DEPARTMENT OF HEALTH & HUMAN SERVICES
Office of the Secretary
Office of Public Health and Science

Office for Human Research Protections
The Tower Building
1101 Wootton Parkway, Suite 200
Rockville, Maryland 20852

Telephone: 240-453-8298
Fax: 240-453-6909
E-mail: Lisa.Buchanan@hhs.gov

Telephone: 240-453-8120
Fax: 240-453-6909
E-mail: Lisa.Rooney@hhs.gov

[NOTE: THIS LETTER REFLECTS A CORRECTION IN THE ISSUE DATE. FEBRUARY 17, 2011 ISSUE DATE HAS BEEN CORRECTED TO FEBRUARY 17, 2012.]

February 17, 2012

Kathryn W. Irvine Tasker
Interim Vice President, Research Administration
Hebrew Rehabilitation Center for Aged
1200 Centre Street
Roslindale, MA 02131

Bruce E. Jarrell, M.D., FACS
Vice Dean for Research and Academic Affairs
University of Maryland Baltimore, School of Medicine
655 W. Baltimore Street
Room 14-031
Baltimore, MD 21201

Evan D. Kharasch, M.D., Ph.D.
Interim Vice Chancellor for Research
Washington University School of Medicine
660 South Euclid, Box 8027
St. Louis, MO 63110

RE: Human Research Protections under Federalwide Assurances FWA-00000885, FWA-00002284 and FWA-00007145

Research Project: Trochanteric Padding to Prevent Hip Fractures (also known as the Hip Impact Protection Program (HIP PRO))
Principal Investigator: Douglas P. Kiel, M.D. (Hebrew Rehabilitation Center for Aged)
Principal Investigator: Jay Magaziner, Ph.D. (University of Maryland Baltimore, School of Medicine)
Principal Investigator: Stanley Birge, M.D. (Washington University School of Medicine)
HHS Protocol Number: 5R01AG018461

Dear Ms. Tasker and Drs. Jarrell and Kharasch:

Thank you for your responses to the Office for Human Research Protection's (OHRP) June 23, 2011 determination letter that requested that your institutions provide corrective actions to address noncompliance with Department of Health and Human Services (HHS) regulations for the protection of human research subjects (45 CFR part 46) regarding the above-referenced research. We have reviewed your responses and note the following:

A. <u>Determinations Regarding this Study from OHRP's Letter dated June 23, 2011:</u>

(1) We determined that, when obtaining informed consent from subjects after the research team became sufficiently aware of the risk of increased falling on the protected side, the research team failed to disclose to subjects or their legally authorized representatives (LARs) a description of reasonably foreseeable risks to the subjects, in contravention of the requirements of HHS regulations at 45 CFR 46.116(a)(2). Specifically, we determined that by October 2004, if not earlier, investigators had become sufficiently aware of the risk of increased falling to the pocketed side and the associated risk of possible hip fractures, but failed to inform subjects who were enrolling during this time of these reasonably foreseeable risks. Further, we determined that investigators failed to provide subjects with significant new findings about these risks developed during the course of the research which may have related to the subjects' willingness to continue participation, in contravention of the requirements of HHS regulations at 45 CFR 46.116(b)(5).

(2) We also determined that investigators failed to report unanticipated problems, i.e., increased falling to the pocketed side and the associated risk of possible fractures, to their respective institutional review boards (IRBs), institutional officials, the funding agency and OHRP, in contravention of the requirements of HHS regulations at 45 CFR 46.103(a) and 46.103(b)(5).

To address the above determinations, OHRP required that your institutions develop a plan for contacting research subjects who were enrolled into this study or their LARs to inform them of undisclosed risks associated with their participation in this research. Specifically, the investigators should have provided subjects or their LARs with additional information about the subjects' exposure to increased falls and hip fractures on the padded side. This information should have been provided to the subjects or their LARs either at the time of enrollment, for those subjects who were enrolled after the Fall of 2004, or sometime during the course of the research, for those subjects who were enrolled prior to the Fall of 2004, but were still participating in the research in the Fall of 2004.

