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Joseph Bloom, M.D.
Dean
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**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. Bloom:

The Office for Human Research Protections (OHRP) has reviewed Drexel University College of Medicine’s (DUCM) January 5, 2004 response to OHRP’s November 12, 2003 letter.

DUCM stated in its January 5, 2004 response that the above-referenced research project did not receive any funds or sponsorship from any federal department or agency. OHRP notes that during the period during which the above-referenced study was conducted at Allegheny University Hospital, Hahnemann Division and at Drexel University College of Medicine (1996 - 2002), the Multiple Project Assurance (M-1532) in effect at that time was applicable to all research involving human subjects, regardless of sponsorship.

Based upon its review, OHRP makes the following determinations of noncompliance 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 institutional review board (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.

In its November 12, 2003 letter, OHRP presented the allegation that human subjects research involving the phase I trial described in the above-referenced research publication was conducted without IRB review and approval. In response, DUCM asserted in its January 5, 2004 response that this research was conducted under the above-referenced research project.

On June 4, 1998; June 1, 1999; August 24, 2000; and December 21, 2000, persons with chronic inflammatory demyelinating polyneuropathy (CIDP) were enrolled as subjects in the above-referenced research.

OHRP finds that the protocol approved by the DUCM IRB did not contemplate the enrollment of subjects with CIDP and, as a result, the enrollment of four subjects with CIDP constitutes 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.

The following points support this finding:

(a) There are no specific references to CIDP in the protocol.

(i) Four consent forms were submitted with the initial IRB application.

These consents are entitled:

- High-dose cyclophosphamide for the Treatment of Severe Aplastic Anemia (SAA);
- High-dose cyclophosphamide for the Treatment of Paroxysmal Nocturnal Hemoglobinuria (PNH);
- High-dose cyclophosphamide for the Treatment of Refractory Severe Felty's Syndrome (RSFS); and
- High-dose cyclophosphamide for the Treatment of Pseudo-Felty's or Large Granular Lymphocyte Syndrome (PFS).

OHRP notes that the four consents mirror the subsections in the “Background and Rationale” section of the protocol. There is no reference to CIDP in any of the consent forms or in the “Background and Rationale” section of the protocol.

(ii) None of the references at the end of the protocol refer to CIDP.

(b) When the term “refractory autoimmune diseases” is used in the protocol, only two examples of refractory autoimmune diseases are provided throughout the protocol: Felty’s Syndrome and Pseudo-Felty’s Syndrome.

(i) The October 1996 version of the protocol submitted to the IRB contains the following objective: “To determine whether this regimen is efficacious in treating refractory cases of autoimmune disorders, i.e., Felty’s and Pseudo-Felty’s Syndromes not responsive to conventional therapeutic approaches.”

(ii) Section 3.1, entitled “Background and Rationale,” focuses on Severe Aplastic Anemia (SAA) and contains the following subsections: PNH, Allogeneic BMT for SAA, Immunosuppressive therapy for SAA, high-dose cyclophosphamide without BMT for SAA, and Management of PNH. The last subsection is entitled “Refractory Autoimmune Disorders – Felty’s syndrome and pseudo-Felty’s syndrome.” This subsection consists entirely of one paragraph about Felty’s syndrome and another about pseudo-Felty’s syndrome. The section ends with the following statement: “This being the background, we hypothesize that the severe neutropenia of both FS and P-FS could benefit from high-dose cyclophosphamide, which could also produce an improvement in both the associated autoimmune diseases and, in the case of LGL syndrome, the lymphoproliferative disorders.”

(iii) The inclusion criteria in the protocol state: “In addition, all patients with severe autoimmune disorders refractory to conventional treatment, specifically Felty’s syndrome and pseudo-Felty’s syndrome, will be included.”

(iv) Section 9.0, entitled “Statistical Considerations,” contains the following statement: “There are two distinct studies entailed in this project. One is a pilot study to evaluate the efficacy of cyclophosphamide in treating PNH and refractory autoimmune disorders, i.e., Felty’s syndrome and pseudo-Felty’s syndrome; the other is a Phase II trial to estimate the effectiveness of high-dose cyclophosphamide in SAA.”

