DEPARTMENT OF HEALTH & HUMBAN 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.Buchanana@hhs.gov

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

June 23, 2011

Note:
Cogent points are highlighted in yellow. FallGard, the hip protector in this study is no longer on the market.

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 correspondence in response to our December 7, 2009 request that your institutions evaluate allegations of noncompliance with Department of Health and Human Services (HHS) regulations for the protection of human research subjects (45 CFR part 46) and our subsequent questions and concerns regarding the above-referenced research.

This research study (HIP PRO) was a large, multicenter, randomized controlled clinical trial to study the effect of hip protection underwear on preventing hip fractures. The study involved the use of a type of underwear containing a single pocket and a hip pad covering either the left or right hip of enrolled nursing home residents. The use of this one-sided protection was a departure from the way that hip protection underwear is actually used clinically, where hip protection, if offered, is provided on both hips. The purpose behind this aspect of the study design was that each subject could serve as their own control: they would each have a "protected" and an "unprotected" hip. According to documents provided to us, a total of 2054 subjects were enrolled into the study between autumn of 2002 and summer of 2006.

As described below, during the conduct of the study, an unexpected development took place: there was growing evidence (which reached high levels of statistical significance) that, for unclear reasons, subjects appeared to be falling more often to the "protected hip" side. This was a risk that was new, and had not been described in the initial consent form for the study. The subjects in the study were never informed about that new risk.

Based on the information provided by the complainant and the institutions, we make the following determinations. We believe it is important to recognize that some of the documents described herein, which were provided by the complainant, were never made available to the IRBs or the DSMB.

A. Determinations Regarding this Study:

(1) A complainant alleged, and we determine, 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 a description of reasonably foreseeable risks to the subjects, in contravention of the requirements of HHS regulations at 45 CFR 46.116(a)(2). In specific, a complainant alleged that when informed consent was obtained from some subjects they were not informed of the risk of increased falling to the pocketed side of the undergarment being tested and the associated risk of possible fractures. Based on the documentation provided we determine 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. Moreover, a complainant alleged, and we determine, 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, in

contravention of the requirements of HHS regulations at 45 CFR 46.116(b)(5). We base these determinations on the following evidence:

(a) In February of 2004, the Steering Committee for the HIP PRO study was proposing a change to the study, in which a new type of pad would be used. (Draft memorandum from Steering Committee to Data and Safety Monitoring Board (DSMB) dated February 2, 2004.) This change was being suggested for two reasons. One was a pilot study which looked at how the contour of the current hip pad might not be fully covering the entire hip bone of subjects. The second reason was that a significant number of the fractures being seen in the HIP PRO study were unexpectedly taking place on the side of the protected (padded) hips. For example, according to a chart documenting the hip fractures that took place at the St. Louis site through October 12, 2003 (the first year of the study), nine of eleven (more than 81%) took place on the side that was protected.

(b) In an email to the other HIP PRO investigators dated March 20, 2004, Dr. Birge (the Washington University (WU) investigator), in discussing an upcoming meeting of the DSMB to review the request for changing the pad used in the study, stated: "We need to be prepared to address the striking increase in hip fractures on the protected hip vs. the unprotected hip. . . . .What is of interest is that suspected hip fractures (injurious falls), table B, are occurring at twice the frequency on the padded side as the unpadded side. 40 vs. 24. . . . . Conclusion: the pad at best is 20% effective or at least the pad is not increasing the risk of hip fracture as table C suggests." On March 22, 2004, Dr. Kiel (the Hebrew Rehabilitation Center for Aged (HRCA) investigator) responded to this concern in part as follows: "I think it will be important to point out that fractures on the unpadded side are in the adjudication pipeline and that there has been a bit of a lag in adjudication of fractures."

