DEPARTMENT OF HEALTH & HUMAN SERVICES

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Office of Public Health and Science

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February 6, 2007

Samuel L. Stanley, Jr., M.D.
Vice Chancellor for Research
Washington University School of Medicine
660 South Euclid
Box 8027
St. Louis, MO 63110

RE: Human Research Subject Protections Under Federalwide Assurance (FWA) 2284

Research Activities:	**Research Conducted at the Washington University General Clinical Research Center (GCRC)**
Principal Investigators:	**Samuel Klein, M.D., Bettina Mittendorfer, Ph.D., Kevin Yarasheski, Ph.D., Dominic Reeds, M.D., Dennis Vallareal, M.D., Kenneth Polonsky, M.D., A. Vijaijan, M.D., John Newcomer, M.D., Dan Haupt, M.D.**
Protocol Numbers:	**99-0876, 00-0075, 00-0306, 00-0429, 00-0860, 00-0962, 01-0134, 01-0759, 01-0767, 02-0440, 02-0558, 02-0948, 02-1089, 02-1203, 03-0452, 03-0675, 03-0715, 03-0779, 04-0141, 04-0554, 04-0595, 04-1033, and GCRC 892.3**

Dear Dr. Stanley:

The Office for Human Research Protections (OHRP) has reviewed the June 7, 2006 and January 12, 2007 reports submitted by the Washington University School of Medicine (WUSM) in response to OHRP's February 15, 2006 letter regarding allegations of noncompliance with Department of Health and Human Services (HHS) regulations at 45 CFR part 46.

Based on the review of your reports, OHRP makes the following determinations regarding the above-referenced research:

(1) In its February 15, 2006 letter, OHRP presented an allegation that the WUSM institutional review board (IRB) and the investigator failed to ensure that risks to subjects were minimized by using procedures which unnecessarily expose subjects to risk, as required by HHS regulations at 45 CFR 46.111(a)(1). In specific, it was alleged that:

> (a) Unlicensed personnel performed muscle biopsies and manipulated intravenous lines and "Harvard Pumps" as part of research protocols on the General Clinical Research Center (GCRC).
>
> OHRP notes that WUSM's June 7, 2006 report stated the following:
>
> > (i) "Dr. Yarasheski is adequately trained and certified to perform muscle biopsies and does not expose research participants to unnecessary risk."
> >
> > (ii) "Furthermore, Missouri state law does not prohibit PhDs from performing muscle biopsies which are done solely for research purposes, and not to diagnose or treat a patient."
> >
> > (iii) "To the extent that non-physicians may have primed IV lines and manipulated infusion rates on Harvard and IMED pumps, such actions did not involve the 'practice of medicine' and therefore did not require a medical license under Missouri state law."
>
> Based on the above statements and other materials provided in your reports, OHRP finds that the above allegation could not be substantiated.
>
> (b) Research protocols on the GCRC utilized "Harvard Pumps" which contained labels indicating that these pumps were not approved for use on humans.
>
> OHRP notes that WUSM's June 7, 2006 report stated the following:
>
> > "The Harvard infusion pumps that have been used for research on the GCRC do not fall under the purview of the FDA [Food and Drug Administration] investigational device exemption (IDE) regulations (21 CFR 812.2(a)) because (i) the use is for research only and not intended to treat patients for a medical condition; and (ii) the apparatus is a non-significant [risk] device that does not require a FDA approved IDE."
>
> Based on the above statements and other materials provided in your reports, OHRP finds that the above allegation could not be substantiated.
>
> (c) Certain orders for medications under Protocol # 03-0452 for narcotics were written by an untrained individual and were not reviewed by a physician.
>
> OHRP notes that WUSM's June 7, 2006 report stated the following:
>
> > (i) "This protocol involved developing a set of standard orders for the

> GCRC nurses to follow during each in-patient admission for this study. These orders were developed by Dr. Klein and the study coordinator, with review and input from the GCRC nurses. The orders are signed by a physician and given to the nurses each time a participant is admitted to the GCRC. The GCRC nurses administer all medications as ordered by the physician. This is standard operating procedure for all GCRC protocols."
>
> (ii) "... in Protocol #03-0452, there was a standing order for Percocet."
>
> (iii) "Dr. Klein, Jennifer McCrea, and the RSA [research subject advocate] have no knowledge of any narcotic orders that were written incorrectly, and or investigation otherwise has revealed no evidence of noncompliance with WUSM or BJH [Barnes-Jewish Hospital] policy."

Based on the above statements and other materials provided in your reports, OHRP finds that this allegation could not be substantiated.

(2) In its February 15, 2006 letter, OHRP presented an allegation that investigators involved in human subjects research on the WUSM GCRC obtained informed consent under circumstances which did not provide the prospective subject or their legally authorized representative sufficient opportunity to consider whether to participate in the research and which minimized the possibility of coercion or undue influence, as required by HHS regulations at 45 CFR 46.116. In specific, it was alleged that a subject in renal failure received over 40 needle sticks for intravenous line placement and this subject was encouraged to continue participation in the study (GCRC # 892.3) regardless of the potential negative health risks.

OHRP notes that WUSM's June 7, 2006 report stated the following:

> (i) "Study volunteers for this protocol are admitted to the GCRC for a week long stay and receive infusions on three separate days during the stay."
>
> (ii) "The research participant, identified as Patient A, is an older woman with chronic renal disease. It is true that the GCRC nurses had a difficult time starting an IV on this participant and that she was stuck multiple times."
>
> (iii) "The RSA met with Patient A privately and stressed that she could stop the study at any time she wanted and that she would receive a portion of the monetary compensation based on the schedule approved by the IRB. The RSA discussed with the participant the risks associated with repeated attempts to start an IV, and the participant stated that 'they did not hurt' and that she was committed to remaining in the study."
>
> (iv) "The RSA discussed the situation with the GCRC Medical Officer and

> together they consulted with the IRB. The IRB advised that so long as the PI and study coordinator were continuing to provide and maintain informed consent and the participant was not being put at any additional risk, the participant had the right to choose to continue in the study."

