DEPARTMENT OF HEALTH & HUMAN SERVICES

Office of the Secretary
Office of Public Health and Science

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February 14, 2006

Roberto Peccei, Ph.D.
Vice Chancellor - Research
University of California, Los Angeles
2147 Murphy Hall, Box 951405
Los Angeles, CA 90095-1405

RE: Human Research Subject Protections Under Multiple Project Assurance (MPA)-1127 and Federalwide Assurance FWA- 4642

Research Project: Protocol TSVS-701-25G: A Prospective, Non-Randomized, Multicenter Clinical Evaluation of the 25-Gauge Millennium TM Transconjuctival Sutureless Vitrectomy System (TSVS) with Entry Site Alignment System (ESAS)
Principal Investigator: Steven Schwartz, M.D.
UCLA IRB #: 01-11-057-01

Research Project: 25-Gauge Vitrectomy System Registry
Principal Investigator: Anurag Gupta, M.D.
UCLA IRB #: 04-07-004

Research Project: Clinical Characterization, Genetic Testing, and Visual Function in Patients with Stargardt's Disease
Principal Investigator: Steven Nusinowitz, Ph.D.
UCLA IRB #: 04-10-010

Research Project: Genetic Studies in Inherited Ocular Disorders
Principal Investigator: Anthony Aldave, M.D.
UCLA IRB #: 94-07-243-23

Research Project: Research on intra-ocular pressure of patients receiving Bausch and Lomb 25-Gauge Trocar System
Principal Investigator: Steven Schwartz, M.D., Anu Gupta, M.D., and Christine Gonzalez, M.D.

Dear Dr. Peccei:

The Office for Human Research Protections (OHRP) has reviewed the University of California, Los Angeles's (UCLA) March 16 and November 10, 2005 reports responding to allegations of noncompliance with Department of Health and Human Services (HHS) regulations for the protection of human research subjects (45 CFR part 46) involving the above-referenced research.

Based upon its review, OHRP makes the following determinations regarding the above-referenced research:

(1) In accordance with HHS regulations at 45 CFR 46.103(b) and 46.109(a), the institutional review board (IRB) must review and approve all non-exempt human subject research covered by an assurance. OHRP finds that the following non-exempt human subjects research activities were conducted without appropriate IRB review and approval:

(a) Research reported in the abstract: Ultrasound Biomicroscopic Evaluation of Sclerotomies Created by Transconjunctival 25 Gauge Vitrectomy. C.R. Gonzales, A. Gupta, S.Y. Lee, J.Y. Freeman, M.F. Estafanous, A.E. Kreiger and S.D. Schwartz. *Invest Ophthalmol Vis Sci* 2003;44:E-Abstract 3008.

Your November 10, 2005 report states that "...1) the abstract was published and presented prior to the IRB approval of the retrospective study IRB #04-07-004-01 (approval date August 17, 2004), 2) although UBM was performed as part of the clinical care of patients, it was not a data collection point for the prospective study IRB #01-11-057-01 and, 3) a discrepancy between the number of subjects (eyes) enrolled into the prospective study (10) and the number of subjects (eyes) reported in the poster presentation (23). **Therefore, the above-referenced abstract describes research that was not reviewed and approved by the UCLA IRB**.[emphasis in original]"

(b) Research reported in the abstract: Transient Post-Operative Hypotony Following Transconjunctival 25 Gauge Vitrectomy. A. Gupta, C.R. Gonzales, S.Y. Lee, J.Y. Freeman, M.F. Estafanous, A.E. Kreiger and S.D. Schwartz. *Invest Ophthalmol Vis Sci* 2003;44: E-Abstract 2026.

Your November 10, 2005 report states that "...1) the abstract was presented and published prior to the retrospective study IRB #04-07-004-01 approval by the IRB on August 17, 2004, and 2) the application to the IRB for the prospective study IRB #01-11-057-01 describes that only 23 eyes at UCLA would be evaluated (of the 93 total for the multicenter study) and the abstract reports that '100 consecutive eyes' were evaluated. The explanation provided by Dr. Schwartz regarding the discrepancy in the number of eyes indicates that the data obtained from the additional eyes was through the routine care of patients not obtained under the approved research project. **Therefore, the above-referenced abstract describes research that was not reviewed and approved by the**

UCLA IRB.[emphasis in original]"

Corrective Action: OHRP acknowledges UCLA's statements that education corrective action plans have been developed to require the Retina Division faculty, fellows and clinical research staff to attend an intensive IRB Workshop presented by the UCLA Office for Protection of Research Subjects, as well as the "Introduction to Clinical Research for Residents and Clinical Fellows." The Retina Division will also be asked to submit a strategic plan for increased oversight of the conduct of human subjects research including implementation of procedures to ensure investigator accountability as well as delegation of authority. The Retina Division must also institute a mechanism for the review/internal audit of current research in order to ensure compliance with UCLA IRB policies and Federal regulations governing human subjects research.

