DEPARTMENT OF HEALTH & HUMAN SERVICES

Office of the Secretary
Office of Public Health and Science

Office for Human Research Protections
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August 24, 2006

Richard Sheridan, J.D.
General Counsel
Scripps Health
4275 Campus Point Court
San Diego, CA 92121

RE: Human Research Subject Protections Under Multiple Project Assurance (MPA)-1294 and Federalwide Assurance FWA- 7338

Research Project: A Multicenter, Randomized, Double-Blind Study of the Sirolimus Coated BX Velocity Balloon Expandable Stent in the Treatment of Patients with De Novo Coronary Artery Lesions SIRIUS Protocol: P00-6302
Principal Investigator: Dr. Maurice Buchbinder
Project Number: L01-003

Research Project: Symbiot III: A Prospective Randomized Trial Evaluating the Symbiot III Covered Stent System in Saphenous Vein Grafts
Principal Investigator: Dr. Maurice Buchbinder
Project Number: L02-008

Research Project: JOSTENT SVG Trial: Investigational Device Exemption Protocol for the Jomed JOSTENT Coronary Stent Graft System
Principal Investigator: Dr. Maurice Buchbinder
Project Number: L01-025

Research Project: TAXUS IV-SR: Treatment of De Novo Coronary Disease Using a Single Paclitaxel-Eluting Stent
Principal Investigator: Dr. Maurice Buchbinder
Project Number: L02-011

Research Project: A Multicenter, Non-Randomized Study of the 4.0 mm Sirolimus-Eluting BX Velocity Balloon-Expandable Stent in The Treatment of Patients with De Novo Native Coronary Artery Lesions SIRUS - 4.0
Principal Investigator: Dr. Maurice Buchbinder

Project Number: L03-020

Research Project: Carotid Revascularization with EV3 Arterial Technology Evolution CREATE Trial
Principal Investigator: Dr. Maurice Buchbinder
Project Number: L04-007

Research Project: A Randomized Study Comparing the Edwards Self-Expanding LifeStent vs. Angioplasty Alone In Lesions Involving the SFA and Proximal Popliteal Artery RESILIENT Study
Principal Investigator: Dr. Maurice Buchbinder
Project Number: L04-012

Research Project: D.E.S.cover Registry Protocol
Principal Investigator: Dr. Maurice Buchbinder
Project Number: L04-016

Research Project: SVG Protection is a Distal Embolic Protection Randomized Trial – Spider
Principal Investigator: Dr. Maurice Buchbinder
Project Number: L04-020

Research Project: Carotid Artery Stenting with Emboli Protection Surveillance Post Marketing Study - CASES study
Principal Investigator: Dr. Maurice Buchbinder
Project Number: L04-024

Research Project: WATCHMAN Left Atrial Appendage System for Embolic PROTECTion in Patients with Atrial Fibrillation (PROTECT AF)
Principal Investigator: Dr. Maurice Buchbinder
Project Number: L04-030

Research Project: Carotid RX ACCULINK/ACCUNET Post-Approval Trial to Uncover Unanticipated and Rare Events CAPTURE
Principal Investigator: Dr. Maurice Buchbinder
Project Number: L04-031

Research Project: The SLK-View Side-Access Coronary Stent Non-Randomized Pivotal Study
Principal Investigator: Dr. Maurice Buchbinder
Project Number: LM03-008

Dear Mr. Sheridan:

The Office for Human Research Protections (OHRP) has reviewed Scripps Health's (Scripps) August 7, 2006 report responding to determinations of noncompliance with Department of

Health and Human Services (HHS) regulations for the protection of human research subjects (45 CFR part 46).

