DEPARTMENT OF HEALTH & HUMAN SERVICES

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February 27, 2008

Jeffrey M. Cheek, Ph.D.
Associate Vice Provost for Research Compliance and Operations
University of Washington
Office of Research
G80 Gerberding Hall
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Seattle, WA 98195-1202

RE: Human Research Subject Protections under Federalwide Assurance (FWA) 6878

Research Project: Diet and Primary Cardiac Arrest
Principal Investigator: David Siscovick, M.D.
Project Number: #5R01HL041993-13; HSD Application #95-1041-C/E

Research Project: Human Genetic Variation and Sudden Cardiac Arrest Risk and Outcomes
Principal Investigator: David Siscovick, M.D.
Project Number: HSD Application #07-6927-D

Dear Dr. Cheek:

Thank you for your January 11, 2007 and August 26, 2007 reports regarding indications of noncompliance with Department of Health and Human Services (HHS) regulations for the protection of human subjects (45 CFR part 46) involving the above-referenced research.

Based on the information submitted to us, we make the following determinations regarding the above-referenced research:

(1) HHS regulations at 45 CFR 45.116 stipulate that no investigator may involve a human being as a subject in research covered by the regulations unless the investigator has obtained the legally effective informed consent of the subject or the subject's legally authorized representative, except when the institutional review board (IRB) has waived the requirements to obtain such informed consent in accordance with the requirements of 45 CFR 46.116(c) or (d). We note that the provisions of 45 CFR 46.116(c) would not have been applicable to this research. 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. We determine that informed consent was not obtained from cardiac arrest subjects enrolled in the above-referenced research and the University of Washington's (UW's) IRB failed to find and document at its initial review in 1988, or at any subsequent continuing review prior to 2006, of the above-referenced research the four required criteria for waiver of informed consent for the blood draw from cardiac arrest cases and for access to emergency service records.

We also determine that the June 2006 so-called "reaffirmation" of the wavier of informed consent was not retroactively effective for the preceding 19 years of the study. Therefore, the above-referenced research involving blood draws and access to emergency services records represents research that was conducted without satisfying the informed consent requirements, or waiver thereof, under HHS regulations at 45 CFR 46.116.

In specific, we note the following:

(a) In the IRB application submitted for initial IRB review in 1988, the principal investigator did not request a waiver of consent for the blood draw from persons in out-of-hospital primary cardiac arrest, nor did he request a wavier of consent for access to the Emergency Medical Service Medical Incident Reports that were used to help determine eligibility for the interview portion of the study.

We note that in response to question H in Section VIII of the initial IRB application, "Will written consent forms be used?" the principal investigator checked "yes", with no further explanation.

Our review of the IRB file revealed that the first mention of a waiver of informed consent occurred in a proposed modification request from the principal investigator in July 1994, approximately six years after the study was approved. However, this request for waiver of informed consent was <u>not</u> for the initial blood draw by paramedics during cardiac arrest of the cases, nor was it for access to emergency services records related to the cardiac arrest.

(b) The IRB application submitted for initial review appeared to indicate that the principal investigator was not aware that the persons in cardiac arrest from whom paramedics were drawing blood samples for research purposes were human subjects of the research at the time of the blood draw.

The principal investigator described the research procedures to be followed in Part B, Appendix II, Section VII, subsection B of the initial IRB application submitted in 1988. The principal investigator's research plan involved having paramedics draw blood for research purposes from <u>all</u> persons experiencing out-of-hospital pulseless cardiac arrests attended by paramedics from March 1, 1988 to February 28, 1989 in Seattle and suburban King County, Washington.

A "case" was defined as someone who experienced a sudden pulseless condition and absence of evidence of a noncardiac condition as the cause of the cardiac arrest. To

be excluded from the definition of "case" were persons who were non-residents of King County, or persons with no spouse to interview, aged less than 25 or greater than 75, or a history of clinical heart disease or significant prior comorbidity that may have altered his/her dietary intake.

The principal investigator stated the following:

> A potential subject's eligibility will be assessed by a review of the paramedic incident reports…Approximately four weeks after the cardiac event, a letter will be sent to the spouse of those individuals deemed eligible for the study. The letter will describe the study and inform the spouse that a nurse/interviewer will be calling shortly to further assess eligibility and request participation in a more extensive in-home interview.

In response to Part B, Appendix II, Section VII, subsection D, question 4, "Source of subjects," the principal investigator responded: "Cases to be identified from Medic One and King County Emergency Medical Services' incident reports followed by an initial telephone screen..."

In response to question 5, "Who will approach subjects and how. Explain steps taken to avoid coercion," the principal investigator responded as follows:

> The spouse of *potential* <emphasis added> cases will receive a letter describing the study, followed by a telephone screen made by a nurse/interviewer. If the person is deemed eligible, an in-home interview is requested...

The investigator's responses on the IRB application appear to indicate that he did <u>not</u> consider the persons who have had cardiac arrests and their blood drawn for research purposes by paramedics to be subjects until <u>after</u> he made a preliminary determination about their eligibility using paramedic incident reports that was then confirmed in a telephone screen with the spouse.

