DEPARTMENT OF HEALTH & HUMAN SERVICES

Office of the Secretary
Office of Public Health and Science

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September 4, 2002

Winfred M. Phillips, D.Sc.
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University of Florida
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PO Box 113125
Gainesville, FL 32611-3125

RE: Human Research Subject Protections Under Multiple Project Assurance (MPA) M-1266

Research Project: Neural Tissue Transplantation in Syringomyelia: Feasibility and Safety
Principal Investigator: Dr. Edward D. Wirth
HHS Project Number: 5M01 RR0082-27
IRB Project Number: 325-1996

Research Publication: Wirth ED et al. Feasibility and Safety of Neural Tissue Transplantation in Patients with Syringomyelia. Journal of Neurotrauma. 2001;18:911-929.

Dear Dr. Phillips:

The Office for Human Research Protections (OHRP) has reviewed the University of Florida Gainesville's (UF) May 10, 2000, August 10, 2000 and May 10, 2002 reports and letters regarding the above-referenced research.

Based upon its review, OHRP makes the following determinations relative to UF's protections for human subjects in this research project:

(1) Department of Health and Human Services (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.

OHRP finds that an Oversight Committee, intended to "periodically monitor the study data for adverse effects, problems that may arise from the consent process, and to recommend whether the study should be continued or modified," had not met; as stipulated in the IRB-approved protocol. The protocol indicated that the Oversight Committee was to meet via teleconference approximately twice per year and produce an annual report to be submitted to the UF IRB.

Corrective action: OHRP acknowledges that in its May 10, 2000 letter to OHRP, UF reported the fact that the Oversight Committee had not met, as stipulated in the UF IRB-approved protocol. OHRP notes that the UF IRB counseled the principal investigator in the above-referenced research on the need to submit all proposed changes in approved research to the IRB for review and approval. The UF IRB required the principal investigator to convene an Oversight Committee which met on August 18, 2000; and its report was received by the UF IRB on September 7, 2000. In addition, the UF IRB has modified its continuing review report form to require that if such a committee has been listed in the protocol, the principal investigator should provide information on all oversight committee reviews to the IRB, as well as its latest report. OHRP finds that these corrective actions adequately address the above finding and are appropriate under the UF MPA.

(2) In its letter of March 5, 2002, OHRP expressed concern that the investigators, in contravention of the requirements of HHS regulations at 45 CFR 46.103(b)(4)(iii), may have deviated from the IRB-approved protocol because the complainant did not have both clinical and radiological evidence of progressive syringomyelia, and thus may not have met eligibility criteria for this study. OHRP acknowledges UF's position that the inclusion/exclusion criteria and the informed consent did not require radiological evidence of progressive syringomyelia, and UF's statement that "[w]hile we understand that the 'study design' section of the protocol and the report published by Dr. Wirth contained summary language that loosely combined two out of the 14 distinct inclusion criteria, we have confirmed with the principal investigator that these references were summary in nature and not intended in any way to contradict the actual inclusion/exclusion criteria expressly detailed...in the protocol."

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

During its review, OHRP found substantive discrepancies and ambiguities within different sections of the IRB-approved protocol (e.g., study design section, inclusion criteria, and informed consent document) regarding patient eligibility for the above-referenced research. OHRP finds that in failing to resolve these discrepancies during the initial and continuing review of the research prior to September 1999, the UF IRB failed to ensure that the requirements of HHS regulations at 45 CFR 46.111(a)(1) were satisfied. Specifically, OHRP notes the following:

(a) With respect to the IRB-approved protocol in effect at the time of the complainant's enrollment in May 1999, the study design section (UF's August 10, 2000 report, Tab 2A, p. 20) stated that, "approximately 10 patients with *clinical and radiological evidence of progressive syringomyelia* [italics added for emphasis] will be enrolled." In addition, the published report on the first two subjects enrolled in the study (Wirth et al. Feasibility and Safety of Neural Tissue Transplantation in Patients with Syringomyelia. J Neurotrauma 2001;18:911-929) stated that, "[p]atients were considered for participation in the study if they presented with *both clinical and radiological evidence of progressive syringomyelia* [italics added for emphasis]..."