Required Action: By March 28, 2006, please provide OHRP with a copy of the human subjects research oversight strategic plan drafted by the Retina Division as well as a copy of the review/internal audit mechanism and any audit reports generated so far from this mechanism.

(2) It was alleged that the following abstracts describe prospective human subjects research conducted without IRB review and approval.

(a) 25-Gauge Transconjunctival Vitrectomy Safety: Post–operative Complications. C.W. Mango, A. Gupta, C.S. Chen, L. Savar, C.R. Gonzales, D. Telander, R. Wirthlin, A.E. Kreiger and S.D. Schwartz. *Invest Ophthalmol Vis Sci* 2005;46:E-Abstract 5459.

(b) 25-Gauge Transconjunctival Vitrectomy Safety: Cataract Progression. A. Gupta, C.S. Chen, L. Savar, C.R. Gonzales, D. Telander, C.W. Mango, R. Wirthlin, A.E. Kreiger and S.D. Schwartz. *Invest Ophthalmol Vis Sci* 2005;46:E-Abstract 5458.

(c) 25-Gauge Transconjunctival Vitrectomy: Intraoperative Safety. C.S. Chen, A. Gupta, L. Savar, C. Gonzales, D. Telander, C. Mango, R. Wirthlin, A.E. Kreiger and S.D. Schwartz. *Invest Ophthalmol Vis Sci* 2005;46:E-Abstract 5455.

Your November 10, 2005 report states that "the three above-referenced abstracts were conducted under IRB #04-07-004-01 "25 Gauge Vitrectomy System Registry," which was reviewed and approved under expedited criteria by the UCLA IRB....Of note, in the three published abstracts the research is identified as 'prospective' studies, when in fact all three are 'retrospective' in nature."

OHRP makes no finding regarding these allegations.

(3) It was alleged that the following abstract describes retrospective research that was not approved by the IRB: Improved Surgical Outcomes of Inferior Retinectomy With Radical

Anterior Base Dissection and Lens Removal in Patients With PVR. P.A. Quiram, C.R. Gonzales, A. Gupta, S.D. Schwartz, M.O. Yoshizumi and A.E. Kreiger. *Invest Ophthalmol Vis Sci* 2005;46: E-Abstract 5476.

Your November 10, 2005 report states that "the above-referenced abstract was a retrospective study reviewed and approved by the UCLA General Institutional Review Board under IRB #G03-03-034. The research was initially approved on March 13, 2003...."

OHRP finds that this allegation cannot be substantiated.

(4) HHS regulations at 45 CFR 46.116 state that no investigator may involve a human being as a subject in research unless the investigator has obtained the legally effective informed consent of the subject or the subject's legally authorized representative. In our July 1, 2005 letter, OHRP expressed concern that screening for protocol #04-10-010 was conducted without the appropriate informed consent of the subjects. In specific, OHRP noted that:

(a) The protocol proposed to enroll patients with a diagnosis of Stargardt's disease. In specific, OHRP noted the following:

(i) Page 9 of the Application to Involve Human Subjects in Research states, "Patients who fit the ocular albinism or Stargardt's diagnosis will be given a recruitment letter."

(ii) Page 9 of the Application to Involve Human Subjects in Research states, "Patients will already know their diagnosis prior to participation in these studies."

(iii) The letter inviting patients to participate in the study (including the initial screening visit) states, "As a patient at the Jules Stein Eye Institute, we understand that you or a family member has been given the diagnosis of Stargardt's disease."

(b) However, all subjects are required to undergo an initial screening visit in which numerous tests are to be conducted. In specific, OHRP noted the following:

(i) Page 12 of the Application to Involve Human Subjects in Research states, "Patients or their health insurance company will be billed for the initial office visit and testing, because this is standard of care for the diagnosis of Stargardt's disease."

(ii) Page 15 of the Foundation for Blindness grant application for this study states, "Patients...will be invited to have a thorough evaluation by

our doctors that includes the tests listed below, so that our physicians can confirm the diagnosis and establish the present status of their condition. The various assays that are described will provide a baseline for determining changes with time and will be essential data if clinical treatment trials are to be designed." This description of the tests for the initial screening makes it clear that the data will be used for research purposes.

(iii) The use of the data for research purposes and the fact that subjects were required to undergo the initial screening tests if necessary to confirm the Stargardt diagnosis indicate that the tests are part of the research.

(c) The protocol did not require that informed consent be obtained from subjects until after the initial screening visit and confirmation of the diagnosis of Stargardt's disease. Page 13 of the Application to Involve Human Subjects in Research states, "If a patient is potentially eligible for the study based on his or her examination, the physician-investigator will describe the study, the nature of subject participation, and alternatives to participation."

(d) The IRB considered the initial screening visit to be part of the research. Page 7 of the December 6, 2004 memo to Dr. Nusinowitz stated, "The Committee notes that the clinical evaluation procedures for eligibility screening are done during the initial visit, therefore they are considered research procedures...."