Further, OHRP required that you provide our office with corrective action plans that would help ensure that researchers:

(a) when obtaining informed consent, disclose to subjects or their LARs a description of reasonably foreseeable risks to the subjects, in accordance with HHS regulations at 45 CFR 46.116(a)(2);

(b) where appropriate, provide the respective IRBs and subjects with significant new findings developed during the course of research which may relate to the subject's willingness to continue participation in accordance with HHS regulations at 45 CFR 46.116(b)(5);
(c) report unanticipated problems to their respective IRBs, institutional officials, the funding agency and OHRP, in accordance with HHS regulations at 45 CFR 46.103(a) and 46.103(b)(5) and the institutions' policies and procedures for making such reports.

Hebrew Senior Life (HSL) Corrective Actions:

HSL plan to notify subjects and LARs:
According to your response, HSL intends to provide written notice to subjects enrolled on or after August 19, 2004 of OHRP's determination that there was information that suggested the possibility of an increased risk of falling to the padded side that should have been presented to subjects. You note that the HSL IRB will continue to consider how best to work with the participating nursing homes to develop three outreach efforts tailored to notify: (a) former subjects who continue to make their own health care decisions; (b) former subjects who were cognitively intact when enrolled in the HIP PRO Study but whose health care decisions are now made by a LAR; and (c) the next-of-kin of former subjects who have since passed away.

HSL's research program actions:
HSL will:

- conduct an in-house training program for their research team and research oversight personnel and implement a process to offer on-going training for their research community to address changes in the regulations, corresponding guidance, and best practices;
- revise policies and procedures to reflect and incorporate guidance from OHRP, the Food and Drug Administration (FDA), the Office of Research Integrity (ORI), professional associations and other thought leaders on the issues raised by OHRP; and
- work with the IRB to evaluate the structure, expertise and composition of the IRB and make any necessary adjustments.

HSL's investigator-specific actions:
The investigator must:

- acknowledge, in writing, the findings of non-compliance with HHS regulations and expectations for future communications with the IRB and the data safety monitoring board (DSMB);
- engage in structured, one-on-one mentoring, as determined and arranged by HSL, to address skills of scientific leadership and communication;
- attend an intensive off-site training program, approved by HSL, focusing on issues and various legal requirements relating to human subject protections; and
- submit to more frequent IRB reviews of on-going and future studies for which this investigator serves as a principal investigator, until such time as the HSL IRB deems this additional continuing review to be no longer necessary.

Washington University (WU) Corrective Actions:

WU's plan to notify subjects and LARs:
According to your response, your institution has only the consent forms (with subjects' and LARs' names) and the name of the nursing home at which the participant resided, and not the subjects' or LARs' addresses. You further pointed out in your response that "it is…unlikely that many of the subjects will be alive today." As such, you proposed the following:

1. Identify by a phone call the name of the current administrator of each of the participating nursing home facilities in the HIP PRO study. With this information, a certified letter will be mailed to the administrator. The letter will request the administrator's assistance in determining the following:

    - Whether the participating resident is still alive.
    - In the case of participating residents who resided in their facility during the study, but subsequently transferred to another facility, assistance will be requested to obtain the last known address of the resident or their LAR.
    - If the participant expired while residing in the facility, the date of death. The letter will offer the administrators of the nursing home facilities two options:

        (a) The first option will be to provide the investigator with the contact information (last known address) of the resident or their LAR or the date of their death if known.
        (b) If the facility administrator is reluctant or refuses to disclose this information to the investigator, then a second option will be offered. The second option would ask the administrator to mail to the participant or their LAR the subject notification letter. The letters, stamped envelopes, and a stipend to reimburse them for their time and effort would be provided to the facility.

2. With this information, a subject notification letter will be mailed to the resident or their LAR either by the investigator or by the facility. The envelopes would be stamped "Forward or Return to Sender."

WU research program actions:
New presentations will be developed and delivered by key staff of the Human Research Protections Office (HRPO) and the Office of the Vice Chancellor for Research that will review the following:

- Pertinent regulations and WU policies regarding disclosure of reasonably foreseeable risks to subjects in accordance with 45 CFR 46.116(a)(2);
- Policies requiring the investigator, where appropriate, to provide the IRB and subjects with significant new findings developed during the course of research which may relate to the subject's willingness to continue participation in accordance with HHS regulations at 45 CFR 46.116(b)(5);

- Pertinent regulations and WU policies for reporting of unanticipated problems to the IRB, institutional officials, funding agency and OHRP in accordance with HHS regulations at 45 CPR 46.103(a) and 46.103(b)(5); and
- How to assess findings or events during the conduct of research that may indicate new risks and the threshold for reporting to the IRB.

