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: 240-453-8238
FAX: 240-453-6909
E-mail: kcooper@osophs.dhhs.gov

February 24, 2006

Richard Homan, M.D.
Philadelphia Health and Education Corporation
(Drexel University College of Medicine)
245 N. 15th Street
19th Floor
Philadelphia, PA 19102-1192

RE: Human Research Subject Protections Under Multiple Project Assurance (MPA) M-1532 and Federalwide Assurance FWA-5917

Research Publication: Brannagan TH, et al. High-dose cyclophosphamide without stem-cell rescue for refractory CIPD. Neurology 58: 1856-58.

Research Project: "High-dose Cyclophosphamide for the Treatment of Severe Aplastic Anemia, Paroxysmal Nocturnal Hemoglobinuria and Refractory Autoimmune Disease, Felty's Syndrome and Pseudo-Felty's Syndrome"

Project Number: 60733

Principal Investigator: Isadore Brodsky, M.D.

Dear Dr. Homan:

The Office for Human Research Protections (OHRP) has reviewed Drexel University College of Medicine's (DUCM) January 11, 2006 response to OHRP's October 27, 2005 letter.

The above-referenced study was approved in October 1996 by the Institutional Review Board (IRB) at MCP-Hahnemann School of Medicine of Allegheny University of the Health Sciences and was closed in November 2002. OHRP notes that during the time period in which this study was conducted, MCP Hahnemann School of Medicine had a Multiple Project Assurance in which the institution agreed to apply the protections of 45 CFR 46 to all studies, regardless of funding. MCP Hahnemann School of Medicine became part of Drexel University School of Medicine, under FWA #5917. In January 2006, the FWA was updated to list Philadelphia

Health and Education Corporation as the named institution, with Drexel University College of Medicine as a component.

OHRP acknowledges that DUCM stated in its January 11, 2006 response that it concurs with the findings of noncompliance made in OHRP's October 27, 2005 letter.

In its October 27, 2005 letter, OHRP made the following findings regarding the above-referenced research:

> (1) Department of Health and Human Services (HHS) regulations at 45 CFR 46.103(b) and 46.109(a) require that the IRB review and approve all nonexempt human subjects research covered by an assurance. HHS regulations at 45 CFR 46.103(b)(4)(iii) require that the IRB review and approve all proposed changes in a research activity, during the period for which IRB approval has already been given, prior to initiation of such changes, except when necessary to eliminate apparent immediate hazards to the subjects.
>
> OHRP found that the protocol approved by the DUCM IRB did not contemplate the enrollment of four subjects with chronic inflammatory demyelinating polyneuropathy (CIDP) and, as a result, the enrollment of those four subjects with CIDP constituted the conduct of nonexempt human subjects research without IRB review and approval as well as the implementation of a protocol change without prior IRB review and approval.
>
> **Corrective Actions**: DUCM stated in its January 11, 2006 response that the IRB had instituted "a policy in January 2003 requiring investigators to submit separate protocols and consent forms for each of the targeted diseases they intent to study or treat....We have changed our guidelines and the standard operating procedures to reflect this change in policy." DUCM also stated that IRB reviewer checklists were revised.
>
> OHRP finds that the above corrective actions adequately address the above finding and are appropriate under the DUCM FWA.
>
> OHRP notes that there does not appear to be any evidence of the above-mentioned policy change in the any of the following DUCM IRB documents:
> - Guidelines for Biomedical and Behavioral Research Involving Human Subjects, approved November 5, 2003
> - Human Protocol Processing Form, Revised November 1, 2003
> - Protocol Summary Outline Form, Revised October 1, 2003
> - General Checklist for Reviewers
>
> OHRP suggests that the above-mentioned policy be incorporated into DUCM IRB's written procedures and reflected in forms and checklists.

(2) OHRP found that the six informed consent documents reviewed and approved by the DUCM IRB for the above-referenced study omitted or failed to adequately address the following elements required by HHS regulations at 45 CFR 46.116(a):

(a) Section 46.116(a)(1):An explanation of the purposes of the research and a complete description of the procedures to be followed, and identification of any procedures which are experimental.

