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May 10, 2010

Kevin J. Tracey, MD
Vice President for Research
North Shore - Long Island Jewish Health System
350 Community Drive
Manhasset, NY 11030

RE: Human Research Protections Under Federalwide Assurance FWA-2505

Research Project: Preventing Morbidity in First Episode Schizophrenia, Part II

Principal Investigator: Delbert Robinson, MD

HHS Protocol Number: R01 MH060004-02

Dear Dr. Tracey:

Thank you for your reports of August 5, 2009 and April 1, 2010 in response to our June 29, 2009 letter requesting that your institution investigate the following allegations of noncompliance with Department of Health and Human Services (HHS) regulations for the protection of human research subjects (45 CFR Part 46) involving the above-referenced research. As described more fully below, we did not find any of the allegations to be substantiated.

A. Determinations regarding the above-referenced research

(1) A subject enrolled in the above referenced study, extending follow-up to 52 weeks for what was originally a 12 week clinical trial comparing aripiprazole (Abilify) and risperidone (Risperdal) for treatment of first episode schizophrenia, alleged that the investigators failed to obtain and document his legally effective informed consent as required by HHS regulations at 45 CFR 46.116 and 46.117. Specifically, the subject stated that, although he was asked and agreed to participate in the follow-up study, he was not provided with all of the basic elements of informed consent required under HHS regulations at 45 CFR 46.116(a), nor was he asked to sign a consent form.

We determine that the subject did receive legally effective informed consent as required by 45 CFR 46.116, including all of the basic elements set forth under HHS regulations at 45 CFR 46.116(a). The informed consent form for the above referenced research approved by the North

Shore-Long Island Jewish (NS-LIJ) Health System/Zucker Hillside Hospital institutional review board (IRB) on July 28, 2008 described the study's purpose to "compare two medications, aripiprazole (Ablify) and risperidone (Risperdal), for the treatment of patients experiencing their first episode of schizophrenia and related disorders." While OHRP recommends against use of the word "patient" in informed consent forms because it conflates research with treatment, this description of study purpose meets the requirements of 45 CFR 46.116(a)(1). In addition, the IRB-approved consent form included: (1) the expected duration of participation (52 weeks); (2) a description of all procedures (including randomization to one of two study drugs, study visits and medical examinations, and possible cross titration to the other study drug if the initial drug proved ineffective); (3) possible risks and discomforts of the study drugs and other procedures involved in the research; (4) potential research benefits; (5) a description of appropriate alternative procedures (including receipt of the study drugs or other antipsychotic medications outside of the research); (6) a description of privacy and confidentiality protections; (7) a statement regarding the availability of compensation for research-related injury, (8) contacts for questions and in the event of injury, and (9) a statement that participation is voluntary and subjects may withdraw at any time. As with the consent process for the 12 week clinical trial, in addition to signing the consent form, the subject completed a Study Information Review in which he correctly answered ten questions about the research, including the question of whether he was required to stay in the study or could leave any time after enrollment. Thus, OHRP concludes that the informed consent process included all of the elements of informed consent required under HHS regulations at 45 CFR 46.116(a).

Moreover, OHRP finds that the subject signed the consent form on August 1, 2008, enrolling in Part II of the research which extended the clinical trial to 52 weeks. Thus, OHRP concludes that the requirements of HHS regulations at 45 CFR 46.117 were met.

(2) A subject alleged that the investigators made changes to research without prior IRB review and approval, in contravention of the requirements of HHS regulations at 45 CFR 46.103(b)(4)(iii). Specifically, the subject alleged that he complained repeatedly about intolerable side effects (including insomnia, severe anxiety, poor concentration, restlessness, poor judgment, affected coordination, and affected speech) but the medication was not discontinued, as required under the IRB-approved protocol.

The protocol for the above research establishes titration schedules for both study drugs, each with six increasing dose levels of medication. The protocol states that dosing may be advanced more slowly, or lowered, for subjects who develop side effects that do not improve with allowed adjuvant medications.

