DEPARTMENT OF HEALTH & HUMAN SERVICES

Office of the Secretary
Office of Public Health and Science

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February 11, 2002

Daniel R. Masys, M.D.
Institutional Official for Human Subjects
University of California, San Diego
9500 Gilman Drive
La Jolla, CA 92093-0052

RE: Human Research Protections Under Multiple Project Assurance (MPA) M-1274

Research Project: Safety and Tolerability of Rapidly Titrated Risperidone
Related Publication: Safety and Tolerability of Rapidly Escalating Dose-Loading Regimen for Risperidone, Feifel, D., et al, Journal of Clinical Psychiatry 2000; 61: 909-911.
Principal Investigator: David Feifel, M.D.
Protocol Number: 000827X

Dear Dr. Masys:

The Office for Human Research Protections (OHRP) has reviewed your February 7, 2002 report regarding the above referenced research conducted at the University of California, San Diego (UCSD) that was submitted in response to OHRP's January 8, 2002 letter.

OHRP also acknowledges that UCSD has asked the principle investigator to retract the article because the publication is written in the style of a prospective trial and may cause some confusion, and has launched an inquiry into this matter. OHRP looks forward to receiving the report of this inquiry when it becomes available.

In its January 8, 2002 letter OHRP made the following determinations:

(1) 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 found that when the UCSD IRB approved the above-referenced research under an expedited review procedure, it approved a waiver of informed consent but failed to make and document the required findings under 45 CFR 46.116(d).

Corrective Action: OHRP acknowledges that the UCSD IRBs currently use a checklist when reviewing proposals of informed consent waiver. This checklist becomes a part of the project file and details the required findings under HHS regulations at 45 CFR 46.116(d). OHRP finds that this corrective action adequately addresses the finding and is appropriate under the UCSD MPA.

(2) OHRP found that the UCSD IRB frequently approves research contingent upon substantive modifications or clarifications without requiring additional review by the convened IRB. The IRB appears to approve protocols pending receipt of revised applications, modifications in informed consent documents, and clarification of experimental procedures. Such documents are then reviewed by "the IRB chair or her/his designee(s)" rather than going to the full IRB. OHRP noted several instances in which major clarifications/revisions directly relevant to the determinations that the IRB must make under HHS regulations at 45 CFR 46.111 were requested without requiring subsequent review by the convened IRB.

Corrective Action: OHRP acknowledges UCSD's statements that your operational definition of a substantive revision of a research plan is that the element needing clarification or amendment would materially affect the risk-benefit assessment of the overall research plan from the perspective of the human subjects. OHRP finds that the UCSD's policies detailed in your February 7, 2002 response appear to be adequate, including ensuring that when the committee cannot enunciate with sufficient clarity what changes would satisfy its requirements for approval, a study will be deferred. OHRP remains concerned that, although this policy seems adequate, it did not appear to be followed at the meetings of September and October of 2001. For example,

(a) The IRB approved project #011083 reviewed on October 4, 2001 pending receipt of information to "[c]larify the nature of the mandatory companion studies CALGB 8461 and 9665. What is the ethical justification for requiring participation in these studies in order for subjects to have access to a phase III therapeutic study that likely offer improved survival over standards care (designed to benefit subjects directly). Does this not constitute coercion to participate in the companion studies?" In addition, the IRB requested clarification of whether or not the study involved the inclusion of children, since the protocol was discrepant on this matter. However, the IRB did not appear to make the determinations required under 45 CFR 46.404-408 regarding the involvement of children in research.

(b) The IRB approved project #011089 reviewed on October 4, 2001 pending receipt of "revision of the application to expand the statistics section. The PI is requested to

include in the revision answers to such questions as what is the endpoint and sample size; revision of the application and consent to state what tests will be done with blood that is drawn...."

(c) The IRB approved project #010574 reviewed on September 6, 2001 pending receipt of information regarding "newly recognized complications associated with Olanzapine related to weight gain and diabetes....What medical evaluations will be done for the subject's safety in this regard? Are there plans to monitor the glucose and weight gain? The application and consent should reflect this information."

(d) The IRB approved project #010972 reviewed on September 6, 2001 pending receipt of clarification of "the i.v. administration of cimentidine prior to each rituximab dose. Is this GI prophylaxis justified given the toxicity profile for rituximab?....Clarify how the subjects will be monitored for hyperglycemia....."

It does not appear in the above cases that the IRB had sufficient information to make the determinations required for approval of research under HHS regulations at 45 CFR 46.111, including an assessment of the risk benefit ratio. By March 22, 2002, please clarify when this policy regarding which protocols need to come back to the convened IRB went into effect and provide OHRP with minutes of the last three IRB meetings.

Please submit to OHRP your response to the above determinations no later than March 22, 2002. If upon further review of the concerns and questions, UCSD identifies instances of non-compliance with the HHS regulations for protection of human subjects, please include detailed corrective action plans to address the noncompliance.

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.
Compliance Oversight Coordinator
Division of Human Subject Protections

cc: Ms. Lucille Pearson, UCSD
Mr. Gary Rossio, San Diego VA Medical Center
Dr. J. Allen McCutchan, UCSD IRB Chair

Dr. Richard Kornbluth, UCSD IRB Chair
Dr. John Mather, ORCA, Dept of Veterans Affairs
Dr.Greg Koski, OHRP
Dr. Melody Lin, OHRP
Dr. Michael Carome, OHRP
Dr. Jeff Cohen, OHRP
Mr. George Gasparis, OHRP
Dr. Kamal Mittal, OHRP
Mr. Barry Bowman, OHRP