(b) Section 46.116(a)(2): A description of any reasonably foreseeable risks or discomforts to the subject.

(c) Section 46.116(a)(3): A description of any benefits to the subject or to others which may be reasonably expected from the research.

Corrective Actions: DUCM stated in its January 11, 2006 response:

"Future studies will not be approved until they have been thoroughly reviewed to make sure the protocol and consent forms are consistent and complete...As noted above, the IRB will also employ a revised and expanded checklist so that the members can determine whether any elements on the consent form have been omitted and whether the consent form agrees with the protocol. We are also providing additional training for IRB members and staff and for investigators at meetings or seminars, and through improved information on our website."

OHRP finds that the above corrective actions adequately address the above finding and are appropriate under the DUCM FWA.

OHRP makes the following additional determinations concerning the above-referenced research:

(3) HHS regulations at 45 CFR 46.111(a)(1) require the IRB to determine that risks to subjects are minimized by using procedures which are consistent with sound research design and which do not unnecessarily expose subjects to risk.

Protocol Objective 2.2 is "To determine whether the addition of G-CSF to high-dose cy [*sic*] will shorten the time to recovery in SAA."

(a) Protocol Section 8.0 entitled "Risks" consists of one paragraph:

The risks of this study are expected to be similar to current autologous transplant protocols employing cyclophosphamide. CMV infection, interstitial pneumonitis, idiosyncratic cardiomyopathy, hemorrhagic cystitis and hepatic disease may each occur and be associated with mortality. Alopecia, some degree of sterility which may be permanent, and hyperpigmentation are universal. Nausea and vomiting is [*sic*] treated

> with antiemetics. Additional weeks of aplasia requires [*sic*] antibiotic and transfusion support. Herpes virus infections may be treated with Acyclovir.

There is no mention of the risks of G-CSF in the paragraph above.

(b) All four consent forms submitted with the initial IRB application contain the following statement: "Ten days after starting cyclophosphamide you will be given G-CSF, a drug that helps normal blood cells grow, by vein once every day to try to help your blood cells grow faster." The consent forms also state, "G-CSF may cause headache, fever, chills, decreased appetite, pain in bones, chest, belly, joints and rash [*sic*]." OHRP notes that the consent form contains information about protocol procedures (administration and risks of G-CSF) that are absent from the protocol.

OHRP finds that the IRB failed to obtain sufficient information about the addition of G-CSF referenced in Objective 2.2 in order to determine that risks to subjects were minimized in this study.

Corrective Actions: DUCM made the following statement in its January 11, 2006 response:

> "To prevent this problem from occurring in the future, the IRB will stress to the investigators, the IRB staff and IRB members the importance of obtaining sufficient information through published articles, PDR, or appropriate Websites about the drugs to be studied to make sure that the risks are well reviewed and documented on the protocol and the consent form... The Office will also train investigators to provide references to evaluate and/or substantiate risks and include information on all the risks which are anticipated and related to the study drug on the protocol and on the consent form."

OHRP finds that the above corrective actions adequately address the above finding and are appropriate under the DUCM FWA.

OHRP notes that HHS regulations at 45 CFR 46.107(a) state, in pertinent part, the following:

> Each IRB shall have at least five members, with varying backgrounds to promote complete and adequate review of research activities commonly conducted by the institution. The IRB shall be sufficiently qualified through the experience and expertise of its members, and the diversity of the members, including consideration of race, gender, and cultural backgrounds and sensitivity to such issues as community attitudes, to promote respect for its advice and counsel in safeguarding the rights and welfare of human subjects. In addition to possessing

> the professional competence necessary to review specific research activities, the IRB shall be able to ascertain the acceptability of proposed research in terms of institutional commitments and regulations, applicable law, and standards of professional conduct and practice. The IRB shall therefore include persons knowledgeable in these areas.