(e) Dr. Nusinowitz objected to considering the screening tests as part of the research, largely on financial grounds. Section B, paragraph 5 of his January 5, 2005 response to the IRB chair's December 6, 2004 memo stated, "...we are not willing, or financially capable, of covering the first visit for everyone who comes in with a Stargardt's diagnosis.... So we cannot afford to treat the initial visit as part of the study."

Corrective Actions: OHRP acknowledges that the UCLA IRB has reminded the principal investigator than all potential research subjects are to be consented prior to the initial visit. UCLA acknowledged that the screening procedures done at the initial visit are for research purposes and that financial concern is not a basis for considering the screening procedures as not part of the research. The UCLA IRB has requested that no subjects be contacted, recruited or enrolled in the study until the IRB concerns are addressed and requested changes have been reviewed and approved by the IRB. In addition, the UCLA IRB Reviewer Checklist has been modified to specifically address this issue. By March 28, 2006, please provide OHRP with an update on how the IRB's concerns are being addressed.

(5) HHS regulations at 45 CFR 46.116 require that informed consent information be in language understandable to the subject or the subject's legally authorized representative. OHRP finds that the informed consent document approved by the IRB for protocol #04-

10-010 included complex language that would not be understandable to all subjects. In specific, the following terms were not defined or described: genetic testing, genetic material, and corneal abrasions.

Corrective Actions: OHRP acknowledges UCLA's statement that correspondence to the investigator has been sent requesting that the aforementioned terms be written in simple lay language in a perspective that is understandable to the subject or representative. Until the requested changes are reviewed and approved by the IRB, the IRB has requested that no subjects be contacted, recruited or enrolled into the study. As a corrective action to prevent an occurrence in the future, the UCLA Informed Consent Checklist used by the reviewing IRB members has been modified to further define and highlight "understandable" with the term "lay language." These corrective actions adequately address the above finding and are appropriate under the UCLA FWA.

(6) It was alleged that various studies of the 25-gauge vitrectomy system were conducted without appropriate institutional review board (IRB) review and approval, in contravention of the requirements of HHS regulations at 45 CFR 46.109(a). OHRP provided UCLA with copies of email and attachments from Dr. Gupta indicating a request for prospective collection of data for research purposes, including videotaping of surgery, from patients undergoing surgery using the 25-gauge vitrectomy system. In addition, the data log sheet appeared to indicate a prospective collection of data for research purposes.

Your November 10, 2005 report states that "the referenced videotaping of vitreoretinal surgery and the data log sheet were not used for research purposes but designed by the Jules Stein Eye Institute Retina faculty as a remedial teaching tool...."

OHRP makes no finding regarding this allegation.

(7) It was alleged that Dr. Schwartz conducted research involving infants with retinopathy of prematurity without appropriate IRB review and approval, in contravention of the requirements of HHS regulations at 45 CFR 46.109(a). OHRP provided UCLA with a copy of a publication of the Jules Stein Eye Institute Clinical Update which indicated the prospective collection of data from low birth-weight babies.

Your November 10, 2005 report states that "the 'registry' that is referred to in the Jules Stein Eye Institute (JSEI) Clinical Update newsletter is not a registry for research purposes, but for clinical patient care purposes for following patients from birth to outpatient care....The reference in the JSEI Clinical Update newsletter to the Institute's participation in a 'multicenter Photo-ROP trial' was a research project conducted under IRB #00-11-030 'ROP Photographic Screening Trial' which was reviewed and approved by the IRB."

OHRP makes no finding regarding this allegation. OHRP notes that if the purposes of the registry change to include research as one purpose, then the registry activities must be

reviewed and approved by the IRB and informed consent for storage of samples and information must be obtained or appropriately waived as outlined in HHS regulations at 45 CFR 46.116.

OHRP has the following questions and concerns regarding the above-referenced research:

(8) [Redacted]

Please forward your responses to the above findings, questions and concerns so that OHRP receives them no later than March 28, 2006.

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: Ms. Judith L. Brookshire, Director, OPRS, UCLA
Dr. Lawrence E. Wolinsky, IRB Chair, General Biomedical IRB #1, UCLA
Dr. Robert A. Figlin, IRB Chair, Cancer/Infec Dis IRB #2, UCLA
Dr. Nancy Levine, IRB Chair, North General Social-Behav IRB#3, UCLA
Dr. Bruce Kagan, IRB Chair, Neuroscience IRB #4, UCLA
Dr. Alison Moore, IRB Chair, South General IRB #5, UCLA
Dr. Steven Schwartz, UCLA
Commissioner, FDA

Dr. David Lepay, FDA
Dr. Bernard Schwetz, OHRP
Dr. Melody H. Lin, OHRP
Dr. Michael Carome, OHRP
Ms. Shirley Hicks, OHRP
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Ms. Patricia El-Hinnawy, OHRP