(b) The inclusion criteria (UF's August 10, 2000 report, Tab E, p. 19) included the following, among others:

- "Symptoms of progressive syringomyelia, i.e., new onset of increased pain, decreased sensation or decreased hand or motor function.

- Evidence of syringomyelia on MRI exam. The syrinx must be located primarily in the thoracic spinal cord.

- No motor function (Grades A-B on the ASIA/IMSOP Impairment Scale; see Appendix) or incomplete motor function (ASIA Grades C-D below the most caudal end of the syrinx, with or without residual sensory function to be documented on a screening neurological exam. Patients who are Grade D, however, must also have progressive loss of function due to spasticity and /or loss of sensation.

- Determination by the neurosurgeon (R.F.) that the patient would potentially benefit from a surgical procedure to treat the *expanding syrinx* [italics added for emphasis]..."

(c) The IRB-approved consent form (UF's August 10, 2000 report, Tab 2A, p. 41) stated "Dr. Fessler will determine if you would potentially benefit from an operation to treat the *expanding cyst* [italics added for emphasis] in your spinal cord.

(d) On September 1, 1999 the IRB approved a modification to amend the inclusion criteria to included the following: "Evidence of syringomyelia on *MRI exam, which must show a progressively expanding cyst* [italics added for emphasis] with a suitable site for transplantation at spinal level C5 or below..."(UF's August 10, 2000 report, Tab G, p. 19).

Action 1–Required: OHRP acknowledges the above-referenced research has completed enrollment. However, OHRP requests that by October 15, 2002 UF submit a corrective action plan to ensure that all future or ongoing research conducted at UF satisfies the requirements under HHS regulations at 45 CFR 111(a)(1).

(4) Regarding the complainant's allegation that the investigators failed to provide an adequate safe mode of transportation between the institution and the subject's home, OHRP is unable to make a finding.

(5) Regarding the complainant's allegation that he suffered significant injury (i.e., paralysis and increased pain) as a result of his participation in this research, OHRP is unable to make a finding.

(6) HHS regulations at 45 CFR 46.116 stipulate that an investigator shall seek consent only under circumstances that minimize the possibility of coercion or undue influence. Regarding the complainant's allegation that his interaction with the hospital's public relations representative constituted coercion or undue influence, OHRP notes the following:

> (a) The complainant stated that following his screening evaluation in March 1999 he was "introduced to the public relations representative of the university...who informed me I would be interviewed by 60 minutes, 20-20, CNN, etc...."
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> (b) UF stated that subjects were contacted by UF's Public Relations Department "to help protect their privacy and confidentiality in the face of media interest and inquiry" and "should in no way be construed as 'unduly influencing' any subject's voluntary participation in the study."

OHRP is unable to make a finding regarding this allegation. OHRP notes that informed consent is an ongoing process that continues after initial documentation, and that the IRB should ensure that procedures undertaken as part of a research protocol, such as interactions with the hospital's public relations department, are conducted in an environment that minimizes the possibility of coercion and undue influence.

(7) HHS regulations at 45 CFR 46.116 and 46.117 stipulate that, except as provided elsewhere under the HHS regulations, no investigator may involve a human being as a subject in research unless the investigator has obtained and documented the legally effective informed consent of the subject or the subject's legally authorized representative.

OHRP finds that screening procedures were performed expressly for the purpose of determining eligibility for the above-referenced research protocol, without the investigators first obtaining and documenting the legally effective informed consent of the subjects. Specifically, OHRP notes the following:

(a) The IRB-approved consent form (UF's August 10, 2000 report, Tab 2A, p. 41) stated that "[y]ou will have an initial screening clinic visit with Dr. Fessler who will perform a complete physical examination and a complete review of your condition. Dr. Fessler will determine if you would potentially benefit from an operation to treat the expanding cyst in your spinal cord. In order to make his decision, *Dr. Fessler may request additional routine diagnostic tests* [italics added for emphasis], such as MRI. If he determines that you could benefit from the surgery, and you meet the eligibility criteria for this study, you will be invited to participate..."

