DEPARTMENT OF HEALTH & HUMAN SERVICES

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September 14, 2000

Dorothea Wilson
Vice President for Research
University of Texas Medical Branch at Galveston
Suite 6.606 Administration Building
301 University Blvd.
Galveston, TX 77555-0130

RE: Human Research Subject Protections Under Multiple Project Assurance M-1172

Dear Ms. Wilson:

As you know, the Office for Human Research Protections (OHRP) conducted an on-site evaluation of human subject protection procedures at the University of Texas Medical Branch (UTMB) on September 12-13, 2000. The evaluation, conducted by 4 OHRP staff with the assistance of 4 consultants, included meetings with senior institutional officials, over 20 Institutional Review Board (IRB) members, IRB administrative staff, investigators supported by the Department of Health and Human Services (HHS), and investigators conducting research involving prisoners as subjects. The evaluation involved review of IRB files for over 50 protocols, and the minutes of IRB meetings convened during the three years.

In the course of the OHRP review, the IRB chair, IRB members, and IRB administrative staff displayed an enthusiastic and sincere commitment to the protection of human subjects. Furthermore, the volume of research reviewed and the great time and effort devoted to IRB oversight of research is indicative of the extraordinary dedication and commitment of the IRB members and staff. Investigators demonstrated a culture of respect for the IRB process. The staff of the Office of the Vice President for Research was very helpful and accommodating to OHRP during the site visit.

OHRP Findings Relative to Research Involving Prisoners as Subjects

Based upon its evaluation, OHRP makes the following determinations regarding research involving prisoners as subjects at UTMB:

(1) In its review of the complete IRB files and relevant IRB minutes for 25 protocols approved by the IRB for the involvement of prisoners as subjects, OHRP found scant evidence that the IRB made the findings required by HHS regulations at 45 CFR 46.305(a) when it reviewed and approved the research.

(2) HHS regulations at 45 CFR 46.305(a)(1) stipulate that research proposing the involvement of prisoners as subjects may be approved by the IRB only if the research represents one of the categories of research permissible under HHS regulations at 45 CFR 46.306(a)(2).

(a) OHRP finds that the following research projects approved by the IRB for involvement of prisoners as subjects did not represent any of the categories of research permissible under HHS regulations at 45 CFR 46.306(a)(2):

(i) IRB #97-115, Phase I Trial of Perfusion-Induced Systemic Hypothermia for Metastatic Non-Small Cell Lung Carcinoma: A Concept Feasibility Study.

(ii) IRB #97-186, The Pathogenesis of Human Gamma-Herpesvirus Infection.

(iii) IRB #97-298, Validation of Gastric Air Tonometry as a Marker for Mucosal Ischemia.

(iv) IRB #97-312, Morning Versus Evening Induction of Labor.

(v) IRB #97-340, Evaluation of Liver Lymphocytes in Chronic Liver Disease.

(vi) IRB #98-124, Comparison of Cytological Evaluation of the Endocervical Canal and Endocervical Curettage After LEEP Conization.

(vii) IRB #98-354, Auto-Antibodies in Achalasia.

(viii) IRB #99-218, A Phase I/II Escalating, Single-Dose, Cohort Trial to Determine the Safety, Tolerance, Maximum-Tolerated Dose, and Pharmacokinetic Profile of Intrahepatic Delivery (via Hepatic Artery Catheterization) of Doxorubicin (DOX) Adsorbed to Magnetic.....

(ix) IRB #99-403, A Blinded, Prospective Study of Cutting-Needle Versus Coring-Needle Biopsy of Renal Allografts.

(b) OHRP notes that the following research projects approved by the IRB for involvement of prisoners as subjects would only have been permissible under the category of research stipulated by HHS regulations at 45 CFR 46.306(a)(2)(C). However, the IRB failed to approve the research under this category and failed to recognize the requirement for consultation with appropriate experts prior to initiation of the research with prisoners:

(i) IRB #98-402, Texas Repository for AIDS Neuropathogenesis Research.

(ii) IRB #99-265, A Phase I, Limited Center, Sequential Cohort Trial of HIV Vaccine (Polyvalent Peptide Vaccine C4-V3) in Conjunction with Interleukin-12 in Subjects with Maximal Suppression of HIV Replication and CD4 Count > 400 Cells/mm^3.

(iii) IRB #99-320, In vivo and ex vivo Cytokine Production After Interferon-alpha Therapy for Hepatitis C.