OHRP suggests that DUCM carefully ascertain whether there is sufficient experience and expertise amongst its members to adequately review a given study. OHRP notes that DUCM policy 2.1.5(I), approved November 5, 2003, states, "The IRB may invite "consultants" or "subject advocates" competent in special areas to assist in the review of issues that require special expertise, or to assist in gathering information on the issues raised by proposed research." When IRB members participating in the review of a given project appear to lack the necessary subject matter expertise, OHRP further suggests that DUCM IRBs consider using expert consultants, in concordance with DUCM policy 2.1.5(I).

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

> (a) On January 8, 1997, Amendment #1 was approved "ad hoc" by the IRB chair, Dr. Sokil. This amendment involved the "clarifying" of the term "refractory autoimmune disorders," resulting in a revision of the inclusion criteria. Also, two new consent forms were submitted along with this amendment.
>
> (b) On September 26, 1997, an "emergency approval" was granted through expedited review for a subject with graft vs.host disease (GVHD) who did not meet the inclusion criteria for this study.
>
> (c) On July 31, 1998, another emergency exception to the inclusion criteria was granted through expedited review.

Corrective Actions: DUCM stated in its January 11, 2006 response:

> "A different policy is now in effect than the one in place in 1997 and 1998 when the chairs or co-chairs approved several amendments to the protocol that constituted more than minor changes. It is our current policy NOT to approve amendments to the protocols if the original protocol has been approved in a convened meeting except when the requested amendments represent minor changes to the protocol. If the amendment requests inclusion of a different target population or disease entity, we require the investigator to submit a new protocol and consent form for the newly targeted disease or subjects for the IRB to review, request modifications to, or approve such requests."

OHRP finds that the above corrective actions adequately address the above finding and are appropriate under the DUCM FWA.

(5) OHRP finds that the IRB failed to obtain sufficient information to make the determinations required for approval of the above-referenced research under HHS regulations at 45 CFR 46.111.

The principal investigator submitted a "clarifying amendment" in December 1996. The amendment consisted of a one-page memo in which the principal investigator stated the following, in pertinent part:

> In addition to evaluating the immunoablative effect of high-dose cyclophosphamide, paroxysmal nocturnal hemoglobinuria, aplastic anemia, refractory autoimmune disease, Felty's syndrome, and pseudo-Felty's Syndrome, I would like to also include the following refractory autoimmune disorders: refractory autoimmune hemolytic anemia, disseminated lupus erythematosis, lupus anticoagulant, scleroderma, and immune thrombocytopenia purpura.... Actually, these conditions are included in the term 'refractory autoimmune disease' but I now want to specifically mention the diseases to be investigated."

OHRP notes that the investigator did not provide detailed justification for each type of subject population to be studied. For example, the amendment did not include background information on the current treatments being used for each disorder, and the prior use of cyclosphosphamide for each disorder.

Corrective Actions: DUCM stated in its January 11, 2006 response:

> "We entirely agree that the IRB in 1996 failed to obtain sufficient information from the investigator regarding detailed justification of the investigational treatment for each of the targeted populations. It also appears from the documentary record to have failed to obtain sufficient background information on current treatment methods for the targeted disorders and patient groups and for prior uses of cyclophosphamide for each of the targeted disorders."

DUCM also stated that it has new policies that require the use of a checklist for "all protocols involving treatment of patients."

OHRP finds that the above corrective actions adequately address the above finding and are appropriate under the DUCM FWA.

(6) HHS regulations at 45 CFR 46.404-407 require specific findings on the part of the IRB for approval of research involving children. OHRP finds that IRB failed to make the findings required when reviewing research involving children during the April 2001 expedited approval of the enrollment of a minor (16 years old) with systemic lupus erythematosus.

Corrective Actions: In its January 11, 2006 response, DUCM concurred with OHRP that a minor was improperly enrolled in the above-referenced research without the IRB making the findings required in 45 CFR 46.404-407.

DUCM has modified its policy so that when children are involved in research, both the protocol and the consent form are reviewed by its Children and Minors IRB (IRB #4) or a member from IRB #4 who serves as an advocate for the child/minor prior to approval by one of the other committees. In addition, DUCM no longer allows expedited continuing review of studies previously approved by the convened IRB.

