DEPARTMENT OF HEALTH & HUMAN SERVICES

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September 7, 2000

Winfred M. Phillips, Ph.D.
Vice President for Research
University of Florida
123 Tigert Hall
PO Box 113125
Gainesville, FL 32611-3125

RE: Human Research Subject Protections Under Multiple Project Assurance (MPA) M-1266
Research Projects Involving Prisoners As Subjects

Dear Dr. Phillips:

The Office for Human Research Protections (OHRP), formerly the Office for Protection from Research Risks (OPRR), has reviewed your April 27, 2000 letter regarding OPRR's concerns with the University of Florida's (UF's) program for protecting human research subjects. UF has undertaken several corrective actions in response to OPRR's stated concerns, which OHRP acknowledges below. In addition, OHRP makes the following findings and requests for corrective action:

(1) HHS regulations at 45 CFR 46.304(b) require that for the review of research involving prisoners as subjects 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, except that where a particular research project is reviewed by more than one IRB only one IRB need satisfy this requirement. The prisoner, or prisoner representative, must be a voting member of the IRB, and should be present whenever the IRB reviews research involving prisoners as subjects (including initial review, continuing review, review of protocol amendments, and review of any unanticipated problems involving risks to the subjects or others).

(a) OHRP acknowledges that Chaplain Seymour is now listed as a voting alternate member of the institutional review board (IRB), whose vote will be counted in the quorum during the review of all protocols involving prisoners as subjects, and during the review of protocols for which primary member William Allen or alternate member Barbara Noah are not present.

(b) OHRP acknowledges UF's finding that a prisoner representative was not present during continuing review of a nonfederally funded study "Patterns of Cognition in Residents of a Forensic Center" (PI: Dr. Duane Dede).

(c) OHRP acknowledges UF's corrective action plan to include a new field in its database to highlight vulnerable subject groups such as prisoners, in order to ensure the presence of the prisoner representative at meetings at all meetings where prisoner research is reviewed.

(d) OHRP respectfully disagrees with your statement that Subpart C of the Department of Health and Human Services (HHS) regulations protecting human research subjects (45 CFR Part 46) does not require the presence of the prisoner representative at convened meetings at which protocols involving prisoners are reviewed. HHS regulations at 45 CFR 46.304 require that the IRB include a prisoner representative in "carrying out responsibilities" under Subpart C, such as the review of research involving prisoners. Thus, the prisoner representative must be present when the convened IRB reviews research involving prisoners, and must participate in any action taken by the IRB with respect to protocols involving prisoners as subjects.

(2) 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. Additionally, where the convened IRB specifies conditions for approval of a protocol that are to be verified by the IRB chair or another IRB member designated by the chair, the approval period must begin on the date the protocol was reviewed by the convened IRB, not on the date approval is verified by the IRB chair or his or her designee.

(a) In its letter of March 28, 2000, OPRR found that the IRB failed to conduct continuing review at least annually for IRB-01 protocol #423-98 (Lactosorb® Mandibular System for Mandibular Fracture Repair; principal investigator: James G. Green, M.D., D.D.S.) and that the IRB incorrectly determined the time for continuing review based upon the date final approval was issued, rather than the date of the convened IRB meeting when the review was conducted, and conditional approval given.

(b) In its letter of April 27, 2000, UF asked OPRR to reconsider whether the initial date of the review period could be computed from the date of final approval by the IRB chair or the chair's designee, for protocols given prior conditional approval by the convened IRB pending specified changes. OHRP finds that UF's proposed procedure would not be consistent with HHS regulations at 45 CFR 46.109(e). However, UF indicated that it would adopt an interim procedure for continuing review, whereby the review period would be computed from the date of convened IRB review and conditional approval.

OHRP acknowledges that IRB-02 has amended its procedures to ensure that if the IRB is unable to conduct continuing review of a protocol prior to its expiration date, the protocol will be suspended and the PI instructed that no further research may be conducted unless and until the protocol is reviewed and approved by the IRB.

