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Lessons from the Markingson Controversy

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On May 8, 2004, Dan Markingson, an adult, committed suicide while participating in a University of Minnesota Department of Psychiatry drug study ("CAFÉ") comparing three approved medications (Olanzapine, Quetiapine and Risperidone) in treating first-episode psychosis. It is unknowable whether the study caused, contributed to, or delayed Mr. Markingson's suicide, but it did not prevent it. The principal investigator was Dr. Stephen Olson, a psychiatrist and associate professor in the department of Psychiatry.

Mr. Markingson's mother, Mary Weiss, was extremely distressed by her son's death, especially given her belief that Dr. Olson ignored repeated requests to drop Mr. Markingson from the study. With enthusiastic support by Carl Elliot, a professor in the Center for Bioethics and the Department of Pediatrics at the University of Minnesota, Ms. Weiss sought to right the wrong with appeals to the University, the FDA, the courts, licensing boards, the media, the bioethics profession, and anyone else who would listen to her pleas. A recent Google search on "markingson minnesota" yielded 335,000 hits.

At least 10 investigations were conducted:

- The State of Minnesota Office of the Ombudsman for Mental Health and Mental Retardation, in a letter dated 6/17/05, found that "there did not appear to be adequate evidence that the client met the criteria for inclusion in the study," "it may be prudent to include some medication monitoring by means of measuring medication levels in blood or urine specimens to determine whether or not the client is taking the prescribed medication" (a non-standard procedure), and "the CAFÉ Study's protocol for monitoring the medication that was dispensed was not followed for the medication the client received for the last two weeks he was alive." However, the letter did not say that these flaws contributed to Mr. Markingson's death.
- FDA's Minneapolis District Office, in an Establishment Inspection Report dated 7/22/2005, found no regulatory compliance issues.
- The District Court for the County of Hennepin, Minnesota, in an order dated 2/11/08, granted a summary judgment dismissing Ms. Weiss's claims against Dr. Olson, Dr. Schulz (departmental chair), the University, and the study sponsor. Summary judgment is reserved for claims that, seeing the facts in the best light for the plaintiff, do not meet minimum legal standards for the case to go to trial.
- The University of Minnesota Department of Psychiatry, in a "Special Report" dated 9/29/2009, did not look specifically at the Markingson matter. Looking more broadly, it "did not identify any substantive, systemic issues across the department that would suggest risk to the use of human subjects in research studies." However, it did recommend improvements to the training programs, billing systems, and "culture and work environment within the department."
- The Minnesota Board of Medical Practice, in a letter to Ms. Weiss (unavailable) dated 7/15/10, found the "facts of the case did not provide a sufficient basis…to take disciplinary action."
- The Minnesota Board of Social Work entered into an Agreement for Corrective Action (unavailable) with the study coordinator, Jean Kenney. However, it appears that the conduct at issue was in Ms. Kenney's role as a study coordinator, not as a licensed social worker, and did not harm Mr. Markingson.

- FDA's Minneapolis District Office, in a second Establishment Inspection Report, dated 11/20/14, found no regulatory compliance issues.
- The University of Minnesota contracted with AAHRPP to assemble an external Review Team. This team, in "An External Review of the Protection of Human Research Participants at the University of Minnesota with Special Attention to Research with Adults Who May Lack Decision-Making Capacity," dated 2/23/15, did not look specifically at the Markingson matter. However, it did find that "many weaknesses in policy and practice were evident and require attention." For example: "inadequate and inconsistent attention to the process of consent, capacity to consent, the use of surrogate decision-makers, and general efforts to address vulnerability of potential research subjects to coercion and undue influence" and "the University's written policies with regard to who may serve as legally authorized representative for subjects who lack capacity to consent do not appear to be fully consistent with regulatory interpretation by the federal Office of Human Research Protections." (AAHRPP accredited the University in April 2004 (just prior to Mr. Markingson's death) and subsequently renewed the University's accreditation.)
- The Office of the Legislative Auditor (OLA), State of Minnesota, in "A Clinical Drug Study at the University of Minnesota Department of Psychiatry: The Dan Markingson Case," dated 3/19/15, was highly critical of the University. However, it found no instances of noncompliance with the regulations protecting human subjects.
- The University of Minnesota Institutional Review Board, in "Final IRB Investigation Report into Fairview Concerns Regarding Psychiatry Research Studies at the University of Minnesota," dated 5/15/15, found no regulatory compliance issues by researchers in the Department of Psychiatry. However, it found tension and distrust between some researchers and some providers of clinical care.

What can we learn from the Markingson matter?

- The University of Minnesota's systems for protecting human research subjects had weaknesses, as did other aspects of its clinical research program. One can assume that many, if not all, major research centers have their own weaknesses, so quality management systems are essential.
- These weaknesses existed despite the University's accreditation by AAHRPP shortly before Mr. Markingson's death and subsequent reaccreditation (probably following various improvements in policies and procedures, as happens at most or all research institutions over time). In other words, AAHRPP accreditation is a strong indication, but not a guarantee, of high-quality human subjects protection.
- The FDA found no regulatory compliance issues in two investigations, meaning that there were no regulatory compliance issues, that it did not discover any that did exist, or that the regulations are too limited in scope. FDA investigators are not known for whitewashing errors at research sites.
- Nobody, including the University, has published a comprehensive, objective, detailed review, with regulatory citations, of all the actual and alleged flaws in the conduct of the study. Such a review would make it much easier to assess the substance of the issues.
- Mr. Elliot and others inflamed public opinion with character attacks and references to bloody corpses, Nazi medical experiments, etc. Numerous parties, including those inexpert in the regulations governing human subjects protection and/or without full knowledge of the facts, have voiced strong opinions on the Markingson matter. Measured responses based on actual facts can get lost in a storm of malice, vitriol and ignorance.

- The investigators had no legal obligation — and perhaps a legal prohibition — to involve Ms. Weiss, Mr. Markingson's mother, in the informed consent process. However, if the investigator did not ask Mr. Markingson's permission to include her, it might have been wise to do so.
- Conduct of the CAFÉ study at the University was flawed, which can probably be said of most studies at most sites. In retrospect, such errors can be embarrassing, especially in the hands of angry adversaries unfamiliar with — or uninterested in — the specifics of the regulations.
- Many of the accusations related to alleged faults in due process, conflicts of interest, and other ways in which the University handled the matter. Such accusations might be minimized but are probably unavoidable.
- Defense of a clinical study based on regulatory compliance begs the question as to whether the regulations are adequate. The circumstances of Mr. Markingson's death provide an opportunity to ask such questions.
- The public cannot be expected to understand the subtleties of controversies like this one. The OLA's highly critical report, despite finding no instances of noncompliance with the regulations governing human subjects protection, still reads as highly critical. On the other hand, the Court's summary judgment was based on the law, not the facts of the case.

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