DEPARTMENT OF HEALTH & HUMAN SERVICES

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August 21, 2003

Michael M. Gottesman, M.D.
Deputy Director for Intramural Research
National Institutes of Health
Building 1, Room 114
Bethesda, Maryland 20892

RE: Human Research Subject Protections Under Multiple Project Assurance (MPA) M-1000

Research Project: Pathophysiology of Voice Disorders
Intramural Institute: National Institute on Deafness and Other Communication Disorders (NIDCD)
Principal Investigator: C.L. Ludlow, M.D.
Protocol Number: 92-DC-0093

Research Project: Efficacy and Pathophysiology of Botulinum Toxin for Treatment of Involuntary Movement Disorders
Principal Investigator: Mark Hallett, M.D.
Protocol Number: 85-N-195

Dear Dr. Gottesman:

The Office for Human Research Protections (OHRP) has reviewed NIH's (NIH) December 7, 2001 and April 11, 2003 reports that were submitted in response to OHRP's October 29, 2001 and March

10, 2003 letters to NIH regarding the allegations of possible noncompliance with the Department of Health and Human Services (HHS) regulations for the protection of human subjects (45 CFR Part 46) involving the above-referenced research. OHRP acknowledges NIH's April 11, 2003 report that stated the complainant was not a participating subject for the research project entitled "Behavioral Medicine Future Years" [NIH project # Z01 MH00182-13].

Based upon its review of NIH's December 7, 2001 and April 11, 2003 reports, as well as additional documentation submitted by NIH on May 30, 2003, OHRP makes the following determinations regarding the above-referenced research:

(1) In its October 29, 2001 letter, OHRP presented the allegation that the investigators failed to obtain the legally effective informed consent of a subject prior to enrollment in the above-referenced research projects, as required by HHS regulations at 45 CFR 46.116. In specific, it was alleged by the complainant that she underwent research interventions including a sodium amytal interview, psychiatric exams and vocal chord testing for the above-referenced research projects without giving her legally effective informed consent for such research interventions.

(a) NIH's December 7, 2001 report stated the following:

(i) "On 3/6/95 the complainant came to the NIH and went over the consent with the patient care coordinator, she initialed and dated the sections relevant to the speech recording and the sodium amytal interview, and signed the consent form for protocol 92-DC-0093, 'Pathophysiology of Voice Disorders.' The complainant's signature was witnessed by the patient care coordinator."

(ii) "The same day, 3/6/95, the complainant received speech testing by the speech pathologist."

(iii) "On 4/18/95, the complainant met with the staff otolaryngologist and another physician on the project who reviewed the neurophysiological laryngeal electromyography testing, a family history and pedigree analysis by a social worker, and a psychiatric interview. The complainant initialed and dated each of the relevant sections of the consent and signed the final page. Her signature was witnessed by the 2 physicians."

(iv) "Conclusion: The complainant's allegations are incorrect, on each occasion prior to any of the research procedures she gave informed written consent to

participate in each of the research procedures that were administered. **The research procedures consented for and administered were: speech testing, sodium amytal interview, neurophysiological laryngeal electromyography, family history and pedigree testing by a social worker, and a psychiatric interview by a psychologist."** (emphasis added)

(b) NIH's December 7, 2001 report enclosed copies of the informed consent documents that were signed by the complainant on March 7, 1995 and April 18, 1995.

In its March 10, 2003 letter, OHRP expressed concerned that the speech testing research procedure performed on March 6, 1995 as described in (1)(a)(ii) above was administered prior to obtaining and documenting the legally effective informed consent of the complainant for such research intervention since the informed consent document for protocol 92-DC-0093 was signed by the complainant on March 7, 1995.