(c) Also on March 22, 2004, Dr. Evan Hadley, the acting program official for the study at the funding agency, the National Institute on Aging (NIA), sent a memorandum to the members of the DSMB. The memorandum noted that NIA had some questions about the request by the HIP PRO investigators to change the pad being used in the study. Dr. Hadley noted that it would be useful to separately look at two questions: one, should the study involving the current pads be stopped, and two, should there be a study involving the new pad. With regard to the first question, Dr. Hadley asked the following: "Do the trial data show sufficiently conclusively that the current pads have an adverse effect to warrant stopping the trial of these pads? If so, what should be done at this point to inform participants, their care providers, and the public about these pads? . . . . The investigators state that study results to date have raised concerns about the design of the pads, noting that 11 fractures have been observed on the padded hip out of 16 hip fractures observed. . . . . Does this finding indeed provide enough support for a problem in pad design such that the pad should not continue to be tested in the trial?"

(d) The draft minutes (dated April 16, 2004) of the March 24, 2004 meeting of the DSMB recount the following discussion of this issue: "The DSMB reviewed the hip fracture numbers on padded and unpadded hips. Although the number of fractures was greater on padded sides than unpadded sides, several caveats were discussed. First, there has been a lag in the Clinical Endpoint Committee review process such that and [sic] there are more fractures to be adjudicated, some of which occurred on unpadded hips. Second, information on whether residents were wearing hip pads at the time of the fractures is not available. Finally, since a formal interim analysis was not indicated, the decision about switching to the new . . . pad or stopping the study early cannot be made at this time." The DSMB agreed to meet in July 2004 to review interim analyses. Also, "Dr. Kiel will ask Dr. Birge if data on asymmetry in the fall rate caused by hip pads is available."

(e) A WU Continuing Review Report that was signed by Dr. Birge on May 25, 2004 provides that "Concern over hip fractures on padded hips has resulted in the development of an improved hip pad. The new data are currently being reviewed by independent experts. Contingent upon the recommendations of these experts and the DSMB board, the new pad will be introduced in August 2004."

(f) In a June 22, 2004 email from Dr. Birge to Dr. Kiel, he states that "the morale of my staff is wanning [sic] as they continue to see most of the hip fractures on the padded hip. Because St. Louis has had 20 fractures, it is becoming increasingly difficult to make the case that our number of fractures is too few to draw conclusions. They are asking if it is ethical to continue recruiting subjects if the results are indicating no efficacy. The staff is also being asked by the [nursing home] staff what are we finding? Some of the [nursing] homes have had 4 fractures of which 2 or 3 have been on the padded hip. Their enthusiasm for the study is also wanning [sic]. Ultimately this will effect [sic] compliance. I am not sure we should discuss these issues on our conference call in the presence of the coordinators. . . . . At some point we need to send this information on to the DSMB. They may have some questions as well."

(g) The Maryland Medical Research Institute (MMRI) served as the HIP PRO data coordinating center. Bruce A. Barton, PhD. was a statistician and the HIP PRO investigator from MMRI, and was also a member of the HIP PRO Steering Committee. In an August 19, 2004 email sent to the other HIP PRO investigators, he commented on the statistical significance of the data relating to the fact that subjects appeared to be falling more frequently to the "protected" hip side:

"If you look at the 'serious falls' that were sent to us for adjudication as possible fractures, there is a preponderance of those falls on the padded side – 68% on the padded side, 32% on the unpadded side ($p<0.01$). So, what do we tell the DSMB? If I were on the DSMB, I would question the entire study design at this point (i.e., putting one pad on people)."

"I think that we need to have a very, very, very serious talk about where we are going with this study and with this study design. Granted, there is a very small chance that this is a spurious finding (i.e., the $p<0.01$), but the DSMB will not buy that at all. And I do not see where a new pad is going to solve this problem. Based on these results, we should question whether it is ethical to continue with this study design. I am very uncomfortable going to the DSMB at this point (I have not circulated any of these data to them – only the results of the biomechanical testing). I would almost rather cancel the call, giving them some reason or another, than try to come up with an explanation between now and Monday morning and potentially shoot ourselves in our collective feet. . . . . I will try to put a good face forward for the DSMB, but I am very uncomfortable at this point."