(b) The IRB-approved protocol (UF's August 10, 2000 report, Tab 2A, p. 22) stated that "[e]ach patient will undergo a comprehensive interview in which the history of the initial injury, if applicable, and development of new symptoms will be reviewed in detail...A thorough neurologic and general physical examination will be performed on each patient. The social worker...will also complete a detailed psychological evaluation of each patient..."

(c) The IRB-approved protocol contained a "Psychosocial Worksheet for Neural Tissue Transplantation Subjects" (UF's August 10, 2000 report, Tab A, Appendix) which includes identifiable private information on the subject including name, date of birth, social history, financial data, and a "Brief Mental Health Exam."

(d) UF's May 10, 2002 letter further described the screening and consent process as follows:

> "...patients who were interested in the possibility of surgical treatment, including fetal transplant, for the syringomyelia underwent an initial clinic visit with Dr. Fessler that took place before they were invited to participate in the research...If a patient wished to explore the fetal transplant option, Dr. Fessler provided the patient a copy of the research informed consent and invited the patient back for a two-day screening visit to further evaluate the patient's surgical options.
>
> On day one of the return visit, with informed consent in-hand, patients underwent further education and evaluation regarding their surgical options. This evaluation included a meeting with the transplant team, a pain assessment, respiratory effort testing, and MRI. *On the morning of day-two, if the patient was still interested in the fetal transplant option, the patient signed the study informed consent, and underwent evaluation and screening for eligibility to participate in the study* [italics added for emphasis]. If the subject met eligibility criteria, he/she returned a few weeks later to undergo the fetal tissue transplant.

> The IRB did not waive requirements for documenting or obtaining informed consent. All subjects enrolled in the protocol executed legally
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> effective informed consent *before they underwent any study interventions* [italics added for emphasis]."

Action 2–Required: OHRP acknowledges the above-referenced research has completed enrollment. OHRP requests that by October15, 2002 UF submit a corrective action plan covering all ongoing and future research to ensure that no research-related interventions are conducted prior to the investigator obtaining and documenting legally effective informed consent in accordance with, and to the extent required by, HHS regulations at 45 CFR 46.116 and 46.117.

(8) HHS regulations at 45 CFR 46.116(a) stipulate the basic elements for required for informed consent. OHRP expressed concern in its March 5, 2002 letter that the informed consent documents reviewed and approved by the UF IRB between September 4, 1996 and September 9, 1999 failed to include a complete description of the procedures to be followed as required by HHS regulations at 45 CFR 46.116(a)(1). Specifically, the IRB-approved protocol stated that patients with a positive pregnancy test were to be excluded from this study, yet the informed consent document did not mention that a pregnancy test was required. OHRP acknowledges UF's statements in its May 10, 2002 letter that no women of childbearing age were enrolled in the study. Further, the UF IRB has corrected this oversight by amending the reviewer's checklist such that whenever a protocol lists pregnancy in the exclusion criteria, reviewers will ensure that the informed consent document contains a statement that informs women of childbearing age of the pregnancy test requirement. OHRP finds that UF has adequately addressed this concern.

(9) Under HHS regulations at 45 CFR 46.111(a)(7), the IRB shall determine that there are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data. In its letter of March 5, 2002, OHRP expressed concern regarding the complainant's allegation that the name of another subject who had previously participated in the research protocol was disclosed to the complainant. OHRP acknowledges UF's statement in its August 10, 2000 report, that "it is possible that someone outside the study team inadvertently revealed the name of another participant to the complainant." OHRP acknowledges UF's efforts to provide guidance on privacy and confidentiality issues to investigators, research staff, and other personnel. OHRP finds that UF has adequately addressed this concern.

Please do not hesitate to contact me should you have any questions.

Sincerely,

Leslie K. Ball, M.D.
Compliance Oversight Coordinator
Division of Compliance Oversight

cc: Dr. R. Peter Iafrate, Chair IRB-01, UF
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