Action 1 - Required: UF must submit a corrective action plan to ensure on a permanent basis that continuing review of research by the IRBs occurs at least annually.

(3) HHS regulations at 45 CFR 46.107(e) stipulate that no IRB member may participate in the IRB's initial or continuing review of a project in which the member has a conflicting interest, except to provide information requested by the IRB. This regulation limits the participation of a member with conflicting interest to providing information, and expressly prohibits participation in "initial or continuing review of any project." It is therefore inappropriate for an IRB member with a conflict of interest, in contrast to an IRB member who abstains due to lack of expertise or for any reason other than a conflict of interest, to participate in the initial or continuing review of a protocol or be counted in the quorum for any action which follows such review.

In its letter of March 29, 2000, OPRR requested that UF modify its Policy and Procedure Manuals for IRBs 01 and 03 to indicate that IRB members with conflicts of interest who abstain from voting may not be counted for the purposes of meeting IRB quorum requirements. UF indicated that it would adopt an interim policy of excluding IRB members with conflicts of interest from the quorum count.

Action 2 - Required: UF must submit a corrective action plan to ensure on a permanent basis that IRB-01 and IRB-03 do not include in the quorum count IRB members who abstain from voting on an action because of a conflicting interest.

(4) For research involving prisoners, HHS regulations at 45 CFR 46.305(a)(7) require that where the IRB finds there may be a need for follow-up examination or care of subjects after the end of their participation, there must be adequate provision for such examination or care, taking into account the varying lengths of individual prisoners' sentences, and for informing subjects of this fact.

(a) In its letter of March 29, 2000, OPRR expressed concern that prisoner subjects in IRB-01 protocol #423-98 were not afforded adequate follow-up care for potential complications from the research interventions that could require additional medical and surgical care, including but not limited to: (i) failure of the device to provide adequate fixation; (ii) failure resulting in delayed or non-union; infection; local or systemic reaction to the implant material or its breakdown products; (iii) bending, breaking, loosening, or migration of the devices; (iv) temporomandibular joint pain; and (v) malocclusion.

(b) UF's April 27, 2000 letter to OPRR states that UF believed the prisoners in IRB-01 protocol #423-98 would be afforded adequate follow-up care in accordance with 45 CFR 46.305(a)(7) because the study afforded a year of post surgery follow-up,

as compared to the three months provided under standard care. OHRP notes that many of the potential complications that could require follow-up care could occur well after one year.

(c) UF's April 27, 2000 letter acknowledges that prisoner subjects participating in IRB-01 #423-98 who are subsequently released are informed that they are responsible for the costs of additional treatment for such things as removal of metal plates and screws after they are released.

(d) Given the variety and expense of potential complications that may arise from this prison research, and the informed consent statement that prisoners are financially responsible for additional treatment requested after release, OHRP remains concerned that the IRB may have failed to ensure adequate provision for follow-up examination or care for prisoner subjects in IRB-01 protocol #423-98, in accordance with 45 CFR 46.305(a)(7).

(5) HHS regulations at 45 CFR 46.116 require that the information provided in informed consent documents be in language understandable to the subject. In addition, 45 CFR 46.116(a)(1) requires that the information provided to subjects during the informed consent process include a complete description of the procedures to be followed, and identification of any procedures which are experimental. Regarding IRB-01 protocol #423-98, OHRP acknowledges UF's findings that the informed consent document reviewed and approved by the IRB:

(a) Contained inaccurate information regarding FDA approval for marketing the Lactosorb bone plating device.

(b) Should have included the following information:

(i) A statement that use of the Lactosorb® plates and screws for treatment of lower jawbone fractures is experimental.

(ii) A description of the plan to administer intravenous and oral antibiotics to subjects following the surgical intervention.

(iii) A description of the nature of the follow-up evaluations at 2 weeks, 6 weeks, 3 months, 7 months, and 1 year.