(h) The following day, August 20, 2004, Dr. Barton sent another email, again to the other HIP PRO investigators, further discussing the "maldistribution of falls" issue:

"The issue with the maldistribution of falls is something we need to consider in more detail. I have been on DSMB's that have stopped studies in this situation – an unexpected result which may impact the safety of the participants. While we may not understand the result, that does not mean that it is not real. I think that we have to pay attention to this result as a possible SAE (even if we did not define it that way). Any adverse event that causes a hospitalization is, by definition, an SAE. If the DSMB does not pick up on it (and they probably will not – I did not emphasize it in any way in the report beyond stating the numbers without any p-value attached to it), we need to think seriously about looking more deeply (and even designing some sort of pilot study) to look at some issues that may be contributing to this result. I share Stan's frustration – but obviously from the other side of this issue."

"However, we need to work together constructively to do what is best for the participants – both in terms of safety and efficacy. Let's start that process today with our call at 4."

(i) In his August 20, 2004 report to the DSMB, Dr. Barton gave the following analysis of the differences between fractures on the protected and unprotected hips: "It is of interest that the [fracture] rate per 100 person years in the hips assigned to wear hip protectors is 3.03, similar to the hypothesized 2.8. However, the rate in the hips assigned to not wear hip protectors is 1.96, substantially below the hypothesized 5.6. It is not clear why this latter result could occur. We do note that, among the patients with serious falls (falls serious enough to be investigated for fractures but which were not), there were 32 serious falls on the padded side and 12 on the unpadded side. Again, it is not clear why this latter result could occur." Consistent with what he had mentioned in his August 20th email to his fellow investigators, he did not point out to the DSMB the statistical significance of these numbers (even though, in parts of his report discussing other issues, he did include information on statistical significance – such as noting a p-value of 0.27 in concluding that the results thus far did not

demonstrate, using an intent to treat analysis, that the hip protectors were effective in reducing the rate of fractures).

(j) The "special" meeting of the DSMB took place on August 23, 2004. With regard to the issue of subjects falling more frequently on the protected hip side, the minutes from the meeting indicate that Dr. Barton presented the relevant data, but they do not indicate his mentioning the statistical significance of these numbers, nor mentioning the concerns he had expressed in his emails to his fellow investigators. The following discussion of this issue took place, as summarized in the minutes:

"Dr. Nevitt asked if these results support the conclusion that wearing the hip pad is harmful to residents. Dr. Rubinstein disagreed. The DSMB discussed alternative reasons for more frequent suspected fractures on the padded hip such as favoring the protected hip during a fall, bumping the padded hip on doors or furniture, other facility architectural features (position of the bed and bath), and gait/balance issues. Dr. Romashkan said that fragile elderly react differently to a hip pad than normal individuals. Dr. Barton said that the time distribution of fractures showed a median time from enrollment to hip fracture of 154 days with no sign of early injury when hip pads were first used. Dr. Kiel added that no study of hip pads have shown them to be harmful. The DSMB asked if there had been any kinematic gait studies conducted in fragile elderly wearing hip pads. Dr. Kiel said that such studies had not been done. They also asked if the sidedness of repeated falls could be investigated to see if nursing home residents in HIP PRO habitually fall on the same side. Dr. Kiel responded that it was not possible to collect valid data on the details of every nursing home fall. Data on the side on which each fall occurred is not available."

The DSMB then switched to a "closed session," during which it concurred with the HIP PRO investigators that the new pad "represents a substantially improved and superior design that is much more likely than the current pad to successfully prevent hip fractures." Accordingly, it endorsed ending the current study (which used the original pad design), and beginning a new study with the redesigned pad. With regard to consent issues, it recommended that the applicable IRB at each of the participating institutions should approve a plan for informing current subjects of the switch to the new pad. It also expressed its feeling that "the description of the new pad does not differ enough to require, on this basis alone, a reconsent process."