In addition, by February 2012, continuing review forms will be revised to more specifically solicit information from the investigator that will allow the IRB to appropriately determine if there are new risks to subjects.

WU's investigator-specific actions:
According to your response, the study investigator will be required to attend a course on research methods, ethical conduct of research and good clinical practice. In addition, the Human Research Quality Assurance program will monitor the conduct of this investigator's studies for regulatory compliance.

University of Maryland Baltimore (UMB) Corrective Actions:

UMB's plan to notify subjects and LARs:
According to your response, the UMB IRB determined that all individuals who participated and all LARs who provided consent for individuals to participate in this study must be notified. As such, the IRB required that the investigator visit each nursing home to ascertain which subjects continue to live at the nursing home or obtain the individual's new address in the event that they no longer reside at the nursing home. During the indicated visits, the investigator will also obtain information regarding the subject's LAR, if applicable. After the investigator has completed the dictated nursing home visits, he will be required to search the national death registry to ascertain if any subjects are now deceased. The investigator will be required to provide this information to the IRB in spreadsheet format along with the mailing addresses for the living subjects and LARs. The IRB determined that subject notification letters will be marked confidential and sent via certified mail with return receipts. The letters will contain the contact information for the UMB Human Research Protections Office (HRPO) Research Subject Advocate. The IRB determined that neither the investigator nor his staff may contact the subjects or LARs and that no contact information for the investigator would be provided. No attempts will be made to contact families of deceased subjects.

UMB research program actions:
The UMB Human Research Protections Office (HRPO) provided extensive training to the research community. The methods of training on this topic included Grand Rounds, webinars, and individualized lectures. The HRPO plans to continue educational efforts. Fiscal year 2012 will include additional personalized education sessions for individual researchers on obtaining legally effective consent. Informed consent discussions and processes will be observed following the personalized education sessions. To measure the effectiveness of this process, HRPO staff will re-visit selected researchers who have received the intervention after time has

elapsed and observe the consent process again to determine compliance with regulatory requirements.

UMB investigator-specific actions:
According to your September 24, 2010 response to OHRP's questions and concerns, all of the investigator's interventional studies were placed on suspension and audited.

OHRP's Response to the Proposed Corrective Action Plans:

We have reviewed each of your responses, including plans to notify research subjects and draft subject notification letters to address the fact that investigators failed to provide subjects with significant new findings about these risks developed during the course of the research which may have related to the subject's willingness to continue participation, as required by HHS regulations at 45 CFR 46.116(b)(5). According to documents provided to us, a total of 2054 subjects were enrolled in the study between autumn of 2002 and summer of 2006. As such, we expect that your institutions will each implement a plan that will notify as many affected research subjects and LARs as possible.

We appreciate each of your institution's efforts in developing a corrective action plan for notifying former subjects or their LARs of the information they should have received while enrolled in the research, and in drafting notification letters. We note that each of the proposed plans needs to more clearly define the populations being notified and the draft notification letters need to include additional information that we think the former subjects or their LARs need to know. Please revise your proposed notification plans and notification letters to conform to the following parameters:

1. Please include in each notification plan a provision for notification of all currently living research subjects who were participating in this research on August 1, 2004 or who were enrolled after this date.

2. Please include in each notification plan a provision for notification of all LARs who provided consent to subjects' research participation, for subjects who were participating in this research on August 1, 2004 or who were enrolled after this date, regardless of whether the former subjects are living or deceased.

3. Please inform us of any plan for notification of next-of-kin for subjects that enrolled themselves (without an LAR) but are currently incompetent or deceased. If you do not have such a plan, please provide the rationale for not informing such next-of-kin.

4. Please revise all notification letters to include the following information:

   (a) A description of the purpose of the study and why the notification letter is being sent to that recipient (e.g., the recipient was identified as research subject, the subject's LAR or the subject's next-of-kin).