(c) Included complex language that would not be understandable to all prisoner subjects (e.g., "chronic inflammation," "improved radiographic follow-up," "radiopaque," "CTs," "MRIs", "plain radiographs," and "palpability").

Action 3 - Required: UF must submit a corrective action plan to OHRP to ensure that its IRBs understand and implement the requirements of 45 CFR 46.116, including appropriate use of language in informed consent documents, and accurate and complete description of experimental procedures.

(6) UF requests that OHRP reconsider its statement that when the convened IRB stipulates as a condition for approval express revisions requiring simple concurrence by the investigator, the revisions must be approved by an IRB member in accordance with 45 CFR 46.110(b)(2). Under HHS regulations, there are only two avenues for IRB approval of research: 45 CFR 46.108(b) [majority vote of the convened IRB] and 45 CFR 46.110(b) [expedited review by the IRB Chair or his or her designee]. A person who is not an IRB member may not approve research under HHS regulations.

OHRP finds that UF's practice of permitting an individual who is not an IRB member to approve explicit changes to research protocols recommended by the IRB is not in accordance HHS human subject protection requirements at 45 CFR 46.108(b) and 46.110(b)(2).

Action 4 - Required: UF must submit a corrective action plan to ensure that the approval of any and all protocol changes required by the IRB is conducted by the IRB chair, or an IRB member designated by the chair, in accordance with HHS regulatory requirements at 45 CFR 46.108(b) and 46.110(b)(2).

(7) HHS regulations at 45 CFR 46.103(f) require that an institution with an approved assurance shall certify that each *application* for research has been reviewed and approved by the IRB. In its letter of April 27, 2000, UF proposes to provide the primary IRB reviewer of each new protocol submitted for IRB approval, in lieu of the full grant application, a copy of those portions of any corresponding federal grant application that are considered relevant to human subjects.

(a) A May 31, 2000 OPRR memorandum discussing IRB Review of Applications for HHS Support (copy enclosed) states that:

(i) The IRB's review should ensure that all research described in the application or proposal is entirely consistent with any corresponding protocol submitted. The review need not be undertaken by every IRB member, but a designated reviewer should document that the proposed research is consistent with any relevant protocol.

(ii) It is important for designated IRB reviewers to have ready access to **the entire** application or proposal (exclusive of appendices) because information related to the protection of human subjects sometimes appears only in seemingly peripheral sections. Examples include information about (i) the number and qualifications of collaborating investigators and other members of the research team; (ii) cooperating institutions or performance sites that may require separate or additional IRB review or an Assurance of Compliance; (iii) characteristics of proposed research facilities that may affect subject safety or the confidentiality of data; (iv) the feasibility of financial commitments made to subjects; and (v) the cost of proposed subject protection measures, such as consent monitors or translators.

(b) OHRP finds that the UF's IRBs do not currently review the full grant application for proposed federally funded research as required by 45 CFR 46.103(f).

Action 5 - Required: Each of UF's IRBs must inventory and audit its records for all active Federally supported research protocols to determine whether the IRB received and reviewed a copy of the entire applicable Federal grant application. Where review of the grant application did not occur, at least one IRB member should compare the content of the grant application and the IRB-approved research protocol. Where the grant application and the IRB-approved protocol are discrepant in any way, the IRB must re-review the research protocol in conjunction with the grant application. UF must submit to OHRP a report describing the outcome of this audit and IRB review.

Please submit a response to this letter which includes all required corrective actions no later than October 2, 2000.

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,

Carol J. Weil, J.D.
Compliance Oversight Coordinator
Division of Human Subject Protections

Enclosures: (1) May 31, 2000 memo on review of grant applications

cc: Dr. Michael Carome, OHRP
Dr. Tom Puglisi, OHRP
Dr. Melody Lin, OHRP
Dr. Katherine Duncan, OHRP
Dr. Sanford Leikin, OHRP
Mr. George Gasparis, OHRP
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Dr. R. Peter Iafrate, Chair, IRB-01, UF
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Dr. Roger Bertholf, Chair, IRB-03, UF
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