulations at 45 CFR 46.304 require modification of IRB membership for review of research involving prisoners. In specific, at least one member of the IRB shall be a prisoner, or a prisoner representative with appropriate background and experience to serve in that capacity. When the convened IRB reviews research involving prisoners (including initial review, continuing review, review of protocol modifications, and review of unanticipated problems involving risks to subjects or others), the prisoner or prisoner representative must be present as a voting member. OHRP is concerned that the IRB failed to meet this requirement when reviewing research projects involving prisoners (see OHRP guidance at (http://ohrp.osophs.dhhs.gov/humansubjects/guidance/prison.htm). Additionally, your IRB membership roster fails to include a designated prisoner representative as required at 45 CFR 46.304(b).

Please respond. In your response please provide a curriculum vitae for the prisoner representative serving on the IRB and a justification for having this person serve in this capacity.

(9) Your July 12, 2000 report states that Attachment 6 contains a list of all active research projects involving human subjects. Our review shows that Attachment 6 fails to include several studies that were shown as approved in the minutes of meetings that were enclosed with the July 12 report. Examples include: meeting of August 26, 1999, projects numbered 823, 824, 826, 844; meeting of October 20, 1999, projects numbered 856, 858, 860, 861; meeting of December 16, 1999, projects numbered 865, 871, 872, 873, 874, 875, 876, 877, 880, 881, 882, 883; meeting of May 23, 2000, projects numbered 941 and 942; meeting of June 21, 2000, projects numbered 947, 948, 949, 950, 952, 953. Furthermore, attachment 6 lists project number 936 as approved by the full board on May 2, 2000, however, the July 12, 2000 report did not include meeting minutes for that date and project number 936 does not appear in the minutes of any of the meetings that were submitted to OHRP. Please explain these discrepancies.

(10) Regarding the minutes of the June 21, 2000 IRB meeting, OHRP has the following concerns and comments.

(a) Regarding RCHS #947, item 4, and RCHS # 948, item 5, OHRP is concerned about the IRB's substitution of "patient" or "participant" for "subject," in informed consent forms because the substituted terms may lead the prospective subjects to believe they are receiving "standard" treatment rather than participating in a research project. Please respond.

(b) Regarding RCHS # 950, item 1 indicated that changes to the study were faxed to the IRB coordinator but they were not available to the board for review. Unless the changes were minor, it appears that such changes should have been reviewed at a convened meeting of the IRB before the study was approved. Please respond.

(c) Regarding the genotype test referenced in item 4 for RCHS #950, it appears that the IRB did not evaluate the appropriateness of including the test in the study, nor did it review the wording of the description to assure that it accurately explains the risks and benefits of the test. Please respond.

(d) Regarding item 5 for RCHS #950, the action taken by the board, removal of the wording "ECR approval" without knowing what the term means or whether it is important that it be explained to prospective subjects, appears to be inappropriate. Please respond.

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

(12) 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. Please respond.

(13) OHRP has the following additional concerns and guidance about specific items in the Manual of Policies and Procedures.

(a) Neither the Manual of Policies and Procedures, at items III.C.5.f, III.D.6, IV.A.1, nor Attachment 5, initial application, specifically describe the documents that must be received by the IRB for each research project. The regulations at 45 CFR 46.109(a) require submission and review by the IRB of ". . . all research activities . . . ," which OHRP interprets to include 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.

(b) Regarding item V.A.1 of the Manual, 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. The list is available on the OHRP web site at http://ohrp.osophs.dhhs.gov/humansubjects/guidance/expedited98.htm.

(c) Item V.F, suspension or termination of RCHS approval of all research must be reported to OHRP. Unanticipated problems involving risks to subjects or others and any suspension or termination of IRB approval must also be reported to appropriate institutional officials, the IRB, OHRP and the head of the sponsoring Federal department or agency, as required by HHS regulations at 45 CFR 46.103(a) and 46.103(b)(5).

Please submit to OHRP a written response to the above required actions, concerns and questions no later than March 30, 2001. 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 all 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,

Patrick J. McNeilly, Ph.D.
Compliance Oversight Coordinator
Division of Compliance Oversight

Enclosure: Guidance for Formulating Written IRB Policies and Procedures

cc: E. Charlton Prather, M.D., Chairperson, IRB, FDH/FDCF
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