DEPARTMENT OF HEALTH & HUMAN SERVICES

Office of the Secretary
Office of Public Health and Science

Office for Human Research Protections
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April 10, 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 10, 2005 report 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).

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

(1) HHS regulations at 45 CFR 46.113 require that the institutional review board (IRB) has the authority to suspend or terminate approval of research that is not being conducted in accordance with the IRB's requirements or that has been associated with unexpected serious harm to subjects. In addition, HHS regulations at 45 CFR 46.112, state, in part, that officials of the institution may not approve research if it has not been approved by an IRB. OHRP finds that the IRB voted to suspend the above-referenced research, and that Dr. Wallach rescinded or delayed that suspension, in violation of HHS regulations at 45 CFR 46.113 and 112.

Corrective Action: OHRP acknowledges your statement that you and Dr. Wallach misunderstood the action of the IRB and misunderstood the limits of the Medical Staff's supervisory authority regarding the IRB. OHRP also acknowledges that shortly after the stay of the IRB suspension was put into place, the stay was lifted. The Scripps Legal Office is preparing educational sessions to be conducted with each IRB and hospital Medical Staff to emphasize the respective roles and authorities of the IRB and the Medical Staff.

Required Actions: By May 15, 2006 please provide OHRP with a follow-up report on this matter. In your report, please include a copy of any further IRB deliberations regarding the suspension of Dr. Buchbinder's research and investigations into concerns of noncompliance, as well as any further correspondence between the IRB and Dr. Buchbinder regarding this matter. Please also provide a copy of any reports regarding the evaluation of the functioning of your IRBs in the context of the Medical Staff structure, as mentioned in your August 10, 2005 report.

OHRP has the following additional questions and concerns:

(2) [Redacted]

(3) [Redacted]

[Redacted]

Please provide OHRP with corrective actions to address the above findings and responses to above the questions and concerns no later than May 15, 2006.

(4) OHRP has the following additional guidance regarding the Scripps written IRB procedures:

(a) The Policy regarding "IRB Actions" includes a list of the different types of actions the IRB may take. OHRP recommends that this written procedure include clarification regarding which of these actions require the protocol to be returned to the IRB (e.g., "Require significant modification of the proposal before approval.")

(b) Several of the Scripps written IRB procedures reference the Office for Protection from Research Risks (OPRR). OHRP recommends that these references be changed to OHRP.

(c) The Policy titled "Consent: Who May Give Consent for a Minor." OHRP

notes that parents or guardians do not give consent for minors to participate in research; they give permission. OHRP recommends that this be changed throughout the Policy.

(d) The Policy "Definition of Vulnerable Subjects" gives examples of members of certain groups who may be vulnerable. OHRP recommends adding socially disadvantaged and pregnant women to this list, as they are given as examples in the HHS regulations.

(e) The Policy "Wards of the State" states "Children who are wards of the Commonwealth of Pennsylvania...." Since Scripps in located in California, OHRP recommends that the laws and regulations of California, not Pennsylvania, be referenced here.

(f) The Policy "Prisoners: Additional Requirements for Participation in Research" lists the different categories of permissible research involving prisoners. OHRP recommends that this section include the regulatory requirement for review by the Secretary, HHS for certain categories of research involving prisoners that are supported by HHS.

(g) On page 3 of the Policy "Research Subject Recruitment" under "Advertisements for Research Subject Recruitment" OHRP notes that communications intended to be seen by health professionals, news stories, and publicity intended for other audiences would still need to be reviewed by the IRB if the intention of the materials is to make potential subjects aware of the research. OHRP recommends that the policy and IRB forms be changed to indicate this.

(h) The Policy "Research Subject Recruitment" under "Screening Tests and Interviews Prior to Subjects Enrollment" states on page 3 as follows: "Medically proven and effective procedures that are performed for the medical management of a prospective human research subject and which would have been done whether or not study entry was contemplated...may be performed and the results subsequently used for determining research study eligibility without a requirement for the subject's informed consent." This is not accurate. Informed consent must be obtained prior to using identifiable private information for research purposes, unless appropriately waived by the IRB. OHRP recommends that the written procedures be changed to reflect this.

(i) The Policy "Use of Medical Records in Research" indicates on page 2 that if there is a clear intent to, among other things, share the results outside the division or institution, the activity should be considered research. OHRP notes that even if there was not an intent to share the results outside the division or institution, the activity still might be research, as defined by HHS regulations at 45 CFR 46.102(d). This Policy also states "It is useful to ask oneself this

question: If I knew I would not be able to make the results of this activity public, would I still conduct…this review and analysis? If the answer is no, it should be considered research." OHRP notes that even if the answer was yes, the activity still may be research.

(j) The Policy "Distinguishing between Quality Assurance/Quality Improvement Activity and Research" indicates that several notions are pertinent in determining whether or not an activity is QA/QI or research. OHRP notes that the notions delineated to describe QA activities could also be used to describe research activities and therefore are of limited usefulness.

(k) The Policy "Definitions of Research and Research Activities" indicate on page 2 the definition of research. Please note that the definition of research in HHS regulations at 45 CFR 46.102(d) includes an important element not included in the definition in Scripp's Policy; that is, "including research development, testing and evaluation." OHRP recommends that this phrase be added to the definition in the Policy.

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
Dr. Joel I. Bernstein, Chair, Scripps IRB #3
Dr. Maurice Buchbinder, Scripps
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