DEPARTMENT OF HEALTH & HUMAN SERVICES

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February 12, 2001

Joseph M. Moerschbaecher, Ph.D.
Vice Chancellor for Academic Affairs
Louisiana State University Medical Center
433 Bolivar Street, Room 824
New Orleans, LA 70112

RE: Human Research Subject Protections Under Multiple Project Assurance (MPA) M-1130

Research Project: Tc^{99m} ECD SPET Brain Imaging in Neurologically Normal Individuals and Neurologically and Cognitively Abnormal Nitrogen Tetroxide Exposed Patients
Protocol Number: IRB # 3511
Principal Investigator: Paul G. Harch, M.D.

Dear Dr. Moerschbaecher:

The Office for Human Research Protections (OHRP) has reviewed your report of January 26, 2001 regarding the above referenced research conducted at Louisiana State University Medical Center (LSUMC).

Based upon its review of your May 20, 1999, and January 26, 2001 reports, OHRP makes the following determinations regarding the above reference research:

(1) OHRP finds that when reviewing the protocol application for this research, the Institutional Review Board (IRB) appeared to lack sufficient information to make the determinations required for approval of research under Department of Health and Human Services (HHS) regulations at 45 CFR 46.111. In specific, OHRP notes that an expanded protocol for this project was not included in the report to OHRP and there is no evidence that the IRB ever received more than a protocol summary that was less than one page.

Corrective Action:

OHRP notes that LSUMC now requires the submission of an expanded protocol and that the current IRB policies and procedures state that an incomplete application will not be evaluated by the IRB, but is returned to the Head of the Department. OHRP has determined that this corrective action adequately addresses this finding and is appropriate under the LSUMC Multiple Project Assurance (MPA).

(2) HHS regulations at 45 CFR 46.103(b)(4)(iii) require that institutions have written procedures to ensure IRB review and approval of all proposed changes in a research activity, during the period for which IRB approval has already been given, prior to initiation of such changes, except when necessary to eliminate apparent immediate hazards to the subjects. OHRP finds that protocol modifications were implemented prior to IRB approval. In specific, OHRP notes that the questionnaire originally approved for this project was changed without IRB review and approval.

Corrective Action:

OHRP notes that LSUMC IRB policy requires that such protocol changes cannot be initiated without approval by the IRB. OHRP also acknowledges that the current Guide to the Policies and Procedures of the Louisiana State University Health Sciences Center IRB includes mechanisms to insure that investigators request approval for modifications and that the IRB may require information from outside sources to verify that no material changes have occurred since the previous IRB review. OHRP has determined that these corrective actions adequately address this finding and are appropriate under the LSUMC MPA.

(3) 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 the informed consent document approved by the IRB for this study included complex, technical language that likely would not be understandable to all subjects.

Corrective Action:

OHRP acknowledges that the current Guide to the Policies and Procedures of the LSUHSC IRB clearly states that informed consent documents must be in lay language understandable by a person with ninth grade reading skills and must be clearly understood by the subjects. OHRP also notes LSUMC's current educational efforts to stress that comprehension is a key element in the informed consent process. OHRP has determined that these corrective actions adequately address this finding and are appropriate under the LSUMC MPA.

(4) OHRP finds that the informed consent documents reviewed and approved by the IRB for this project did not adequately address the following elements required by HHS regulations at 45 CFR 46.116(a):

(a) Section 46.116(a)(1): A statement that the study involves research.

(b) Section 46.116(a)(2): A description of all the reasonably foreseeable risks and discomforts (i.e., the risks are not well explained, such as the possible consequences of allergy to the imaging agent or radiation exposure).

(c) Section 46.116(a)(4): A disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject (e.g., undergoing SPECT or psychometric testing outside of the research context).

(d) Section 46.116(a)(8): A statement that participation is voluntary, refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled. The informed consent document states that "...subjects may refuse to participate or withdraw from the study at any time without jeopardizing, in any way, their medical treatment at this institution..." OHRP notes that there may be other penalties or loss of benefits that do not include medical treatment at the institution.