Section 9.3, "Stopping rules," contains the following sentence: "Similar rules apply to patients with PNH and refractory Felty's syndrome and pseudo-Felty's syndrome."

(c) On the two occasions that the principal investigator amended the protocol and specifically listed examples of refractory autoimmune diseases to be studied, CIDP was not included in the lists.

(i) The principal investigator submitted a "clarifying amendment" in December 1996 in which he explained that he wished to add to the list of refractory autoimmune disorders to be included in the protocol, saying, "These conditions are included under the term 'refractory autoimmune disease' but want [*sic*] to specifically mention the diseases to be investigated." He specifically mentioned hemolytic anemia, disseminated lupus erythematosus, lupus anticoagulant, scleroderma, and immune thrombocytopenia purpura. CIDP was not included in the list.

Two additional consents were submitted along with this amendment. One consent was entitled "High-dose cyclophosphamide for the Treatment of Refractory Severe Autoimmune Hemolytic Anemia." The other consent was entitled "High-dose cyclophosphamide for the Treatment of Refractory Autoimmune Disease." Though this is not explicitly stated in the amendment submission or in the consent form, it appears that the principal investigator planned to use this consent for the last four disorders he included in the paragraph above. OHRP again notes that CIDP was not included in the list of refractory autoimmune diseases to be studied.

(ii) In September 1997, the principal investigator asked the IRB for an addendum to allow a patient with advanced graft-versus-host disease (GVHD) to be enrolled in the study, saying that chronic GVHD includes a significant autoimmune component. The rationale in the addendum begins with the following statement: "Under Refractory Autoimmune Disorders in the original protocol are included Refractory Severe Autoimmune Diseases. These conditions include: Autoimmune Hemolytic Anemia, Immune Thrombocytopenia, Evan's syndrome, Felty's syndrome, paraneoplastic penphigies [*sic*], autoimmune neutropenia and systemic lupus erythematosus." CIDP was not included in the list.

(d) The consent document entitled "High-dose Cyclophosphamide for the Treatment of Refractory Autoimmune Disease" that was signed by the four subjects with CIDP was not an appropriate consent document to be used for persons with CIDP.

(i) The first section of the consent is entitled “Purpose of Study” and consists of the following:

You have refractory autoimmune disease, a condition associated with rheumatoid arthritis in up to 1% of the cases. This syndrome causes your white blood cell count to be very low and makes you prone to potentially life-threatening infectious diseases. Your disease has not shown a good response to the standard treatment for this condition.

OHRP notes that CIDP is explained in the following manner on the Web site for the National Institutes of Health, on the National Institute of Neurological Disorders and Stroke’s (NINDS) Chronic Inflammatory Demyelinating Polyneuropathy (CIDP) Information Page at <http://www.ninds.nih.gov/disorders/cidp/cidp.htm>:

CIDP is a neurological disorder characterized by progressive weakness and impaired sensory function in the legs and arms. The disorder, which is sometimes called chronic relapsing polyneuropathy, is caused by damage to the myelin sheath (the fatty covering that wraps around and protects nerve fibers) of the peripheral nerves....It often presents with symptoms that include tingling or numbness (beginning in the toes and fingers), weakness of the arms and legs, loss of deep tendon reflexes, fatigue and abnormal sensations. CIDP is closely related to Guillain-Barre syndrome and it is considered the chronic counterpart of that acute disease.

OHRP notes that it is unlikely that the description of refractory autoimmune disease in the consent form could be construed as including CIDP.

(ii) The “Alternatives” section of the consent document states: “You have been told that the other treatments you can have if you do not join this research study is [*sic*] the administration of low dose methotrexate (an anti-cancer drug) or removal of your spleen.”

OHRP notes that the NINDS Web page referenced above contains the following information in a section entitled “Is there any treatment?”:

Treatment for CIDP includes corticosteroids such as prednisone, which may be prescribed alone or in combination with

immunosuppressant drugs. Plasmapheresis (plasma exchange) and intravenous immunoglobulin (IVIg) therapy are effective. IVIg may be used even as a first-line therapy. Physiotherapy may improve muscle strength, function and mobility, and minimize the shrinkage of muscles and tendons and distortions of the joints.

