DEPARTMENT OF HEALTH & HUMAN SERVICES

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OFFICE OF PUBLIC HEALTH AND SCIENCE

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January 23, 2001

Kern Wildenthal, M.D., Ph.D.,
President, The University of Texas Southwestern Medical Center
5323 Harry Hines Boulevard
Dallas, TX 75235

RE: Human Research Subject Protections Under Multiple Project Assurance (MPA) M-1304
Research Project: Study of the Gulf War Syndrome: Multidisciplinary Pathophysiologic Studies of Neurotoxic Gulf War-Related Syndromes Leading to Diagnosis and Treatment
Principal Investigator: Robert W. Haley, M.D., Director, Epidemiology Division, UTSWMC

Dear Dr. Wildenthal:

The Office for Human Research Protections (OHRP), formerly the Office for Protection from Research Risks (OPRR), has reviewed your November 18, 1999 report responding to OHRP's questions and concerns regarding the above-referenced research and the human subject protection program at the University of Texas Southwestern Medical Center (UTSWMC). OHRP apologizes for the delay in its response.

Based upon its review of your report, OHRP makes the following determinations:

OHRP Findings

(1) OHRP finds that the UTSWMC institutional review board (IRB), when it approved the above-referenced Gulf War Syndrome study on November 23, 1994, failed to ensure that the informed consent process satisfied the requirements of Department of Health and Human Services (HHS) human subject protection regulations at 45 CFR 46.116. Furthermore, OHRP finds no evidence that the IRB approved a waiver of the

requirements for informed consent, in accordance with HHS regulations at 45 CFR 46.116(d).

Required Action: By February 23, 2001, UTSWMC must submit to OHRP a satisfactory corrective action plan to ensure that all IRB-approved protocols include informed consent documentation containing all of the required elements under 45 CFR 46.116(a) (1) through (8), unless the IRB approves a consent procedure which omits or alters some or all of the elements set forth under HHS regulations, or waives the requirement to obtain informed consent, by finding and documenting the criteria stipulated under HHS regulations at 45 CFR 46.116(d).

(2) OHRP finds that the IRB lacked sufficient information when reviewing the Gulf War Syndrome protocol to make the determinations required for approval of research under HHS regulations at 45 CFR 46.111. For example, the IRB appeared to review little information concerning subject recruitment and enrollment, and safeguards to protect the rights and welfare of vulnerable subjects. OHRP further notes that the IRB did not review the Personality Assessment Inventory (PAI) instrument before approving its use in the initial survey protocol.

(3) 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 the UTSWMC IRB has failed to conduct substantive and meaningful continuing review at its convened meetings. In specific, OHRP finds that (i) the Report of the Subcommittee for Continuing Review provided to IRB members does not include a written summary of protocols being reviewed, or a status report on the progress of the research; and (ii) IRB members do not receive copies of the most recent informed consent documentation for protocols undergoing continuing review.

Required Corrective Action: The UTSWMC IRB must must suspend immediately any HHS-supported research studies that are not eligible for an expedited review procedure,

which received initial IRB approval prior to January 23, 2000. OHRP requests that by February 23, 2001, UTSWMC must provide to OHRP a list of all federally supported research projects subject to this suspension.

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

(b) 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).

(4) In response to OPRR's concern expressed in its letter of October 22, 1999, that the minutes of the UTSWMC IRB meetings related to the Gulf War Syndrome protocol often failed to reflect actions taken, the vote on these actions, and the discussion of controverted issues, UTSWMC's report of November 18, 1999 stated that controversial issues are typically resolved prior to voting, so that the IRB votes are usually unanimous. OHRP acknowledges that unanimous votes can reflect that concensus was reached by the IRB following a full and robust debate of controverted issues. However, HHS regulations at 45 CFR 46.115(a)(2) require that minutes of IRB meetings document such discussions of controverted issues and their resolution. Moreover, these regulations require that minutes of IRB meetings reflect for every action taken by the IRB, the number of members voting for, against or abstaining. Recording votes as unanimous is not sufficient. As a result, OHRP finds that the minutes of UTSWMC failed to meet the requirements of HHS regulations at 45 CFR 46.115(a)(2).