Corrective Action:

OHRP acknowledges that the current Guide to the Policies and Procedures of the LSUHSC IRB outlines the necessary elements of informed consent, except "...without penalty or loss of benefits to which the subject is otherwise entitled." OHRP notes that this change will be made to the Guide and this language will be included in all future consent forms and that the IRB will require a revised consent document for protocol #3511. OHRP has determined that these corrective actions adequately address this finding and are appropriate under the LSUMC MPA.

(5) OHRP finds that it would have been appropriate for the informed consent documents to include the following additional element stipulated by HHS regulations at 45 CFR 46.116(b)(3): any additional costs to the subject that may result from participation in research (i.e., the substantial costs incurred by subjects who participated in the research are not enumerated in the informed consent document).

Corrective Action:

OHRP acknowledges that the current Guide to the Policies and Procedures of the LSUHSC IRB notes the importance of including a description of any additional costs to

subjects ~~in the~~ informed consent document. OHRP notes that the IRB will require a revised consent document for protocol #3511. OHRP has determined that these corrective actions adequately address this finding and are appropriate under the LSUMC MPA.

(6) 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. OHRP finds that the first continuing review of this project by the IRB occurred more than one year after initial approval.

Corrective Action:

OHRP notes that the IRB is aware of the HHS regulations in this regard and that subsequent reviews were conducted within the appropriate timeframe. OHRP also acknowledges the extenuating circumstances surrounding this lapse and that the IRB staff has been increased to ensure such lapses do not occur in the future. OHRP has determined that this corrective action adequately addresses this finding and is appropriate under the LSUMC MPA.

As a result of the above determinations, OHRP is closing its compliance oversight investigation of this matter and anticipates no further involvement of OHRP in this matter. Of course, OHRP must be notified should new information be identified which might alter this determination.

At this time, OHRP would like to provide the following additional guidance regarding the Guide to the Policies and Procedures of the LSUHSC IRB:

(1) OHRP recommends that the Guide list all of the criteria for IRB approval of research stipulated by HHS regulations 45 CFR 46.111. On page 6 the Guide only lists a few of these criteria.

(2) OHRP recommends that the list of IRB Chair responsibilities include advising IRB members of all research protocols, and all minor changes in previously approved research protocols that have been approved under an expedited review procedure, as required by HHS regulations at 45 CFR 46.110(c).

(3) Page 15 of the Guide states "...approval period starts...the day that changes required by the Board are finalized and approved by the Chair." OHRP notes that 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. The Guide should be revised accordingly.

(4) OHRP notes that unanticipated problems involving risks to subjects or others must be reported to the appropriate institutional officials, the IRB, the Department or Agency head, and OHRP as required by HHS regulations at 45 CFR 46.103(a) and 46.103(b)(5). The Guide only mentions the reporting of serious adverse events to the IRB and FDA. The Guide should be expanded to include a description of the procedures for prompt reporting of unanticipated problems involving risks to subjects or others to each of the entities referenced at 45 CFR 46.103(a) and 46.103(b)(5).

(5) OHRP recommends that the Guide be expanded to include the regulatory requirements for research involving pregnant women and fetuses (45 CFR Part 46, Subpart B), prisoners (45 CFR Part 46, Subpart C) and children (45 CFR Part 46, Subpart D).

(6) 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.

The continuing review progress report should be expanded to include a status report on the progress of the research, including a description of any complaints about the research, and a summary of any recent literature.

OHRP appreciates your institution's continued commitment to the protection of human research subjects. Do not hesitate to contact me if you have any questions regarding this matter.

Sincerely,

Kristina C. Borror, Ph.D.
Compliance Oversight Coordinator
Division of Compliance Oversight

cc: Dr. Kenneth E. Kratz, IRB Chair, LSU
Dr. Paul G. Harch, PI, LSU
Commissioner, FDA
Dr. David Lepay, FDA
Dr. James F. McCormack, FDA
Dr. John Mather, ORCA, Department of Veterans Affairs
Dr. Greg Koski, OHRP
Dr. Melody H. Lin, OHRP
Dr. Michael A. Carome, OHRP
Dr. Katherine Duncan, OHRP
Dr. Jeffrey M. Cohen, OHRP
Mr. George Gasparis, OHRP
Mr. Barry Bowman, OHRP