In its June 27, 2006 letter OHRP made the following determination regarding human subjects protections at Scripps:

> (1) OHRP found that the Scripps institutional review boards (IRBs) do 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): 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.
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> **Corrective Action:** OHRP acknowledges that the Scripps written IRB procedures now include a description of the reporting of unanticipated problems involving risks to subjects or others to the IRB; however, the written procedures do not include the procedures by which such incidents will be reported to appropriate institutional officials, any department or agency head, and OHRP. While the Scripps written IRB procedures include, verbatim, OHRP's guidance on reporting to OHRP, they do not include the manner in which the Scripps IRB will implement this guidance (e.g., which institutional official or IRB staff member is responsible, to which institutional official reports go, by whom, and how reporting to the HHS department or agency head will occur.) The Scripps written IRB procedures also include the procedures for reporting noncompliance by IRB members and investigators, and which institutional official should receive reports, and reporting to OHRP. The Scripps written IRB procedures still do not include the procedures by which prompt reporting of suspension or termination of IRB approval to appropriate institutional officials.
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> **Required Action:** By September 29, 2006, please provide written procedures the IRB follows for reporting: (a) unanticipated problems involving risks to subjects or others to institutional officials, any department or agency head, and OHRP; and (b) of suspension or termination of IRB approval to appropriate institutional officials.

Based upon its review, OHRP makes the following additional determinations regarding human subjects protections at Scripps:

> (2) OHRP finds that Dr. Buchbinder enrolled a subject in protocol #L04-020 prior to obtaining legally effective informed consent from her, in violation of HHS regulations at 45 CFR 46.116.
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> **Required Action:** By September 29, 2006, please provide a corrective action to address this finding. In your response, please include the actions the IRB will take to ensure that other researchers also do not enroll subjects prior to obtaining legally effective informed consent.
>
> (3) Continuing review of research must be substantive and meaningful. HHS regulations

at 45 CFR 46.111 set forth the criteria that must be satisfied in order for the IRB to approve research. These criteria include, among other things, determinations by the IRB regarding risks, potential benefits, informed consent, and safeguards for human subjects. The IRB must ensure that these criteria are satisfied at the time of both initial and continuing review. In its June 27, 2006 letter, OHRP expressed concern that continuing review of research by the Scripps IRBs may not be substantive and meaningful. In specific, OHRP noted that the minutes of the IRB meetings that OHRP reviewed do not include any discussion or even required revisions to any research protocol under continuing review. In addition, the minutes appeared to indicate that review was conducted by a subcommittee of the IRB.

(4) HHS regulations at 45 CFR 46.110(b)(2) permit use of expedited procedures for review of minor changes in previously approved research during the period for which approval is authorized. In its June 27, 2006 letter, OHRP expressed concern that the Scripps IRBs may have employed expedited procedures to review changes that exceed this limitation. In specific, OHRP noted that the minutes of IRB meetings indicate that a "subcommittee with amendments" reviews amendments and some amendments are voted on en bloc, e.g., the minutes of the July 13, 2005 meeting stated "the remaining amendments were without issue and approved as presented." Similarly, the minutes of the October 12, 2005 meeting stated "The subcommittee on amendment/administrative review presented their materials to the Board. The discussion went as follows: Dr. X presented his review of the amendments and stated that he found no issues and recommended approval of the requested study changes. The Board moved approval of the amendments." In accordance with HHS regulations at 45 CFR 46.108(b), review of proposed protocol changes must be conducted by the IRB at convened meetings at which a majority of the members of the IRB are present, including at least one member whose primary concerns are in nonscientific areas, except where expedited review is appropriate under HHS regulations at 45 CFR 46.110(b)(2).

Corrective Action: OHRP acknowledges that the Scripps IRBs replaced the structure of allowing review by the subcommittee with a review by the convened IRB for those protocols and amendments that do not meet the requirement for expedited review, and require approval by vote. The IRB uses a primary and secondary reviewer system for continuing review and initial review, and uses a review checklist. These corrective actions adequately address concerns expressed in paragraphs #3 and #4, and are appropriate under the Scripps FWA.

OHRP has the following additional guidance:

(5) Your August 7, 2006 report indicates that Dr. Bernstein has stepped down as IRB chair and has been replaced by Dr. Bjork. Please submit an update or renewal of the IRB Registration(s) as outlined at http://www.hhs.gov/ohrp/humansubjects/assurance/renwirb.htm.

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. Barbara G. Bigby, Director, Scripps IRB Office
Dr. Robert L. Bjork, Jr., Chair, Scripps IRB #1 & #3
Dr. Maurice Buchbinder, Scripps
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
Mr. Patricia El-Hinnawy, OHRP
Ms. Carla Brown, OHRP