DEPARTMENT OF HEALTH & HUMAN SERVICES

Office of the Secretary
Office of Public Health and Science

Office for Human Research Protections
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October 31, 2005

John C. McDonald, M.D.
Chancellor/Dean
Louisiana State University Health Science Center Shreveport (LSUHSCS)
PO Box 33932
1501 Kings Hwy
Shreveport, LA 71130-3932

RE: Human Research Subject Protections Under Federalwide Assurance FWA-653

Research Project: Neoadjuvant Zoladex and Flutamide in Bulky and Non-Bulky Clinical Stage C Carcinoma of the Prostate, Phase II
Principal Investigator: Dennis Venable, M.D.
Project Number: SWOG 9109

Dear Dr. McDonald:

The Office for Human Research Protections (OHRP) has reviewed Louisiana State University Health Science Center Shreveport's (LSUHSCS) report of June 12, 2004, submitted in response to OHRP's May 5, 2004 request for information concerning the following allegations of noncompliance with the Department of Health and Human Services (HHS) regulations for the protection of human research subjects, 45 CFR part 46 (HHS regulations).

Based upon its review, OHRP makes the following determinations.

(1) HHS regulations at 45 CFR 46.116 require investigators to obtain legally effective informed consent prior to involving a subject in research. The informed consent information must be in language understandable to the subject or the subject's legally authorized representative. It is alleged that these regulations were violated because a subject was functionally illiterate and did not have a family member present when consent was obtained from him for the above-referenced research study.

OHRP finds the above allegation was not substantiated by the evidence presented. In particular, OHRP notes that (a) the HHS regulations do not require subjects with compromised reading ability to have legally authorized representatives so long as they are able to understand information delivered verbally or by other non-written means; and (b)

there is no evidence that the subject in question lacked that capacity to give voluntary informed consent for the research. OHRP also notes that pre-operative progress notes (dated 4/96) in the subject's medical record indicate that the risks of surgery were explained verbally to the subject and that the subject was therefore adequately informed about the risks of participation in the research. The progress notes state that the examining urologist discussed various options for treatment of the subject's prostate cancer including observation, radiation therapy, hormone treatment, and surgery. The notes expressly state:

> "The patient understands risks of surgery including bowel injury, neuromuscular injury, incontinence, and the chance for transfusions, MI, and DEATH (capitalizations in original).
>
> The patient understands the risks AND wants to proceed with surgery. Moderate Risk for Surgery According to Medicine (capitalizations in original) ."

(2) HHS regulations at 45 CFR 46.103(b)(4) require that institutions have written procedures which the institutional review board (IRB) will follow for ensuring prompt reporting to the IRB of proposed changes in research, 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. It is alleged that LSUHSCS failed to comply with protocol requirements regarding the reporting of the subject's death and the potential relationship of the death to study interventions.

OHRP finds the above allegation was not substantiated by the evidence presented. The Southwest Oncology Group (SWOG) protocol required that LSUHSCS report any adverse experience, and all deaths, considered drug-related. A SWOG Notice of Death form was signed and mailed July 24, 1996, nine days following the subject's death. The form stated that physicians felt the death was not related to study drugs.

(3) HHS regulations at 45 CFR 46.116 prohibit any oral or written exculpatory language in the informed consent process, through which the subject is made to waive, or appear to waive, any legal rights. OHRP finds the following language in the IRB-approved informed consent document signed by the subject in the above research to be exculpatory:

> By your consent to participation in this research study, you give up your property rights that you may have in your bodily fluids, substances or tissues.

(4) OHRP finds that LSUHSCS does not have written IRB procedures that adequately describe the following activities, as required by HHS regulations at 45 CFR 46.103(a) and 46.103(b)(4) and (5):

> (a) The procedures which the IRB will follow for conducting its initial review of

research.

(b) The procedures which the IRB will follow for conducting its continuing review of research.

(c) The procedures which the IRB will follow for reporting its findings and actions to investigators and the institution.

(d) The procedures which the IRB will follow for determining which projects require review more often than annually.

(e) The procedures which the IRB will follow for determining which projects need verification from sources other than the investigators that no material changes have occurred since previous IRB review.

(f) The procedures which the IRB will follow 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.

(g) The procedures for ensuring prompt reporting to the IRB, appropriate institutional officials, any department or agency head, and OHRP of: (a) any unanticipated problems involving risks to subjects or others; (b) any serious or continuing noncompliance with 45 CFR Part 46 or the requirements or determinations of the IRB; and (c) any suspension or termination of IRB approval.

For OHRP guidance on written IRB procedures, see http://www.hhs.gov/ohrp/humansubjects/guidance/irbgd702.htm.

At this time OHRP has the following additional concern and recommendations:

(5) [Redacted]

(6) HHS regulations at 45 CFR 46.116(a)(2) require that, in seeking informed consent, a description of reasonably foreseeable risks and discomforts to subjects must be provided. It is alleged that the IRB-approved informed consent document for the above research did not adequately describe the risks of surgery because surgery risks were discussed in a subsection under the heading Zoladex, which did not draw appropriate attention to them as risks independent from potential drug complications.

OHRP notes that the original SWOG consent form did list surgical side-effects separately, although it did not cite the risk of death. The informed consent document approved by the LSUHSCS IRB modified the SWOG format, describing surgery risks (not including death) together with those of taking Zoladex, under the heading of Zoladex. OHRP recommends that the placement of surgical risks in the informed consent document approved by the LHUHSCS IRB be separated from the discussion of drug risks

(7) The LHUHSC IRB membership roster lists Betty Johnson, M. Prestidge Rogers, and Michael A. Manheimer as "Ex-Officio" IRB members. LHUHSC IRB staff confirmed to OHRP that these individuals are nonvoting members of the IRB. OHRP considers all individuals listed on the IRB membership roster to be voting members of the IRB. OHRP recommends that individuals who are neither primary nor alternate members of the IRB should not be listed on the LHUHSC IRB membership roster.

Required Action: By November 14, 2005, please provide OHRP with a corrective action plan in response to the findings in (3) and (4), and the concern in (5) above. In your response, please provide a copy of any revised IRB policies and procedures.

OHRP appreciates your continued commitment to the protection of human research subjects. Please feel free to call me if you have any questions.

Sincerely,

Carol J. Weil, J.D.
Division of Compliance Oversight
Office for Human Research Protections

cc: Mr. Michael Manheimer, LSUHSCS, Director, Grants Administration, IRB Administrator
Dr. Steven A. Conrad, LSUHSCS IRB Chair
Dr. Bernard Schwetz, OHRP
Dr. Melody H. Lin, OHRP
Dr. Michael Carome, OHRP
Dr. Kristina Borror, OHRP
Ms. Shirley Hicks, OHRP
Ms. Pat El-Hinnawy, OHRP
Ms. Janet Fant, OHRP
Commissioner, FDA

Dr. David Lepay, FDA
Dr. Lana Skirboll, Director, Office of Science Policy, NIH
Dr. Joan Mauer, NCI