OHRP notes that it is unlikely that the description of alternatives in the consent form could be construed as being applicable to persons with CIDP.

Since the protocol approved by the IRB did not contemplate the enrollment of subjects with CIDP, the enrollment of four subjects with CIDP constitutes (1) the conduct of non-exempt human subjects research without IRB approval and (2) the implementation of a protocol change without prior IRB review and approval.

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

(a) Section 46.116(a)(1):

(i) An explanation of the purposes of the research.

In particular, OHRP notes the following about the consent entitled "High-dose Cyclophosphamide for the Treatment of Refractory Autoimmune Disease" (the consent form signed by the four subjects referenced in the allegations of noncompliance) :

- The section entitled "Purpose of the Study" consists of the following two paragraphs:

You have refractory autoimmune disease, a condition associated with rheumatoid arthritis in up to 1% of the cases. This syndrome causes your white blood cell count to be very low and makes you prone to potentially life-threatening infectious diseases. Your disease has not shown a good response to the standard treatment for this condition.

This study will test if high-dose cyclophosphamide, a kind of anti-cancer drug treatment, will cure this disorder in a large number of patients, and to see if G-CSF, a drug which

will shorten the time for blood counts to return to normal
[sic].

- This section does not adequately define the general term “refractory autoimmune disease,” which is referred to as a disease, a condition and a disorder at various times in the section.
- It is misleading to use the phrase “cure this disorder” without explanation. Given that the protocol refers to this study as a Phase II study, it is also misleading to imply that a large number of patients will be enrolled and “cured”. There is no explanation of what cyclophosphamide is, if it is a drug or a biologic and if it has been approved by the FDA or not . There is no explanation for the use of high doses of this substance. The term “G-CSF” is not spelled out or explained, and the sentence referencing it is grammatically incomplete.

As a result, OHRP finds that the above-referenced informed consent document fails to adequately describe the purpose of the research.

(ii) A complete description of the procedures to be followed, and identification of any procedures which are experimental.

The section entitled “Procedures and Duration” in the consent form entitled “High-dose Cyclophosphamide for the Treatment of Refractory Autoimmune Disease” consists of the following:

You understand that the following things will be done to you. (Experimental procedures are underlined.) You will get high-dose cyclophosphamide (50 mg/kg/day) by vein once a day for four straight days. Ten days after starting cyclophosphamide you will be given G-CSF (5 ug/kg/day) by vein once every day until your blood cell counts have recovered. Multiple samples of blood and perhaps bone marrow will be taken. Some of the samples may be used for research. Approximately 2 teaspoons of blood will be taken each time and ½ teaspoon of bone marrow will be taken. Blood samples will be drawn once before the study, then once a week for about 3 months. Bone marrow biopsies will be done once before the study, then every 6 months for one year and then once a year for 3 years.

- The paragraph above fails to provide specifics about the administration of both the cyclophosphamide and the G-CSF. It also would have been helpful to provide specifics about the setting

of the research procedures (e.g., inpatient hospital ward versus outpatient clinic).

- One sentence above states that “perhaps” bone marrow samples will be taken, but a few sentences later it specifies the intervals in which bone marrow biopsies will be done.
- It is unclear what is meant by the phrase “taken each time” in the following sentence in the paragraph above: “Approximately 2 teaspoons of blood will be taken each time....”
- The paragraph above states, “Some of the samples will be used for research.” There is no indication whether the samples will be used for this research study or stored for a definite or indefinite period of time to be used for other research studies.
- In Section 7.0, entitled “Toxicity and Complications,” Subsection 7.1 on page 12, the protocol states that subjects will be administered antiemetics to prevent or treat nausea. There is no mention of the use of antiemetics in the consent form.
- In Section 6.0, entitled “Treatment Program,” the protocol states on page 11, “Malnutrition is expected due to lack of food intake after treatment. Intravenous alimentation should be initiated until oral food intake becomes adequate as recovery ensues.” There is no mention of intravenous alimentation in the consent form.
- The protocol states on page 11, “Patients will receive fungal prophylaxis using fluconazole until a fungal infection is documented or clinically suspected, at which point intravenous fungal therapy should be initiated.” There is no mention of the intravenous fungal therapy in the consent form (and no mention of the risk of fungal infection in the “Risks” section of the consent form).
- Protocol Section 6.4, entitled “Post-treatment Evaluation,” includes tests to be conducted during the initial post-treatment period prior to marrow recovery and after evidence of marrow recovery. There is no information about these tests in the consent form.

