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: 301-435-0668
FAX: 301-402-2071
E-mail: pmcneilly@osophs.dhhs.gov

December 4, 2002

C. Bradley Moore, Ph.D.
Vice President for Research
The Ohio State University
Office of Research
208 Bricker Hall
190 North Oval Mall
Columbus, OH 43210-1321

RE: Human Research Subject Protections Under Multiple Project Assurance (MPA) M-1238

Research Publication: Charcot-Marie Tooth Neuropathy Gene Mutation and Their Role in Pathogenesis
Principal Investigator: Zarife Sahenk, M.D.

Dear Dr. Moore:

The Office for Human Research Protections (OHRP) has reviewed the Ohio State University's (OSU) September 27, 2000 and November 4, 2002 reports submitted in response to OHRP's August 7, 2000 and September 25, 2002 letters, respectively, regarding the above-referenced research.

Based on the review of your reports, OHRP makes the following determinations regarding the above-referenced research:

(1) Department of Health and Human Services (HHS) regulations at 45 CFR 46.116(a)(2) require that informed consent include a description of any reasonably foreseeable risks or discomforts to the subjects from participation in the research. OHRP finds that the Institutional Review Board (IRB)-approved informed consent document failed to describe (a) the pain and discomfort associated with injection of local anesthetic; and (b) sudden sharp pain that may occur when the nerve is severed even if local anesthesia is used during the sural nerve biopsy.

Corrective Action: OHRP notes that the informed consent document for the above-referenced research has been revised to include a description of the discomfort associated with injection of local anesthetic and the possibility of pain associated with severing of the sural nerve.

(2) In its August 7, 2000 letter, OHRP presented an allegation that the OSU IRB and the investigator failed to ensure that risks to subjects were minimized by using procedures which are consistent with sound research design and do not unnecessarily expose subjects to risk, as required by HHS regulations at 45 CFR 46.111(a)(1). It was specifically alleged that (i) the location of the incision of the sural nerve biopsy could have been performed at a more distal site, thus minimizing the potential area of sensory deficits; and (ii) prior to performing sural nerve biopsy, screening the subject with an electromyogram (EMG) or nerve conduction velocity (NCV) study could have allowed a better estimation of the distribution of the sural nerve innervation and of the expected area of sensory deficits post biopsy.

OHRP notes that OSU's September 27, 2000 report stated the following:

> (a) "The sural nerve at the ankle level is subject to repeated trauma due to rubbing by shoes, therefore the specimen taken at this level is less than optimal for evaluation."
>
> (b) "An incision at the ankle level predisposes patients to more frequent postoperative infections, because the skin and the subcutaneous tissue is significantly thinner than the site of the lower calf midline incision, therefore compromising repair of the surgical incision and wound healing."
>
> (c) "... although EMG/NCV tests may be used to provide clinical diagnostic information when disorders of nerves or muscles are suspected, such tests provide no information regarding the size of the area of skin innervated by the sural nerve. In addition, EMG/NCV studies are expected to be abnormal in persons diagnosed with CMT1A even before the onset of clinical symptoms."

Based on the above statements and other materials provided in your reports, OHRP finds that the above allegation could not be substantiated.

(3) In its August 7, 2000 letter, OHRP presented an allegation that the investigators failed to obtain legally effective informed consent under circumstances that provided the subject with sufficient opportunity to consider whether or not to participate and that minimized the possibility of coercion or undue influence, as required by HHS regulations at 45 CFR 46.116. OHRP is unable to make a finding regarding this allegation.

(4) Based on the review of your reports, OHRP finds that OSU has adequately addressed the additional questions and concerns raised in its September 25, 2002 letter.

At this time OHRP would like to provide OSU with the following guidance:

> (5) HHS regulations at 45 CFR 46.116(a)(1) stipulate that informed consent include a description of the procedures to be followed and identification of any procedures which are experimental. OHRP notes that your November 4, 2002 report stated:
>
> > (a) "... the examinations done in the University Hospital pathology Laboratory were critical in establishing the extent of the Subject's neuropathy and, most importantly, in selecting the most viable sections of the nerve to transplant into Study mice."
> >
> > (b) "... the Investigator clarified that the morphological studies performed in the University Hospital Pathology Laboratory were a small, but critical step in the research design and necessary for selecting viable nerve tissue from the resected sural nerve to transplant into the Study mice."
>
> OHRP believes that since the transfer of tissue samples to the University Hospital Pathology Laboratory were part of the research design, and not solely for routine pathological analysis required by hospital policy, it appears that it may have been appropriate to include the description of such a procedure in the informed consent document.

As a result of the above determinations, there should be no need for further involvement of OHRP in this matter. OHRP appreciates the continued commitment of your institution to the protection of human research subjects. Please do not hesitate to contact me should you have any questions.

Sincerely,

Patrick J. McNeilly, Ph.D.
Compliance Oversight Coordinator
Division of Compliance Oversight

cc: Dr. Judith Neidig, Director, Office of Responsible Research Practices, OSU
Dr. Susan Koletar, Chair, Biomedical Sciences IRB, OSU
Dr. Don Dell, Chair, Behavioral and Social Science IRB, OSU
Commissioner, FDA
Dr. David Lepay, FDA
Dr. Melody H. Lin, OHRP
Dr. Michael Carome, OHRP
Mr. George Gasparis, OHRP

Dr. Jeffrey Cohen, OHRP
Dr. Harold Blatt, OHRP
Mr. Barry Bowman, OHRP