(c) We note that in your January 11, 2007 response to our initial inquiry letter, you made the following statement:

> "… there is no explicit documentation of the IRB's consideration and approval of the waiver, nor of the IRB's determination of the regulatory basis for approving the waiver. We concur with OHRP's indication of serious or continuing noncompliance."

<u>Corrective Action</u>:

You stated in your January 11, 2007 response that UW has implemented two new procedures to ensure compliance with 45 CFR 46.116(d), is undertaking a systematic review of all ongoing studies to determine whether there are any other instances of undocumented waivers of consent, and has been educating IRB members and staff about the waiver of informed consent procedure and new waiver checklists.

We acknowledge that the UW IRB made and documented the four specific criteria required at 45 CFR 46.116(d) when it approved the waiver of the requirements of obtaining informed consent referenced above for the new repository study On July 13, 2007.

(2) We determine that UW failed to report serious and continuing noncompliance to us, as required by HHS regulations at 45 CFR 46.103(a) and 46.103(b)(5). In specific, the UW IRB became aware in June 2006 that the above-referenced research had been reviewed at least annually for 19 years without the IRB making and documenting the required findings for waiver of informed consent. This serious and continuing IRB noncompliance was not reported to us.

Corrective Actions: You reported that UW is implementing significant changes in its institutional reporting procedures, including: reassignment of the responsibility for reporting IRB noncompliance; establishment of written procedures for identifying, managing, and reporting IRB noncompliance; and education of IRB members and staff about IRB noncompliance.

(3) We determine that when reviewing the above-referenced research at initial and continuing review from 1988 through 2006, the UW IRB failed to obtain sufficient information to make the determinations required for approval of research under HHS regulations at 45 CFR 46.111.

(a) § 46.111(a)(1) The UW IRB failed to obtain sufficient information during initial IRB review in 1988 about the procedures to be followed in the study in order to determine if risks to subjects were minimized. In specific, the IRB failed to obtain sufficient information about the procedure for the drawing of blood by paramedics from persons suffering from pulseless primary cardiac arrest.

(b) § 46.111(a)(7) The UW IRB failed at various times to obtain sufficient information about whether there were adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data. As stated in UW's January 11, 2007 response:

- "In 1993, expedited review was used to approve a modification in which additional assays would be performed on existing blood samples, with funding provided by a private company. There is no information in the file that would allow a reviewer to assess the risk/benefit associated with this

modification, specifically any confidentiality and privacy risks such as whether the company would be given access to the data…."

- "In the past ten years, several modifications have been approved to allow new assays or genetic analyses of retrospectively and prospectively collected blood samples, with little information provided by the investigator about the confidentiality and privacy risks associated with these analyses, or about the relationship to the specific aims of the study."

Corrective Actions: Regarding provisions to protect privacy, we acknowledge the following statement made in your January 11, 2007 response:

> Our investigation suggests that this problem is specific to this study, or similar studies involving blood and genetic analysis that are reviewed by the UW IRBs whose focus is social and behavioral science research. Corrective actions include:…this study has been re-assigned to a biomedically focused IRB and is being re-reviewed in its entirety; the guidelines used to assign studies to specific UW IRBs are being revised…; all studies currently in the portfolios of the UW social/behavioral IRBs will be reviewed to ensure that a social/behavioral IRB rather than a biomedical IRB is the most appropriate review body.

We note that the UW IRB properly asked for and received information related to the blood draw procedure when reviewing the new repository study. We further note that the new repository application appropriately solicits information related to privacy and confidentiality in a number of sections.

(4) HHS regulations at 45 CFR 46.110(b)(2) permit use of expedited procedures for review of minor changes to previously approved research during the period for which approval is authorized. We determine that the UW IRB has employed expedited procedures to review changes that exceed this limitation.

Corrective Actions: You acknowledged in your January 11, 2007 response that the expedited review process has been inappropriately used in place of convened IRB review for many substantive modifications to the above-referenced research. You stated, "The most recent occurrence involved a modification by expedited review on 7/14/06. This modification should have been reviewed by the full convened IRB, because it involved a significant expansion of the genetic analyses performed in the study."

The corrective actions underway for this determination include those aimed at correcting the problems with this particular study, and those aimed at the general problem of too liberal use of expedited review for modifications of studies that were initially reviewed by a convened IRB. The investigator was asked to provide an entirely new application for this study. This new application was reviewed by a convened UW biomedical IRB as a "new" study, and oversight for this study was transferred to a biomedical IRB. To address the general problem, written guidance is being developed to assist IRB staff and chairs in triaging modification requests to expedited versus convened IRB review.

We determine that the corrective actions and responses above adequately address our determinations and are appropriate under your institution's assurance. As a result, there should be no need for further involvement by our office in this matter. Please notify me should new information be identified which might alter this determination.

Recommendation:

At this time, given our determination that there was no approval of a waiver of informed consent at initial review of the previous study, we recommend that the UW IRB consider whether any actions need to be taken regarding the use of blood specimens and incident report information being stored in the repository that was obtained without informed consent and without a properly executed waiver of informed consent.

We appreciate 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: Ellen Rubin, Manager of Research Compliance, UW
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