(k) In an August 25, 2004 letter from Dr. Kiel to the members of the IRB that was reviewing the conduct of the study at his institution, he informed them of what happened at the August 23 DSMB meeting. He noted that a "futility analysis" had demonstrated that the existing study, if it continued unchanged, would be unlikely to demonstrate that the current pads were effective in reducing fractures. Accordingly, the DSMB, having been presented with a newly designed pad with "improved biomechanical properties," had recommended that the use of the current pad be discontinued, that a switch to the new pad be made, and that the IRBs involved be

informed of these recommendations. Nothing was mentioned regarding the issue of subjects falling more often to the protected side.

(l) Prior to conducting the HIP PRO study, Dr. Birge had obtained NIH funding to conduct a pilot study (SBIR R43AG12317-02) of hip pads. The data from that pilot study, which had completed enrollment back in 2002, had been used to help convince NIH to fund the HIP PRO study. The pilot study was similar in design to the HIP PRO study in assigning subjects to hip protection on only one side, and ended up enrolling 521 subjects. Among the pieces of information collected in that study was whether a fall by a subject was observed, and if so, in which direction did the subject fall. Apparently, until the issue arose during 2004 about whether subjects in the HIP PRO study were falling more often on the protected side than the unprotected side, Dr. Birge had not analyzed the data from the pilot study regarding this particular issue. When that issue did arise, he went back to that pilot data and performed such an analysis, which was completed by the end of August, 2004. For those subjects whose falls were observed and who were wearing a pad when they fell, the results were as follows:

	Fell to left	Fell to right
Pad on left	21	9
Pad on right	15	37

These numbers appear to indicate a very strong relationship between falling to the side on which the pad was being worn: the Chi-square p-value was 0.003, demonstrating greater significance than even the numbers that were coming out of the HIP PRO study itself.

Dr. Birge did ultimately prepare a manuscript which described the results of the pilot study. The manuscript included the following conclusion:

> "A clinical trial using one-sided protection to assess efficacy of an EPH [external hip protector] is feasible, however adherence and monitoring falls is a challenge. Wearing the EPH may modify behavior and potentially increase the risk of fall and hip fracture. Thus, ineffective EHPs may actually increase the risks of hip fracture making future clinical trials of EPH efficacy critical."

That manuscript also explained a key point about how, if subjects were not falling equally often on the protected and unprotected sides, that fact would have major negative consequences for the ability of a study to answer the main research question, namely whether the pads were actually effective. For example, if the results of a study of one-sided protection showed an equal number of fractures on padded and unpadded hips, then on the assumption that subjects had been falling equally often to the padded and unpadded sides (an assumption which was being made in the HIP PRO study), this would indicate that the pads were completely ineffective. In

contrast, if the truth were that the subjects were falling four times more often to the padded side, then these same numbers would demonstrate that the pad was actually very effective: it would be preventing 75% of the fractures that would otherwise be expected from that four-fold higher number of falls on the padded hip.

According to an August 20, 2010 email from WU, the manuscript was submitted and accepted for publication in October 2009, but was subsequently retracted by its authors in response to threatened legal action.

(m) After apparently sharing this data from the pilot study with Dr. Kiel, Dr. Birge made the following comments to him in a September 1, 2004 email, explaining how the asymmetric falling rate among subjects posed a problem regarding whether they could prove that the old pad was effective, even if it was indeed effective:

"I don't think we should share with the DSMB the data on the old hip pad. It is evident from LCCA [Life Care Centers of America, an operator of nursing homes] data that it has some efficacy. It is also evident that hip fractures are occurring on the padded hip as we have observed. My reasons are that this data raises questions about our experimental design which will have a significant negative impact on our power calculations. If the old pad has about a 70% efficacy as suggested by the LCCA data, then this would support the hypothesis that indeed residents are preferentially falling on to the padded hip to account for our observations. Our power calculations assume that the exposure rate for padded and unpadded hips are the same. If as our pilot data suggests and the limited data from the hip fracture event form indicate, there are twice as many falls on the padded side, our power is reduced by a factor of 4. That assumes that the falls on the unpadded side are reduced by a factor of two and increased by a factor of 2 on the protected side. If the new pad is 100% effective and our effective compliance is 85%, we should have no problem. It may be difficult to sell that to the DSMB."