Required Corrective Action: By February 23, 2001, UTSWMC must submit to OHRP a satisfactory corrective action plan to ensure that minutes of IRB meetings document all information required by HHS regulations at 45 CFR 46.115(a)(2). Please provide copies of the minutes of the most recent meeting of each UTSWMC IRB with your response.

(5) OHRP acknowledges that review by the IRB Chair of the entire grant pertaining to the Gulf War Syndrome protocol complies with HHS regulations at 45 CFR 46.103(f). Please clarify whether the IRB routinely receives and reviews a complete copy of each

grant application submitted to any Federal Department of agency for the funding of research involving human subjects.

OHRP Guidance

OHRP provides the following additional guidance to UTSWMC:

(6) Your response to OPRR's queries in its letter of October 22, 1999, regarding the adequacy of the informed consent process for the above referenced research project suggests some confusion on the part of the UTSWMC IRB about the requirements for waiver of the requirements for an investigator to obtain the informed consent of research subjects versus the requirement for the investigator to document informed consent by use of a written consent form signed by the subject or the subject's legally authorized representative. In order to assist the UTSWMC IRB with its consideration of such waivers in the future, OHRP offers the following guidance:

(a) Under HHS regulations at 45 CFR 46.116(d), the IRB may approve a consent procedure which does not include, or which alters, some or all of the elements of informed consent stipulated by HHS regulations at 45 CFR 46.116, or waive the requirement to obtain informed consent provided the IRB finds and documents all of the following:

(i) The research involves no more than minimal risk to the subjects.

(ii) The waiver or alteration will not adversely affect the rights and welfare of the subjects.

(iii) The research could not practicably be carried our without the waiver or alteration.

(iv) Whenever appropriate, the subjects will be provided with additional pertinent information after participation.

OHRP strongly recommends that whenever the IRB approves a waiver or alteration of some or all of the elements of informed consent, the above findings be fully documented in the minutes of IRB meetings, including protocol-specific information justifying each IRB finding. OHRP acknowledges that the revised written UTSWMC IRB policies and procedures reflect adoption of this recommendation. Under HHS regulations at 45 CFR 46.116(d), if findings regarding waiver or alteration of informed consent are not documented in the minutes of IRB meetings (e.g., in the case of a protocol approved under an expedited review procedure), they must be documented elsewhere by the IRB.

(b) Under HHS regulations at 45 CFR 46.117(c), the IRB may waive the

requirement for the investigator to obtain a signed consent form for some or all of the subjects. In such cases, OHRP strongly recommends that whenever the IRB approves a waiver of the requirement for obtaining a signed consent form, the findings required under 45 CFR 46.117(c) be fully documented in the IRB minutes, including protocol-specific information justifying each IRB finding. OHRP acknowledges that the revised written UTSWMC IRB policies and procedures reflect adoption of this recommendation.

(c) Whenever the IRB approves a waiver of the requirement for obtaining a signed consent form, the IRB must still approve an oral script for the informed consent process that includes all elements stipulated by HHS regulations at 45 CFR 46.116 (unless some elements have been waived by the IRB in accordance with the requirements of HHS regulations at 45 CFR 46.116(d)). Furthermore, in such cases the IRB may require the investigator to provide subjects with a written statement regarding the research.

(7) The UTSWMC IRB written policies and procedures should be expanded to include additional operational details for the following:

(a) The procedures which the IRB follows for determining which projects require review more often than annually (e.g., what criteria does the IRB use for making these determinations).

(b) The procedures for ensuring prompt reporting to the IRB, appropriate institutional officials, any supporting Department or Agency head, and OHRP of (i) any unanticipated problems involving risks to subjects or others and; (ii) any serious or continuing noncompliance with 45 CFR Part 46 or the requirements or determinations of the IRB.

OHRP appreciates UTSWMC's continued commitment to the protection of human research subjects. Should you have any questions, feel free to contact me.

Sincerely,

Carol J. Weil, JD
Division of Compliance Oversight

cc: Dr. Perrie M. Adams, UTSWMC
Dr. Robert Haley, UTSWMC
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Dr. Michael Carome, OHRP
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