(c) OHRP is particularly concerned that some of the protocols referenced above involved greater than minimal risk and did not involve research on practices which had the intent and reasonable probability of improving the health or well-being of the subjects (e.g., IRB #97-115, 99-218, and 99-265)

(d) OHRP finds that the following HHS-supported protocol approved for involvement of prisoners as subjects involves research on a practice which has the intent and reasonable probability of improving the health and well-being of the subjects:

IRB #98-09, Phase III Study of Pentosanpolysulfate (PPS) in Treatment of GI Tract Sequelae of Radiotherapy

However, OHRP finds that the protocol requires the assignment of prisoners to a placebo control group which will not benefit from the research. As such, OHRP finds that enrollment of prisoners in the research may proceed only after OHRP, acting on behalf of the Secretary of HHS, has consulted with appropriate experts, including experts in penology, medicine, and ethics, and published notice in the Federal Register of the intent to approve the research, in accordance with HHS regulations at 45 CFR 46.306(a)(2)(D).

(e) OHRP is concerned that some of the research protocols approved by the IRB for the involvement of prisoners as subjects under 45 CFR 46.306(a)(2)(D), particularly some early phase II clinical trials, may not have presented sufficient probability of improving the health and well-being of the subjects.

OHRP Findings Relative to Systemic Protections for Human Subjects

Based on its evaluation, OHRP makes the following determinations relative to systemic protections for human subjects at UTMB:

(3) OHRP is concerned that when reviewing protocol applications, the IRB often appears to lack sufficient information to make the determinations required for approval of research under HHS regulations at 45 CFR 46.111 and 45 CFR Part 46, Subparts B, C, and D. For example, the IRB appears to review only minimal information regarding (a) subject recruitment and enrollment procedures; (b) the equitable selection of subjects; (c) provisions to protect the privacy of subjects and maintain the confidentiality of data; (d) additional safeguards to protect the rights and welfare of subjects who are likely to be vulnerable; and (e) the justification for involving groups of vulnerable subjects, in particular children and prisoners.

(4) The minutes of IRB meetings, and our discussions with IRB members and staff, indicate that little substantive review takes place at convened meetings of the IRB. Most protocols undergoing initial review are neither individually presented nor discussed at a convened meeting of the IRB.

OHRP does acknowledge that in many cases the initial review of protocols by the IRB Study Sections and by the Subcommittee on Human Research, the memberships of which satisfy the requirements of HHS regulations at 45 CFR 46.107, appears to be substantive.

(5) 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 IRB regularly failed to satisfy these requirements. In specific, OHRP finds that for research requiring continuing review by the convened IRB (a) the continuing review form has routinely failed to provide a

sufficient description of the progress of the research; (b) IRB members do not receive copies of the continuing review reports or the informed consent documents prior to the convened IRB meeting; and (c) individual protocols undergoing continuing review are neither discussed nor acted upon separately by the convened IRB, nor the IRB Study Sections or Subcommittee on Human Research.

(6) 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. OHRP is concerned that on occasion IRB members inappropriately participated in the initial and continuing review of protocols for which they had a conflicting interest. OHRP strongly recommends that IRB members absent themselves from the meeting room when the IRB votes on research in which they have a conflicting interest, and such should be noted in the IRB meeting minutes.

(7) HHS regulations at 45 CFR 46.110(b)(1) limit the use of expedited review procedures to specific research categories published in the Federal Register at 63 FR 60364. OHRP finds that:

(a) The IRB inappropriately confounds the concepts of minimal risk and expedited review.

(b) Use of expedited review by the IRB has not been restricted to these categories. OHRP recommends that documentation for initial and continuing reviews that are conducted utilizing expedited review procedures include citation of the specific permissible categories (see 63 FR 60364) justifying the expedited review.

(8) HHS regulations at 45 CFR 46.110(b)(2) permit use of expedited procedures for review of minor changes to previously approved research. OHRP finds that the IRB has employed expedited procedures to review changes that exceed this limitation.

(9) HHS regulations at 45 CFR 46.116(a) delineate specific elements required for informed consent. OHRP found instances where (a) required elements were omitted; and (b) there were discrepancies between the protocol application and the informed consent documents regarding the purpose, risks, and benefits of the research. In particular, OHRP noted several instances where informed consent documents overstated the potential benefits to subjects and understated or omitted reasonably foreseeable risks to the subjects.

(10) HHS regulations at 45 CFR 46.116 require that the information provided in the informed consent documents be in language understandable to the subject. OHRP finds that given the education level of the expected subject population, especially for research proposing the involvement of subjects as prisoners, the informed consent documents

approved by the IRB frequently include complex language that would not be understandable to all subjects.