(c) NIH's April 11, 2003 report stated the following:

"As described by the NIH investigator, in September, 1989, the complainant enrolled in a study at NIH entitled: Efficacy and Pathophysiology of Botulinum toxin for Treatment of Involuntary Movement Disorders," [*sic*] 85-N-0195. This study included speech testing or recording on multiple occasions and the complainant signed the informed consent document. **In November, 1994, the complainant was seen at NIH for a follow-up examination under the same protocol** (emphasis added). Based on symptom progression, the complainant was invited back to NIH for further evaluation. **On March 6, 1995 when the complainant returned to the NIH she was still considered by the investigator to be enrolled in 85-N-0195 and received both a neurological examination and was seen by the speech pathologist for a review of her recent speech history and a speech recording** (emphasis added). Her consent to participate in the new study, 92-DC-0093, occurred the next day."

(d) Additional documentation submitted by NIH on May 30, 2003 for protocol 85-N-195 included the following:

(i) A copy of the informed consent document that was signed by the

complainant on September 13, 1989 that stated:

> "Under this protocol we would be willing to continue to treat your disorder **for up to two years**." (emphasis added)

(ii) A copy of the November 15, 1994 electromyography report for the complainant that stated:

> "Study performed: Lx EMG w/endoscopic hooked-wire PCA electrode insertion."

Based upon a review of submitted documentation, OHRP finds the allegation that the complainant underwent a sodium amytal interview, psychiatric exams and vocal cord testing for protocol 92-DC-0093 without the investigator obtaining her legally effective informed consent was not substantiated. With regard to protocol 85-N-195, OHRP notes that the IRB-approved informed consent document signed by the complainant on September 13, 1989 did not include a description of any long-term follow-up procedures following study intervention. As described in (1)(d)(i), OHRP further notes that the complainant's participation in protocol 85-N-195 formally ended on September 13, 1991. Accordingly, OHRP finds that the investigator did not obtain and document the legally effective informed consent of the complainant prior to administering the electromyography research procedure as described in (1)(d)(ii) on November 15, 1994 and the speech testing research procedure as described in (1)(a)(ii) on March 6, 1995.

(2) In its October 29, 2001 letter, OHRP presented the allegation that the investigators failed to adequately maintain the confidentiality of data related to a research subject, as required by HHS regulations at 45 CFR 46.111(a)(7). In specific, it was alleged by the complainant that data relating to her psychiatric evaluation and sodium amytal interview were shared with a neurologist who is not associated with the research.

(a) The complainant's August 28, 1995 letter to Dr. Allen Braun [consulting NIH neurologist associated with protocol No. 92-DC-0093] stated the following:

> "I would like to have the records from the March 7, 1995 Neurological Exam sent to me at the above address. If you prefer you can send them to: [complainant's neurologist]"

(b) NIH's December 7, 2001 report stated the following:

(i) "Later on 3/6/95 the complainant was seen by a consulting neurologist, because of her neurological complaints. The examination was negative except for the Complainant's report of spasmodic dysphonia of 20 years duration. An eye consult was recommended because of the Complainant's vision complaints and an MRI because of her complaints of migraine headaches."

(ii) "The information released was not research information, only patient care information was released pertinent to her neurological status and recommendations for clinical care as follows:

- the eye examination results 4/19/95
- the MRI report 4/17/95
- the neurological examination report 3/6/95
- **and patient care recommendations previously sent to the patient**" (emphasis added)

(iii) "There was a reasonable and good faith belief that release of the patient care recommendations was necessary to protect the patient's life. Since the risk to the complainant would have come from her accumulating [*sic*] medications prescribed by the neurologist this was a compelling safety issue. For this reason, the NIH staff sent the patient care recommendations to the prescribing physician."

(c) NIH's December 7, 2001 report enclosed a copy of the May 18, 1995 patient care information letter to the complainant from the principal investigator.

(d) The informed consent documents signed by the complainant on March 7, 1995 and April 18, 1995 for protocol No. 92-DC-0093 stated the following:

(i) "Family History and Pedigree Analysis

All of the information you or your family members provide will be held in total confidence and will not be shared with anyone else at the NIH

or elsewhere."

(ii) "Psychiatric Examination

All of the information you provide will be held in total confidence and will not be shared with anyone else either at the NIH or elsewhere."

(iii) "Affective Analysis of Videotaped Interview

All of the information you provide will be held in total confidence and will not be shared with anyone else either at the NIH or elsewhere."

