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

June 4, 2012

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

RE: Human Research Protections Under Federalwide Assurance FWA-00007145; Research Projects Under Principal Investigator Dr. Stephen Davis

Dear Dr. Jarrell:

Thank you for your March 29, 2012 response to the Office for Human Research Protections' (OHRP) February 16, 2012 letter that requested that the University of Maryland, Baltimore (UMB): (1) 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; and (2) provide responses to identified questions and concerns. Based on the information provided, we make the following determinations.

A. Determinations Regarding Research Projects Under Other Investigators

1. In our February 16, 2012 letter, we determined that the informed consent document for HP-00046741, which was reviewed and approved by the UMB Institutional Review Board (IRB), failed to include a description of the appropriate alternative procedures or courses of treatment that might have been advantageous to the subjects as required by HHS regulations at 45 CFR 46.116(a)(4).

   Corrective Action: The UMB IRB required the investigator for this study to: (a) submit a modification to amend the consent document to include a description of the appropriate alternative procedures or courses of treatment that might have been advantageous to the subjects; (b) confirm that no additional participants would be enrolled until such modification received IRB approval; and (c) re-consent participants using the modified consent document when participants return for follow-up visits. Moreover, UMB has implemented measures to improve processing of consent documents and ensure compliance with 45 CFR part 46. To be specific, we note that as of March 1, 2012 UMB initiated the use of a new consent template; a template that contains all required and

additional elements of informed consent. Lastly, as requested, UMB provided our office with a copy of the IRB meeting minutes where this study was discussed and a copy of the UMB IRB approved modified consent form. We have determined that the corrective actions noted above adequately address our determination and are appropriate under the UMB FWA.

2. In our February 16, 2012 letter we determined that complete IRB records, as outlined under 45 CFR 46.115(a), were not accessible for inspection and copying by authorized representatives of HHS at reasonable times and in a reasonable manner as required by HHS regulations at 45 CFR 46.115(b).

   Corrective Action: UMB has made changes to its electronic protocol management system to ensure that complete IRB records, as outlined under HHS regulations at 45 CFR 46.115(a), are accessible for inspection and copying by authorized representatives of HHS at reasonable times and in a reasonable manner as required by HHS regulations at 45 CFR 46.115(b). We have determined that this corrective action adequately addresses our determination and is appropriate under the UMB FWA.

3. We have determined that the UMB IRB lacked sufficient information to make 45 CFR 46.111 approval decisions regarding Protocol 43796 when the IRB conditionally approved the research on February 17, 2010, instead of deferring approval. To be specific, we note that the UMB IRB conditionally approved Protocol 43796 even though the IRB lacked information regarding recruitment and the consent process. According to a February 19, 2010 IRB conditional approval letter, the IRB asked the investigator to provide a more detailed explanation of the procedures for obtaining informed consent from participants. The letter also asked the investigator to provide a more detailed explanation of the procedures for assessing participant understanding. The letter continued "For example, Will participants be administered the Evaluation to Sign Consent too prior to enrollment?"

   Corrective Action: We acknowledge that: (a) a fully convened panel of the UMB IRB re-reviewed this study on April 15, 2012; (b) UMB has re-educated the UMB Human Research Protections Office (HRPO) staff, IRB panel members, IRB Chair and Vice Chairs on the meaning of the motion of deferral and the motion to conditionally approve a submission with modification required to secure approval; and (c) UMB conducted an audit of IRB meeting determinations and discovered only this instance where the IRB required modifications required to secure approval when the submission should have been deferred. We have determined that these corrective actions adequately address our determination and are appropriate under the UMB FWA.

B. Resolved Concern Regarding Research Projects Under Dr. Davis

1. In our February 16, 2012 letter, we raised a concern that the UMB IRB approved protocol 44874 although risks to subjects may not have been minimized, as required by HHS regulations at 45 CFR 46.111(a)(1). To be specific, we noted that according to the August 26, 2010 IRB meeting minutes for this study, the IRB determined that the study

must be reviewed bi-annually. However, the September 10, 2010 IRB approval letter that was issued to the investigator reflects a 12 month approval period. Given this discrepancy, we asked UMB to explain why the IRB requirement was not implemented and how risks to subjects were minimized by extending the approval period from six months to 12 months.

According to UMB, the IRB six-month approval period requirement was not implemented due to human error. UMB believes that the error did not affect the risks to participants because: (a) the investigator's monitoring plan for this study included a bi-annual review by the Data Safety Monitoring Board (DSMB); and (b) the requisite DSMB reports were submitted to and reviewed by the UMB IRB on a regular basis with a frequency of not greater than six months. Moreover, we note that the fully convened IRB reviewed this study on July 14, 2011 and at that time voted that the review period for this study would now be twelve months.

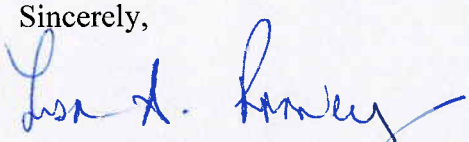
UMB Action: We acknowledge that given this error, UMB has: (a) counseled the HRPO coordinators, the individuals responsible for composing IRB meeting minutes and letters of determinations, on the importance of accurate recording of IRB determinations, including approval periods; (b) eliminated the term "bi-annually" and replaced it with "every six months;" and (c) audited letters of determination issued between January and March of 2012 to determine whether all approval periods described in the IRB determination letters accurately reflected the determinations described in the IRB meeting minutes. We note that the audit revealed that all approval periods were accurately reflected in the IRB determination letters. These actions adequately address our concern.

We acknowledge that the remaining questions and concerns from our February 16, 2012 letter have been adequately addressed.

We determine that the actions noted above adequately address all of the determinations and questions and concerns. At this time, there should be no need for further involvement by our office in this matter. We anticipate conducting a site visit at your institution within the next 12-24 months.

We appreciate the continued commitment of your institution to the protection of human research subjects. Please do not hesitate to contact me if you should have any questions.

Sincerely,



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

cc:
Dr. Jay A. Perman, President, UMB (220 North Arch Street, 14th Floor, Baltimore, MD 21201)
Ms. Susan C. Buskirk, Assistant Dean, Human Research integrity & Compliance, University of Maryland Baltimore, School of Medicine
Dr. Robert Edelman, Associate Director, Clinical Research/IRB Chair, University of Maryland, Baltimore, School of Medicine
Dr. Stephen Davis, University of Maryland, Baltimore, School of Medicine
Dr. Sherry Mills, National Institutes of Health (NIH)
Mr. Joseph Ellis, NIH