"I suggest that our approach to the DSMB is to ignore the issue by concluding that it is an unexplained aberration. Because of our inability to obtain sufficient data on observed falls, we may never be able to account for the aberration. . . . . I have not shared these thoughts with Bruce [Dr. Barton] because I did not wish to distract him from his task at hand. As for the Steering committee I think we need to focus on getting the new pads in the field."

(n) Toward the end of 2004, the HIP PRO investigators proposed conducting an ancillary study to more specifically look into the issue of subjects falling on the padded side. As stated in a draft NIH grant application (which had Dr. Kiel as the lead investigator), they were proposing this in response to a recommendation from the DSMB, which recommendation had been motivated "by an interim analysis of the HIP PRO study that demonstrated an increased number of falls and hip fractures on the padded side." The possibility of such a study was discussed during an October 7, 2004 meeting of the DSMB, as documented in the minutes from that meeting: "Dr.

Hadley [from NIH] described the asymmetry in serious resident falls, which run strongly against the padded hip (z=2.87) and the ancillary study under consideration. It would be a parallel study using bilateral hip pads versus no hip pads which would investigate the difference in serious fall rates. The results would add extra information on whether wearing hip pads is related to increases in serious falls and would address the ethical issues involved in recommending hip pads to fragile elderly people." To our knowledge, this ancillary study was never conducted.

(o) The transition in the HIP PRO study from using the then-current pad to using the newly designed pad took place in October, 2004. Consistent with the recommendations of the DSMB, reconsenting did not take place. Subjects were given a one-page letter that provided them with information about the change from the prior pad to the new pad. In particular, the letter noted the following: "There is also a new development in this project. Preliminary results indicate that the pad has not been effective. Therefore, we have developed an improved hip pad. In laboratory tests, this improved pad has been shown to work better in reducing the impact of a fall. It looks just like the current pad (it is the same size and shape), but feels somewhat softer. It fits into the underwear pocket just like the old one." The letter mentioned nothing about subjects falling more often to the protected side. The investigators continued to enroll new subjects into the study, using the redesigned hip pad, until at least June 2006. The study results relating to the use of the redesigned pad were apparently never published.

(p) The results of the HIP PRO study relating to the use of the pad prior to the redesign were published in *JAMA* in 2007. (Kiel DP, Magaziner J, Zimmerman S, et al. Efficacy of a Hip Protector to Prevent Hip Fracture in Nursing Home Residents: The HIP PRO Randomized Controlled Trial. *JAMA*. 2007;298(4):413-422.) In reviewing the manuscript to determine whether to publish it, the journal editors posed the following questions to the investigators: "A central issue discussed by the reviewers and editors is whether having one hip protector can be generalized to wearing both, and whether wearing one hip protector would influence gait, falling, etc. . . . . Have you made observations of patients with and without a single hip protector, vs two hip protectors, to determine whether gait or other behaviors are affected by having a single hip protector? The investigators provided the following response: "While the hip protectors are very thin and lightweight such that one is not aware of them when walking, we have no information regarding whether wearing one hip protector influences gait or falling. Further, given that more than half the study participants had significant cognitive impairment, predisposition to falling to one side during an unexpected fall seems unlikely. However, we have modified the language . . . . in the revised manuscript to clearly indicate that we were unable to completely exclude the possibility that falling to the protected side was influenced by wearing of the one sided hip protector." It does not appear that *JAMA* was told about the data on this issue generated by the pilot study.

In an editorial that *JAMA* published to accompany the article (Kannus P, Parkkari J. Hip Protectors for Preventing Hip Fracture. *JAMA*. 2007;298(4):454-455), the authors devoted more space to this issue than did the article itself. They first noted the puzzling numbers (13 hip fractures in protected hips versus only 7 in unprotected hips), which suggested to them that either the hip protectors were mechanically ineffective (or even caused fractures), or else "the use of a 1-sided hip protector modified the individual's standing and walking, such that it increased the risk of hazardous fall onto the protected hip." They went on to further discuss this second possibility ("having only 1 hip protected could have modified the propensity to fall to the protected side either because of mechanical positioning of the pad or because of sensory cues from the pad that altered gait"), noting a need to better evaluate this in future studies using the one-sided design.