As a result, OHRP finds that the above-referenced informed consent document fails to adequately describe the procedures to be followed and fails to clearly explain which procedures are experimental.

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

(i) The “Risks” section of the consent form entitled “High-dose Cyclophosphamide for the Treatment of Refractory Autoimmune Disease” consists of the following paragraph:

The risks of high-dose cyclophosphamide may include nausea and vomiting during the first week of treatment, diarrhea, swelling due to water in your tissues, pain in the bladder and bloody urine, heart failure, loss of hair, and a drop [*sic*] your blood cell counts with fever, infection, and bleeding. These risks can lead to death. The treatment may prevent you from being able to have children. G-CSF may cause headache, fever, chills, decreased appetite, pain in bones, chest, belly, joints and rash [*sic*].

- The “Risks” section in the consent form fails to mention that there is a risk associated with having a history of herpes simplex virus infection.
- The “Risks” section also fails to mention the “universal” risk of hyperpigmentation that is included in the “Risks” section of the protocol.
- It is unclear from the presentation and grouping of risks which “risks can lead to death.”
- Rash is listed in the consent form solely as a side effect of G-CSF administration. However, Protocol Section 7.1.7 states “Ten to 20% of patients may develop a diffuse maculopapular rash 24 to 74 hours following cyclophosphamide. The rash usually clears in 24 to 48 hours.” The consent form fails to list rash as a risk of cyclophosphamide administration.
- A number of possible serious side effects of cyclophosphamide are reported in the literature (lower back pain, lower side pain, unusual bruising or bleeding, pinpoint red spots, headache, nasal congestion, agitation, confusion, missed menstrual periods,

decreased appetite, soreness of the mouth and throat) that are not included in the consent form.

- As stated below in (2)(a)(ii) of this letter, the risk of fungal infection is contemplated in the protocol but is not included in the consent form.

As a result, OHRP finds that the above-referenced informed consent document fails to adequately describe the risks and discomforts of the study.

(ii) The same consent document contains a section entitled “Pregnancy Waiver Section,” which states the following: “We do not know what impact these drugs will have on your fertility (your ability to conceive a child or impregnate a female.)” OHRP notes that the “Risks” section of the protocol contains the following statement: “Alopecia, *some degree of sterility which may be permanent* [emphasis added], and hyperpigmentation are universal.” In addition, the “Risks” section of the informed consent document states, “The treatment may prevent you from being able to have children.”

OHRP finds that the “Pregnancy Waiver” section of the informed consent document does not reflect the above-referenced statement contained in the “Risks” section of the protocol and the informed consent document.

(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.

The “Benefits” section of the consent form entitled “High-dose Cyclophosphamide for the Treatment of Refractory Autoimmune Disease” consists of the following paragraph:

The exact chance that this treatment will cure you is unknown. To date no patients with refractory autoimmune disease have been treated with this protocol, although it was proven to be successful in closely allied immune disorders, such as severe aplastic anemia.

This section fails to indicate that the subject may not benefit from participation in the research project. In addition, it is misleading to state that the use of this “treatment” has been proven “successful” without providing additional information about the pilot study of ten subjects to which the principal investigator is referring.

As a result, OHRP finds that the above-referenced consent form fails to appropriately describe the reasonably foreseeable benefits of the research.

OHRP also has the following concerns:

(3) [Redacted]

(4) [Redacted]

(5) [Redacted]

(6) [Redacted]

(7) [Redacted]

(8) [Redacted]

Required Action: By December 15, 2005, please submit to OHRP a corrective action plan that addresses the findings above, and a response to the questions and concerns 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
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