Based on the above statements and other materials provided in your reports, OHRP finds that this allegation could not be substantiated.

(3) In its February 15, 2006 letter, OHRP presented an allegation that investigators involved in human subject research on the WUSM GCRC failed to protect the privacy of research subjects, as required by HHS regulations at 45 CFR 46.111(a)(7). In specific, it was alleged that investigators allowed unauthorized personnel to access a Nursing Test Schedule Book which contained identifiable information about research subjects.

OHRP notes that WUSM's June 7, 2006 report stated the following:

> (i) "The Nursing Test Schedule book was used by the GCRC nurses to schedule research volunteers in the GCRC. Prior to April 2003, the Nursing Test Schedule book contained the following information: Participant/Patient Name, GCRC Protocol Number, Study Name abbreviated to 2-3 words, and date of scheduled visit. Prior to April 2003, all members of the research team had access to the book, including GCRC nurses, study coordinators, dieticians, principal investigators, and the RSA."
>
> (ii) "In April 2003, [the GCRC nurse manager] unilaterally passed an edict that restricted access to the Nursing Scheduling Book to just the GCRC nurses, claiming that greater access would violate HIPAA [Health Insurance Portability and Accountability Act]."
>
> (iii) "The PIs and study coordinators accessed the book to determine GCRC staff and bed availability on certain dates for scheduling purposes. The RSA Accessed the book to determine whether research volunteers were enrolled in more than one study to order to avoid potential conflicts. Dieticians accessed the book to confirm dietary restrictions."
>
> (iv) "The Medical Officer directed the RSA to consult the HIPAA Privacy Officer. The HIPAA Privacy Officer reviewed the situation and opined that it would not violate HIPAA to permit PIs, study coordinators and the RSA access to the Nursing Scheduling Book because access to the book was reasonably necessary to permit them to conduct their research and job duties."

Based on the above statements and other materials provided in your reports, OHRP finds that this allegation could not be substantiated.

(4) In its February 15, 2006 letter, OHRP presented an allegation that investigators involved in human subject research on the WUSM GCRC failed to obtain informed consent using the most current informed consent forms for human subjects enrolled in protocols, as required by HHS regulations at 45 CFR 46.116.

OHRP notes that WUSM's June 7, 2006 report stated the following:

> (i) "In accordance with IRB policy and procedure, the PI is required to obtain the signature of the research participant on a consent form approved by the IRB and stamped by the IRB with an approval and expiration date."
>
> (ii) "However, once the initial consent document is signed by the research participant, the IRB does not require that research participants routinely sign a new consent form with a current, unexpired IRB stamp of approval at each study visit or admission to the GCRC."
>
> (iii) "... [The GCRC nurse manager] unilaterally promulgated a GCRC policy that upon admission to the GCRC, the PI had to provide a signed consent document stamped with the most current HSC approval date, regardless of whether or not the protocol or the consent document had been revised from the original consent signed by the participant when he/she was initially enrolled in the study."
>
> (iv) "At an August 11, 2003 meeting, the GAC agreed that the GCRC policy should be revised so that it no longer required that a new consent form be signed by research participants each year. The HSC was consulted and provided the GCRC nurses an in-service program on informed consent."

Based on the above statements and other materials provided in your reports, OHRP finds that this allegation could not be substantiated.

(5) It is also alleged that protocol violations were reported to GCRC management and the WUSM IRB but no actions were taken to correct the problems.

OHRP notes that WUSM's June 7, 2006 report stated the following:

> (i) "Protocol violations and deviations are reported by the GCRC nurses to the RSA as 'unexpected events.'"
>
> (ii) "The RSA enters the unexpected events in a database that she maintained and uses the information to monitor studies and investigators."
>
> (iii) "Under IRB policy and procedure, it is the investigator's responsibility to report the event to the IRB if it is a protocol deviation or an unanticipated serious adverse event."

> (iv) "[The GCRC nurse manager] had many conversations with the IRB, which are documented in a number of e-mails between her and the former administrator of the IRB. Based on that correspondence, it appears that [the GCRC nurse manager] did not fully understand what constituted a 'protocol violation' that needed to be reported. The IRB conducted an in-service for the GCRC with a PowerPoint presentation explaining the definition of a protocol deviation."

OHRP notes that WUSM has conducted a review of IRB files and provided information on all protocol deviations and the actions taken on each one.

Based on the above statements and other materials provided in your reports, OHRP finds that this allegation could not be substantiated.

As a result of the above determinations, there should be no need for further involvement of OHRP in this matter.

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,

Patrick J. McNeilly, Ph.D.
Compliance Oversight Coordinator
Division of Compliance Oversight

cc: Rose Walker, WUSM, HP Administrator
Dr. Philip Ludbrook, Chair, WUSM IRB #1A-NPC and #4-NPC
Dr. Elizabeth Buck, Chair, WUSM IRB #1-CRC
Dr. H. James Wedner, Chair, WUSM IRB #1 - NPC
Lloyd Vasquez, Chair, WUSM IRB #2 - NPC
Dr. Dorothy Edwards, Chair, WUSM IRB #2 - CRC
Dr. Ed Casabar, Chair, WUSM IRB #3-CRC
Dr. Perry Grigsby, Chair, WUSM IRB #3 - NPC
Dr. John Csernansky, Chair, WUSM IRB #3A-NPC
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