In summary, over a period of several months during 2004, a growing amount of information became available strongly suggesting that something unexpected was taking place in the HIP PRO study. Instead of falling equally to the left and right, as one might have initially supposed, subjects appeared to be falling more frequently to the "protected" side. And although the numbers were relatively small, this disparity achieved a high level of statistical significance. An attempt to evaluate the data from the earlier pilot study strongly confirmed this phenomenon. The investigators themselves, in candid emails to one another, recognized the significance of these findings, and in particular how they might make it difficult to prove that the pad was effective even if that was indeed the case. Dr. Barton, to his credit, highlighted how this phenomenon called into question the proposed redesign of the study (the use of a new pad), which they had no reason to suspect would solve this problem. He also correctly stressed to his colleagues how this raised important issues for the safety of the subjects, even if there was not yet a good explanation for what was happening.

Yet, in the face of these developments, efforts were made to either "slant," or completely fail to report (e.g., the data relating to the pilot study) information to the groups (the DSMB and the IRBs reviewing the study) that might have found this information highly relevant in their deliberations. The result was that, even given the major redesign of the study, and the proposal to do an ancillary study to further explore this issue, the subjects in the HIP PRO study and their representatives failed to receive any information relating to a risk about which the investigators were aware. Had this risk been disclosed to the subjects and their representatives, it is reasonable to conclude that such information might have significantly affected their willingness to continue to participate.

(2) In light of the evidence detailed above, we also determine 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 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).

Required Actions Specific to this Study: Please develop a plan for contacting the appropriate subset of research subjects who were enrolled into this study or their legally authorized representatives (LARs) and informing them of the issues recounted in this letter, including the risk of increased falls and hip fractures on the padded side and that either at the time of enrollment or at sometime during the course of the research (depending on when that particular subject was enrolled), the investigators should have provided them with this undisclosed risk information. Please provide our office with a written report regarding the IRBs' plans for this matter, including the proposed text to be provided to subjects or their LARs.

Additional Required Actions: Please provide our office with a corrective action plan that will help ensure that researchers:

(a) when obtaining informed consent, disclose to subjects or their legally authorized representatives 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 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); and
(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.

Corrective actions taken to address our determinations related to this specific study might include additional oversight of the researchers' conduct. We note that at least one investigator's research privileges have been restricted.

(3) A complainant alleged that when reviewing the protocol at initial review, the respective IRBs lacked obviously relevant information pertinent to making the determinations required for approval of research under HHS regulations at 45 CFR 46.111. In specific, the complainant alleged that data from Dr. Birge's St. Louis pilot study showing that subjects wearing the undergarment had a significant tendency to fall on the pocketed side and that at least one and possibly five hip fractures occurred with the pad in place was not disclosed to the IRB when initially reviewing this study.

Based on the information we reviewed, data analysis for the pilot study was not completed until 2004, and was not available during the initial IRB review of this research. We determine that this allegation is unproven.

We appreciate UMB sharing with us a variety of additional, significant findings of noncompliance that UMB uncovered while conducting their investigation into the allegations noted above. We commend UMB for the comprehensive audit conducted in response to OHRP's

investigation and the proposed, broad corrective action plan to address numerous instances of noncompliance, and we determine that the actions taken to address those additional findings of noncompliance to be appropriate. We also favorably note UMB's conclusion that, had its IRB received the information about the results from the pilot study (which it never received), the IRB "should have required that this specific information" be disclosed to subjects.

UMB, WU and HRCA must provide us with responses to the above determinations by August 5, 2011, including a corrective action plan for each of our determinations. Feel free to contact us if you would like guidance in developing a corrective action plan.

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

Sincerely,

Lisa Buchanan, MAOM
Compliance Oversight Coordinator
Division of Compliance Oversight

Lisa A. Rooney, J.D.
Division of Compliance Oversight
Compliance Oversight Coordinator

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