OHRP finds that the above corrective actions adequately address the above finding and are appropriate under the DUCM FWA.

(7) OHRP finds that there is little evidence that the IRB determined that the selection of subjects was equitable, as required by 45 CFR 46.111(a)(3). In making this assessment, the IRB should take into account the purposes of the research and the setting in which the research will be conducted, and should be particularly cognizant of the special problems of research involving vulnerable populations, such as children, prisoners, pregnant women, mentally disabled persons, or economically or educationally disadvantaged persons.

OHRP notes that the IRB application form used at initial review contained only one question related to recruitment: "B. Recruitment/treatment location(s) of Human Subjects: HUH_X_ MCPH____ Other____ Inpatient_X_ Outpatient____."

Corrective Actions: In its January 11, 2006 response, DUCM stated that it "has established a policy which requires the selection of subjects to be equitable and free of coercion, both explicit and implied."

OHRP notes that the following sentence was added to the general reviewer checklist in the Procedures and Duration section: "It is important to consider equitable selection." However, other than questions on the checklist about advertisements, there are no other questions about recruitment. OHRP notes that additional questions could be asked of the investigator to solicit information that would assist the IRB in implementing the new policy regarding equitable and coercion-free selection of subjects (i.e., Who will approach potential subjects with information about the study? Where will potential subjects first be approached? Will the potential subject's primary care physician be involved in recruitment?)

Required Action: Please explain the procedures by which the IRB will assess whether the selection of subjects is equitable and free of coercion, both explicit and implied.

(8) HHS regulations at 45 CFR 46.111 set forth the criteria that must be satisfied in order for the IRB to approve research. These criteria include, among other things, determinations by the IRB regarding risks, potential benefits, informed consent, and

safeguards for human subjects. The IRB must ensure that these criteria are satisfied at the time of both initial and continuing review.

In conducting continuing review of research not eligible for expedited review, all IRB members should at least receive and review a protocol summary and a status report on the progress of the research, including, amongst other items, the number of subjects accrued.

OHRP expressed concern in its October 27, 2005 letter that the number of subjects enrolled in the above-referenced research exceeded the number of subjects approved to be enrolled by the IRB. The initial IRB application indicated that 5-10 subjects would be enrolled, and the protocol summary indicated that 4-6 patients per year would be enrolled. At the sixth continuing review in August 2002, 32 subjects had been enrolled.

OHRP finds that DUCM IRB failed to adequately review the materials presented at continuing review for the above-referenced research.

Corrective Actions: DUCM stated in its January 11, 2006 response that it concurred with OHRP that the protocol was not amended to increase the number of subjects authorized to be enrolled. DUCM stated that now the IRB has a policy for submitting and reviewing modifications to the protocol that should prevent exceeding the number of subjects approved by the IRB. Investigators have been advised that they must report planned changes using a Study Amendment Request Form and receive IRB approval for the changes.

However, the response does not address the fact that the discrepancies in enrollment numbers were not detected from continuing review to continuing review.

Required Action: By April 15, 2006, please submit to OHRP a corrective action plan that addresses findings #7 and #8 above.

OHRP appreciates your institution's continued commitment to the protection of human research subjects. Do not hesitate to contact OHRP if you have any questions regarding this matter.

Sincerely,

Karena Cooper, J.D., M.S.W.
Compliance Oversight Coordinator
Office for Human Research Protections

cc: Dr. Sreekant Murthy, HPA & Vice Provost for Research Compliance, DUCM
Dr. Harvill Eaton, Provost, DUCM

Dr. Victor Lidz, DUCM
Dr. Patricia Shewokis, DUCM
Dr. Carol Anderson, DU
Dr. David Lepay, FDA
Dr. Lana Skirboll, NIH
Dr. Bernard Schwetz, OHRP
Dr. Melody Lin, OHRP
Dr. Michael Carome, OHRP
Dr. Kristina Borror, OHRP
Ms. Shirley Hicks, OHRP
Dr. Irene Stith-Coleman, OHRP
Ms. Patricia El-Hinnawy, OHRP
Ms. Janet Fant, OHRP