(e) The minutes of the June 19, 1991 National Institute of Neurological Disorders and Stroke (NINDS) subpanel [Institutional Review Board (IRB)] stated the following with regard to the initial approval of Protocol No. 92-DC-0093:

> "Discussion:...There was discussion as to how data, particularly that derived from the psychiatric interview would be handled by the investigator. A particular question was if psychiatric abnormalities were identified would they be shared with the private physician. The investigator indicated that this was a research test and that the research findings were held confidential unless the patient wished to have them discussed with he/she [*sic*] or forwarded to their private physician. Specifically, the investigator indicated that data or information would not be given to other individuals without consent of the patient."

In its March 10, 2003 letter, OHRP expressed concern that the May 18, 1995 patient care information letter sent to the complainant with a copy to the complainant's physician and a subsequent copy to the complainant's neurologist on August 31, 1995, contained research information obtained by the research affiliated social worker and psychologist during the complainant's participation in Protocol No. 92-DC-0093. Based on the information in (2)(a) above, OHRP expressed concern that the complainant did not specifically request or authorize that a copy of the May 18, 1995 patient care information letter be sent to the complainant's

neurologist.

(f) NIH's April 11, 2003 report stated the following:

> "As indicated before, although the protocol consent, in part, indicated that psychiatric examination information would be held in 'total confidence,' information was shared by the investigator because of the investigator's concerns for the patient's safety."

Based on the unequivocal assurances of confidentiality expressly stated in (2)(d) and (e) above, OHRP finds that the principal investigator failed to maintain confidentiality of certain information contained in the complainant's research records by sending

unauthorized copies of the May 18, 1995 patient care information letter to the complainant's physician and neurologist.

(3) HHS regulations at 45 CFR 46.110(b)(2) permit use of expedited procedures of minor changes to previously approved research during the period for which approval is authorized. OHRP noted that on June 23, 1994, the NINDS IRB chairman approved by expedited review an amendment to Protocol 92-DC-0093 to add a ten session pilot study trial of voice therapy with patients with neurogenic adductor and abductor spasmodic dysphonia. Because the above amendment to Protocol 92-DC-0093 exceeds the limitation of minor change, OHRP was concerned that the NINDS IRB may have inappropriately employed the expedited review procedure on June 23, 1994.

NIH's April 11, 2003 report stated the following:

> "It is reasonable to conclude that the amendment to protocol 92-DC-0093 approved by the IRB Chair on June 23, 1994 presented more than a minor change in the approved protocol. On multiple occasions, we have discussed with our IRB Chairs the application of 45 CFR 46.110(b)(2). In the absence of regulatory guidance on the meaning of 'minor changes in previously approved research...' we have recommended a very conservative approach to utilization of this regulatory provision. We will redouble our efforts in this area..."

Corrective Action: OHRP acknowledges NIH's statement. OHRP notes that the joint NINDS/NIDCD/NIA [National Institute on Aging] IRB currently has in place written policies and

procedures to ensure that expedited procedures of minor changes to previously approved research during the period for which approval is authorized will comply with the requirements of HHS regulations at 45 CFR 46.110(b)(2). OHRP finds that this corrective action adequately addresses the above concern and is appropriate under the NIH MPA.

Required Action: By September 26, 2003, NIH must submit to OHRP a detailed corrective action plan to address the above findings (1) and (2). With regard to (2) above, OHRP notes that the principal investigator breached the complainant's confidentiality in a circumstance where serious and compelling concern for the complainant's well-being prompted the unauthorized disclosure of certain research information to private health care professionals. OHRP advises that the possibility of intentional disclosure of confidential information in similar circumstances, if anticipated during the conduct of the research, should be described in the informed consent document as required by HHS regulations at 45 CFR 46.116(a)(5).

OHRP appreciates the commitment of NIH to the protection of human research subjects. Please do not hesitate to contact me should you have any questions.

Sincerely,

Robert J. Meyer
Compliance Oversight Coordinator
Division of Compliance Oversight

cc: Dr. Elias Zerhouni, NIH
Dr. James F. Battey, NIDCD
Dr. Thomas R. Insel, NIMH
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