The subject's medical record reflects that when he complained of discomfort from side effects, his dosing was lowered in accordance with protocol requirements. On August 1, 2008, the date he signed the consent form for the 52-week study, he was on level 5 of the first study medication. On August 8, 2008 he was lowered to level 4 upon his request, after complaining of dry mouth, decreased short-term memory, and trouble articulating. On August 27 he was cross titrated to

the other study medication due to continuing symptoms of paranoia after 16 weeks of treatment. By October 7 the subject was on level 4 of the second medication but began reporting sleep difficulties. Nonetheless, he stated that he wanted to continue in the study. He was given Ambien to treat his sleep problems. On October 14, 2008 he was prescribed Rozerem to help him sleep, a permissible adjuvant medication under the protocol. On October 23, he complained again of sleep difficulties and was prescribed Lorazepam, another adjuvant medication. He asked about decreasing his study medication, but agreed to stay on the same level until his next appointment and try Lorazepam to control sleeping problems. On November 6 his dosing was lowered to study level 3 due to continuing complaints of disturbed sleep. On November 19 the subject reported improvement in both his concentration and his sleep, and was retained on study dose level 3. However, on December 4, the subject reported sleep difficulties again, and at his request his study dose was lowered to level 2. On December 18, the subject reported being happier with level 2 because he could sleep better, though he was still using Lorazepam as a sleep aid. On January 21, 2009, the subject reported increased sleep problems, and at his request his study medication was reduced to level 1 despite the significant risk of relapse which was explained to him. On February 23, he reported mild tremors and continuing insomnia and on March 16, he reported that he had discontinued study medication on February 24 but continued to have sleeping problems. On March 19, the subject telephoned the investigators to state that he wanted to discontinue research.

The record above reflects continuing efforts by the investigators to lower study drug dosing in order to ameliorate side effects, in compliance with protocol requirements. We therefore determine to be unsubstantiated the allegation that investigators made changes to research without prior IRB review and approval.

(3) A subject alleged that the IRB failed to ensure that the study included additional protections for subjects who were likely to be vulnerable to coercion or undue influence, as required by HHS regulations at 45 CFR 46.111(b). Specifically, the subject alleged that he was encouraged to continue in the research study even though the research interventions affected his ability to communicate his desire to discontinue participation, and the study apparently included no additional protections to protect the rights and welfare of vulnerable subjects in these circumstances.

We find that first episode schizophrenics are likely to be vulnerable to possible coercion or undue influence as human research subjects, given the nature and recent onset of their mentally disabling disease. We further find that the NS-LIJ Health System IRB did ensure that the study included appropriate additional protections to protect the rights and welfare of this subject population. First, the IRB's policy 7.4 regarding research involving incapacitated or decisionally impaired subjects ensures that the capacity of potential research subjects is assessed both prior to enrollment and then periodically throughout the course of the research. In keeping with this policy, the above protocol required that detailed psychiatric assessments be conducted throughout the course of subjects' participation to protect subjects who lose decisionmaking capacity during the study. Second, treating clinicians are involved in the initial determination of

subjects' capacity to give informed consent, and close monitoring of subjects is an integral part of the study. Third, a Data Safety and Monitoring Board with access to all relevant clinical data is required to review this protocol every 6 months to assess the adequacy of human subjects protections provided throughout the study.

We appreciate that the complainant felt that study medications prevented him from effectively communicating his desire to discontinue participation in the research. While confusion was a documented side effect of study medications, the subject was able to articulate his desire to lower dosing levels of the medications on several occasions. Since these requests to lower dosing were addressed, and since the subject ultimately did discontinue participation upon his stated request, we conclude that appropriate additional protections were provided to protect the rights and welfare of the subjects enrolled in this research, as required by 45 CFR 46.111(b).

B. Resolved Concern

The NS-LIJ Health System has adequately addressed the following concern we raised in our June 29, 2009 letter:

We expressed concern that Zucker Hillside Hospital (where the above research occurred and which is part of the NS-LIJ Health System) is not listed as a component of the NS-LIJ Health System FWA, and does not have a separate FWA approved by our office.

Institution Response: Your August 5, 2009 report states that Zucker Hillside Hospital is a facility within Long Island Jewish Medical Center, which is listed as a component of the NS-LIJ Health System FWA. This organizational arrangement adequately addresses our concern.

As a result of our determinations, there should be no need for further involvement of our office in this matter.

We appreciate 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,

Carol J. Weil, J.D.
Division of Compliance Oversight

cc:

Ms. Cynthia L. Hahn, Administrator, Office of Research Compliance, NS-LIJ Health System
Dr. Victor Fornari, Chairperson, NS-LIJ Health System IRB #1
Dr. Martin L. Lesser, Chairperson, NH-LIJ Health System IRB #2

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Dr. Delbert Robinson, NS-LIJ Health System

Dr. Margaret Hamburg, Commissioner, Food and Drug Administration (FDA)

Dr. Joanne Less, FDA

Dr. Sherry Mills, National Institutes of Health (NIH)

Mr. Joseph Ellis, NIH

Dr. Thomas R. Insel, Director, National Institute of Mental Health