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 3, 2005

Sten Iwarson, M.D., Ph.D.
Professor
Department of Infectious Diseases
Sahlgrenska University Hospital/Ostra
Gothenburg University
SE 416 85 Gothenburg, SWEDEN

RE: Human Research Subject Protections Under Federalwide Assurance FWA- 848

Dear Dr. Iwarson:

The Office for Human Research Protections (OHRP) has reviewed the Gothenburg University's (GU) May 2, 2005 report and August 23, 2005 letter responding to OHRP's April 26, and June 14, 2005 requests for documents regarding compliance with Department of Health and Human Services (HHS) regulations for the protection of human research subjects (45 CFR part 46).

Based upon its review, OHRP makes the following determinations:

(1) HHS regulations at 45 CFR 46.115(a)(2) require that minutes of institutional review board (IRB) meetings be in sufficient detail to show attendance at the meetings; actions taken by the IRB; the votes on these actions including the number of members voting for, against, and abstaining; the basis for requiring changes in or disapproving research; and a written summary of the discussion of controverted issues and their resolution. OHRP finds that GU's IRB minutes fail to meet these requirements. In specific, OHRP notes that our April 26, 2005 letter requested, among other things, a copy of the IRB agenda and minutes for the most recent IRB meeting. The only document that appeared to be responsive to this request was entitled [English translation], "List of Report Presentation for the Meeting in the Regional Ethics Advisory Committee, Dept. Medicine 2, Monday, 2 May 2005, 1:30pm." This document was a list of protocols.

(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. OHRP finds that the GU IRB does not conduct continuing review of research at least once per year.

(3) OHRP finds that GU 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.
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> (b) The procedures which the IRB will follow for conducting its continuing review of research.
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> (c) The procedures which the IRB will follow for reporting its findings and actions to investigators and to the institution.
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> (d) The procedures which the IRB will follow for determining which projects require review more often than annually.
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> (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.
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> (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.
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> (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.

(4) HHS regulations at 45 CFR 46.108 require that, except when an expedited review procedure is used, the IRB review proposed research at convened meetings at which a majority of the members of the IRB are present. In addition, HHS regulations at 45 CFR 46.107(a) state, in part, that each IRB shall have at least five members. OHRP is concerned that the Rules of Procedure for the GU IRBs state [English translation], "For a quorum, it is required that at least two members are present." OHRP notes that each GU IRB has at least 30 members, according to the list of members provided to OHRP.

OHRP Action

In view of the above determinations and in order to ensure adequate protections for human subjects, the Office for Human Research Protections hereby suspends the Gothenburg University Assurance (FWA -848) in accordance with HHS regulations at 45 CFR 46.103(e), pending satisfactory completion of the required corrective actions described below.

The suspension of FWA-848, effective immediately, removes the Assurance required by HHS regulations at 45 CFR 46.103(a) for all U.S. federally supported research involving human subjects at GU covered by the FWA.

As result, all U.S. federally supported human subjects research projects to which the FWA applies must be suspended. 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 approval requests for such cases to be rare). Furthermore, research activities involving previously enrolled subjects may continue only where it is in the best interests of such subjects. For each affected protocol this suspension must remain in effect until OHRP approval of the FWA is reinstated.

Required Actions Necessary for Reinstatement of FWA-848:

(1) GU must develop a satisfactory corrective action plan to address all deficiencies and concerns described above.

(2) GU must submit written IRB procedures that adequately describe all activities referenced in HHS regulations at 45 CFR 46.103(a) and 46.103(b)(4) and (5).

(3) The IRB must submit a satisfactory plan to re-review all HHS or U.S. federally-supported human subject protocols that have not had adequate continuing review.

(4) No later than October 31, 2005, GU must provide a complete list of all U.S. federally supported research protocols that were suspended. Include the project title, principal investigator, IRB project number, and the Federal department or agency project number. GU should identify those projects for which GU determines that research activities in previously enrolled subjects may continue because it is in the best interests of the individual subjects. Please describe the procedures used to make such determinations.

OHRP encourages GU to develop its corrective action plans expeditiously, and forward them to OHRP for review as soon as possible. OHRP is available to assist GU in the development and implementation of these corrective action plans. Do not hesitate to contact me should you have any questions.

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,

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

cc: Dr. Bo Risberg, Human Protections Administrator, Gothenburg U

Dr. Anders Fasth, IRB Chair, Gothenburg U Hosp / East
Dr. Lana Skirboll, OD, NIH
Commissioner, FDA
Dr. David Lepay, FDA
Dr. Bernard Schwetz, OHRP
Dr. Melody H. Lin, OHRP
Dr. Michael Carome, OHRP
Ms. Shirley Hicks, OHRP
Dr. Irene Stith-Coleman, OHRP
Ms. Patricia El-Hinnawy, OHRP
Ms. Janet Fant, OHRP