(11) HHS regulations at 45 CFR 46.116 prohibit any exculpatory language in informed consent through which the subject is made to release, or appear to release, the investigator or the institution from liability for negligence. OHRP finds that the following boiler-plate language in the sample informed consent document appears to be exculpatory:

> "Neither UTMB nor [the investigator] can assume financial responsibility or liability for the expenses of such treatment."

(12) 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 (see 45 CFR 46.116 and 46.117). Where informed consent is documented in accordance with HHS regulations at 45 CFR 46.117(b)(1), the written informed 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 an informed consent document written in a language understandable to them. OHRP strongly encourages the use of this procedure whenever possible.

OHRP is concerned that the IRB does not routinely require informed consent documents in the native language of likely potential subjects who do not speak English. Furthermore, OHRP is concerned that the IRB on occasion approves protocols for which the investigator has stipulated that individuals who do not speak English will be excluded without providing a justification for such an exclusion criterion.

(13) OHRP is concerned that the IRB Chair and members appear to lack a detailed understanding of the specific requirements of the HHS regulations for the protection of human subjects. As a result, IRB determinations have sometimes deviated from these requirements.

(14) HHS regulations at 45 CFR 46.103(b)(2) require that institutions provide meeting space and sufficient staff to support the IRB's review and recordkeeping duties. OHRP is concerned that the level of staff support provided to the IRB appears to be insufficient. It is OHRP's experience that the volume of human subjects research conducted by UTMB warrants additional full-time IRB staff members.

(15) 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 discussions with IRB members and its review of IRB documents reveal little evidence that the IRB consistently makes the required findings when reviewing research involving children.

(16) HHS regulations at 45 CFR 46.116(d) require that the IRB find and document four specific criteria when approving waiver or alteration of some or all of the required elements of informed consent. OHRP's review of IRB documents reveals no evidence that the IRB consistently satisfies these requirements.

(17) HHS regulations at 45 CFR 46.117(c) require specific findings on the part of the IRB for waiver of the usual requirements for the investigator to obtain a signed consent form from all subjects. OHRP's review of IRB documents reveals no evidence that the IRB makes the required findings when approving such waivers.

(18) OHRP is concerned that the current IRB membership appears to lack the diversity, including consideration of race, gender, and cultural backgrounds and sensitivity to such issues as community attitudes, to promote respect for its advice and counsel in safeguarding the rights and welfare of human subjects, as required under HHS regulations at 45 CFR 46.107(a).

(19) OHRP is concerned that the institution does not have written IRB policies and procedures that adequately describe the following activities, as required by HHS regulations at 45 CFR 46.103(b)(4) and (5):

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

(20) OHRP notes that UTMB is engaged in at least one tissue banking or repository activity. Such activities require the IRB to make determinations concerning (i) the regulatory status and appropriate use of stored biologic samples, and (ii) the informed consent process for research using such samples. OHRP is concerned that the IRB has not developed policies and procedures for oversight of repository activities that ensure compliance with HHS regulations at 45 CFR Part 46 (see guidance at http://ohrp.osophs.dhhs.gov/humansubjects/guidance/reposit.htm).

(21) OHRP is concerned that the deficiencies cited above may be indicative of an IRB overburdened by the large volume of research for which it has oversight responsibility. It is OHRP's experience that such a large volume of human subjects research warrants more than one fully functional IRB.

(22) HHS regulations at 45 CFR 46.117 require that a copy of the informed consent document be given to subjects. OHRP remains concerned that this requirement is not being satisfied for all prisoners involved as subjects in research.

OHRP Action

OHRP acknowledges that UTMB recently has implemented some actions to enhance its system for protecting human subjects, including (i) hiring two additional IRB staff members; (ii) expansion of IRB office space; and (iii) development of a mandatory training program for investigators involved in the conduct of human subject research.

Nevertheless, in view of the above determinations and in order to ensure adequate protections for human subjects, the Office for Human Research Protections hereby restricts the University of Texas Medical Branch Multiple Project Assurance (MPA # M-1172), pending satisfactory completion of the required corrective actions described below.

Required Actions

Action 1 - Required: UTMB must develop and forward the following corrective action plans to OHRP by October 15, 2000:

(a) A satisfactory plan to address all deficiencies and concerns described above. This plan should include (i) revised IRB policies and procedures; (ii) an expanded protocol application form; and (iii) a plan to ensure that all research protocols requiring initial review by the convened IRB are individually presented, discussed, and acted upon during convened IRB meetings. Where HHS regulations require that the convened IRB make specific findings, such findings should be made by the convened IRB, not by subcommittees of the IRB.