(b) A statement that OHRP has determined that during the course of the study, information became available that should have been brought to the attention of the subjects or their LARs;
(c) A description of the information that became available, namely those individuals who participated in the study - which required them to wear an undergarment with padding on one hip - may have had an increased likelihood of falling to the side of the body that was meant to be protected.
(d) A statement that HHS regulations require that subjects be notified of any new risks discovered during the course of the study so that each participant may evaluate their willingness to remain in the study, and that OHRP has determined that this information should have been given to study subjects or their LARs when they consented to join the study (in Fall 2004), or during the course of the study if they were still participating in the study in Fall 2004.
(e) Provision of the url link to OHRP's determination letter of June 23, 2011, regarding the HIP PRO study, and information about how the letter can be made available if the subjects or their LARs do not have internet access.

We consider the sample language below to sufficiently cover these topics:

We have been instructed by the United States Department of Health and Human Services Office for Human Research Protection (OHRP)(the office that is responsible for research ethics involving human subjects) to inform subjects that, during the course of the study, information became available that should have been brought to the attention of the subjects or their legally authorized representatives. You may find it useful to look at the following website for details regarding OHRP's investigation: http://www.hhs.gov/ohrp/detrm_letrs/YR11/jun11a.pdf.

Specifically, individuals who participated in the study which required them to wear an undergarment with padding on one hip may have had an increased likelihood of falling to the side of the body that was meant to be protected. U.S. Department of Health and Human Services regulations require that subjects be notified of any new risks discovered during the course of the study so that each participant may evaluate their willingness to remain in the study. It has been determined that this information should have been given to study subjects or their legally authorized representatives when they joined the study (if that took place in the Fall of 2004 or later), or during the course of the study if they were still participating in the study in the Fall of 2004.

If you do not have access to the internet and wish us to send you a copy of OHRP's letter, please contact us [institution] at [mailing address, telephone number and email address].

Please provide OHRP with the revised plans for notifying subjects or LARs of the information outlined above, the revised draft notification letters, and the number of total subjects or LARs who will be notified by April 6, 2012. Feel free to contact us if you would like additional guidance in revising the notification plans and in drafting the notification letters.

We appreciate the continued commitment of your institutions to the protection of human research subjects.

Sincerely,

Lisa Buchanan, MAOM
Compliance Oversight Coordinator
Division of Compliance Oversight

Lisa A. Rooney, JD
Compliance Oversight Coordinator
Division of Compliance Oversight

cc:
Ms. Zakyia Watkins, Administrator, Hebrew Rehabilitation Center for Aged
Dr. Susan Kalish, IRB Chair, Hebrew Rehabilitation Center for Aged
Ms. Jean Velders, Assoc. Director, Washington University (WU) School of Medicine
Dr. H. James Wedner, IRB Chair/01 NPC, WU School of Medicine
Mr. Lloyd Vasquez, Chair/02 NPC, WU School of Medicine
Dr. Perry Grigsby, IRB Chair/03 NPC, WU School of Medicine
Dr. Philip Ludbrook, Chair/04 NPC, 01A NPC/CRC, WU School of Medicine
Dr. Elizabeth Buck, IRB Chair/01 CRC, WU School of Medicine
Dr. Ed Casabar, 03 Continuing Review Committee Chair, WU School of Medicine
Dr. Michael Darcey, 02 CRC Chair, WU School of Medicine
Dr. Edward Geltman, 03A NPC/CRC Chair, WU School of Medicine
Dr. Kathryn Vehe, 04 CRC Chair, WU in St. Louis
Ms. Susan C. Buskirk, Executive Director, Human Research Protections Program, University of Maryland Baltimore (UMB) School of Medicine
Dr. Robert Edelman, Associate Director, Clinical Research/Professor/IRB Chair, UMB, School of Medicine
Dr. Margaret Hamburg, Commissioner, Food and Drug Administration (FDA)
Dr. Jeffrey Shuren, FDA
Dr. Joanne Less, FDA
Dr. Sherry Mills, National Institutes of Health (NIH)
Mr. Joseph Ellis, NIH
Dr. Richard J. Hodes, Director, National Institute on Aging