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Dear Professors Elliott, Bartels, Liaschenko, Marshall, Song, Turner, Craddock, and Tronto:

I have been asked by the Chair of the Board of Regents to supplement the response he provided today to your letter of November 29, 2010. At the Board's request, my office has reviewed the facts and circumstances surrounding the CAFE research study and the suicide of Dan Markingson to which you refer in your letter. Based on the examinations of this case already conducted by the U.S. Food and Drug Administration (FDA), the Hennepin County District Court, and the Minnesota Board of Medical Practice, assisted by the Minnesota Attorney General's office, the Board of Regents determined that further University resources should not be expended re-reviewing this matter.

It is not clear from your letter that you are completely familiar with the details of these previous reviews, conducted by a number of experts and governmental units independent of the University. None of these reviews were conducted by persons with any financial or professional relationships with the researchers involved in the CAFE study.

Upon receiving the University's prompt report of Mr. Markingson's tragic suicide, the FDA conducted an extensive investigation. In its report, the FDA concluded that there was "no evidence of misconduct or significant violation of the protocol or regulations."

Subsequently, a lawsuit was commenced by Mary Weiss, the mother of Dan Markingson. Following exhaustive factual discovery, all claims against the University (and Dr. S. Charles Schulz) were dismissed by the Hennepin County District Court.

Finally, separate complaints were filed by Ms. Weiss with the Minnesota Board of Medical Practice against Drs. Steven C. Olson and S. Charles Schultz. The complaints involved very extensive allegations against both doctors. The complaints were reviewed by the Board of Medical Practice, and each of them was dismissed in its entirety.

Your letter to the Board of Regents suggests that this case may illustrate "an alarming series of ethical violations and lapses." Our response to the allegations in your letter are as follows:

1. "Recruiting a mentally ill, possibly incompetent subject into a research study, while he was under an involuntary order."

The allegation that Mr. Markingson was improperly admitted into the CAFE study was reviewed by the FDA, the District Court, and the Board of Medical Practice, and found to be completely without merit. It must be understood that Mr. Markingson was determined to be competent to consent to treatment at the time he consented to participate in the study *in the judgment of two courts and independent evaluators.* The District Court judge that ordered Mr. Markingson's stay of commitment and participation in the treatment plan specifically found that "the rights of Respondent [Markingson] have been protected throughout these proceedings," and that "the Dakota County Social Services Department has developed a plan for services to treat the Respondent's mental illness which is agreeable to the Respondent." During that court proceeding, Mr. Markingson appeared in person, was represented by counsel, and, as noted by the court, a Dakota County case manager recommended and endorsed Mr. Markingson's treatment program. In a second, and separate, judicial proceeding, the Hennepin County District Court specifically addressed the allegation that Mr. Markingson had not provided his informed consent to participate in the CAFE study, and dismissed that allegation "based on several undisputable facts."

2. "Large financial conflict of interest on the part of University researchers conducting the study."

Both Dr. Olson and Dr. Schulz received consulting fees from Astra Zeneca. Those amounts were properly reported in the University's REPA system, and all University regulations were followed. The University's examination of this allegation reveals no violation of existing conflict of interest policies.

3. "A payment structure for the study, which includes financial incentives to recruit and retain subjects, rather than provide them with standard therapy."

Studies are commonly based on budgets that increase or decrease depending on the number of participants in the study. The effort and resources expended in a study necessarily are often dependant upon the number of subjects in the study, and it is not inappropriate, unethical, or uncommon for study funding to reflect the number of participating subjects.

4. "An allegedly biased study design aimed at generating positive results for Astra Zeneca, rather than investigating a genuine scientific question."

The CAFE study involved a double-blind comparison of three similar medications. It was designed by Dr. Jeffrey Lieberman, Chair of the Department of Psychiatry at Columbia University. The study occurred at many sites around the country, and was approved by our IRB and, independently, by the IRBs at other leading institutions. There is no factual basis for this allegation.

5. "The failure of University researchers to address the legitimate concerns of Mr. Markingson's mother, Mary Weiss."

Ms. Weiss did express heartfelt concern for the welfare of her son. Her concerns not only were heard at the time, they were carefully reported in the record. However, the record also shows that all of the mental health professionals involved in Mr. Markingson's treatment felt that he was improving. His death was a tragic shock to his caregivers, including his social services case manager and others not associated with the University. Notwithstanding Ms. Weiss' belief, there simply is no evidence that Mr. Markingson's death was causally connected to his participation in the CAFE study.

6. "The apparent development of a specialized unit in Fairview Hospital, designed to identify severely mentally ill subjects for recruitment into research studies."

There is a psychiatry research office on the Riverside campus of the University of Minnesota Medical Center, Fairview. It houses the administrative support for psychiatric studies conducted by University faculty. With IRB approval and with appropriate consent, studies are conducted then that involve mentally ill patients.

7. "A failure of the institutional oversight system for protecting human subjects of research."

The University's IRB properly performed its role in reviewing and approving the CAFE study. The IRB also promptly informed the FDA of Mr. Markingson's unexpected suicide. The FDA, following an extensive investigation, found no evidence of misconduct or violation of the protocols or regulations governing the University's oversight system for the protection of human subjects in research. As noted in Chair Allen's letter to you, the University's system was recently reviewed by the AAHRPP and received full re-accreditation, which is the most comprehensive review and the highest certification that can be awarded in regard to the protection of human subjects.

Unquestionably, Mr. Markingson's suicide was a tragedy. Faculty in our Department of Psychiatry have made great progress in finding effective treatments for mental health disease. The Department's work - much of it involving clinical trials - has made a significant impact through its community clinical outreach and treatment programs. However, these conditions remain today among the most difficult to manage and treat. It is that challenge which our psychiatry faculty is seeking to address with its clinical research.

The University appreciates your sharing these important concerns with us.

Sincerely,

Mark B. Rotenberg
General Counsel