(b) A satisfactory plan to ensure that all IRB members, all IRB staff, and all research investigators are appropriately educated, on an ongoing basis, about the regulatory requirements for the protection of human subjects. This plan should include appropriate resources for IRB members and IRB staff to attend local and national meetings related to the protection of human subjects.

Action 2 - Required: UTMB must suspend immediately any Federally supported research projects that are not eligible for an expedited review procedure and received initial IRB approval prior to September 14, 1999. 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 may 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 substantive and meaningful continuing

review and been re-approved by the convened IRB. OHRP anticipates that implementation of this required action would necessarily include the following steps:

(a) Principal investigators will need to submit new continuing review reports that provide an adequate summary of the progress of the research so that the IRB can make the determinations required by 45 CFR 46.111 and 45 CFR Part 46, Subparts B, C, and D.

(b) The IRB members will need to receive appropriate education regarding the regulatory requirements for the protection of human subjects, with particular emphasis on the requirements of Subparts C and D of 45 CFR Part 46.

(c) Copies of the continuing review reports and the informed consent documents should be distributed to IRB members prior to the convened IRB meeting.

(d) Individual protocols requiring continuing review should be individually discussed and acted upon, and the vote on such actions should be recorded in the minutes of IRB meetings in accordance with HHS regulations at 45 CFR 46.115(a)(2).

Action 3 - Required: UTMB must inventory and audit the IRB records for all Federally supported research previously approved by the IRB under an expedited review procedure to determine whether the research was indeed eligible for expedited review. UTMB must suspend immediately any Federally supported research projects that were not eligible for an expedited review procedure. 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 may 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 initial review and been re- approved by the convened IRB.

Action 4 - Required: By September 28, 2000, UTMB must provide OHRP with a complete list of all suspended protocols, including project title, IRB number, applicable Federal award number, and principal investigator name. Please be aware that any such suspensions must also be reported to the funding department or agency.

Action 5 - Required: UTMB must submit quarterly progress reports to OHRP documenting implementation of the required corrective actions. The first progress report is due December 15, 2000.

Action 6 - Required: The suspension of involvement of prisoners in Federally supported research protocols that was required by OHRP in its July 10, 2000 letter to UTMB must remain in effect until the protocols have been re-reviewed and approved by the IRB, and certified by UTMB, in accordance with all requirements of HHS regulations at 45 CFR Part 46, Subpart C.

Furthermore, prior to any such re-review by the IRB, IRB members should receive appropriate education regarding the HHS regulatory requirements for research involving prisoners as subjects.

Additional Recommended Actions:

Action 7 - Recommended: Given the volume of research involving prisoners as subjects that is being conducted by UTMB and the close relationship between UTMB and the Texas Department of Criminal Justice, OHRP strongly recommends that UTMB implement additional procedures to ensure that prisoners enrolled in research are adequately protected, including the following:

(a) Appointment of more than 1 prisoner, or prisoner representative, to the IRB. Please submit to OHRP by October 15, 2000 a detailed description of the qualifications, background, and experiences of the current and any proposed additional prisoner representatives that justifies their serving on the IRB in this capacity.

(b) Utilization of independent consent monitors to observe and audit the consent process for prisoners at the time of initial enrollment and periodically during their participation in the research, when appropriate.

(c) Implementation of a mandatory training program regarding the ethical principles and regulatory requirements for research involving prisoners as subjects for everyone at UTMB engaged in the conduct of such research.

Action 8 - Recommended: 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.

Action 9 - Recommended: OHRP recommends that more than one primary reviewer be assigned to each protocol undergoing initial review by the convened IRB.

Action 10 - Recommended: 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)]. OHRP recommends that the minutes of IRB meetings clearly reflect these determinations regarding risk and approval period (review interval).

OHRP is available to assist UTMB in the development and implementation of its corrective action plans. Do not hesitate to contact me should you have any questions.

Sincerely,

Michael A. Carome, M.D.
Chief, Compliance Oversight Branch
Division of Human Subject Protections

Enclosure: OPRR Reports 95-01

cc: Dr. John D. Stobo, President, UTMB
Dr. Wayne Patterson, IRB Director, UTMB
Dr. Frank C. Schmalstieg, Chairperson, IRB, UTMB
Commissioner, FDA
Dr. David Lepay, FDA
Dr. James F. McCormack, FDA
Dr. Greg Koski, OHRP
Dr. Melody H. Lin, OHRP
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