

Conflicts of Interest in Clinical Research: Lessons from the Minnesota Markingson Case

E. Sherwood Brown MD PhD Professor of Psychiatry

Joan Reisch PhD Professor of Clinical Sciences & Family and Community Medicine

John Z. Sadler MD Professor of Psychiatry & Clinical Sciences

J. Gregory Wright, AAS, BS, MCM, CIP Manager, UTSW IRB

The University of Texas Southwestern Medical Center, USA

http://www.utsouthwestern.edu/education/programs/ethics_program/index.html

With thanks to Barbi Lange RN, MSHS, CCRC, Clinical Research Nurse Educator, UT Southwestern

Images, left to right, UT Southwestern North Campus, two views of new Parkland Memorial Hospital, Dallas, Texas, USA

UT Southwestern Medical Center

COI in Minnesota Markingson Case

- **OVERVIEW**

I. Brief overview of Minnesota Markingson case

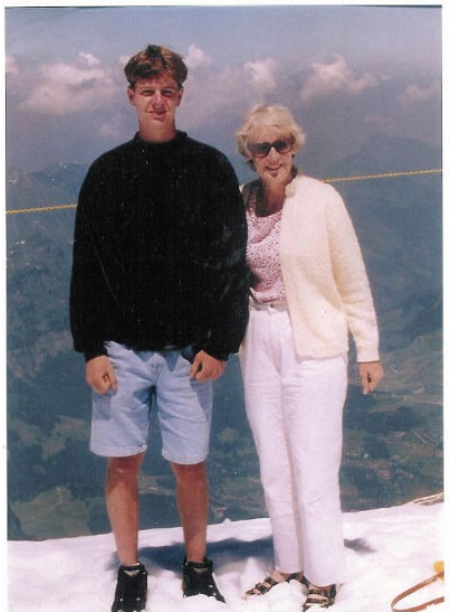
II. What went wrong and how to prevent such catastrophes?

III. Reisch: perspective of research design/statistics

IV. Brown: perspective of the clinical investigator

V. Wright: perspective of research regulation/IRB

VI. Sadler: Conclusions – do's and don'ts



COI in Minnesota Markingson Case

I. Brief overview of Minnesota Markingson case

A. July 2003: 26 year old Dan Markingson develops 1st episode of schizophrenia, first noticed by mother, Mary Weiss.

B. Psychotic ideation involved satanic rituals, potential need to kill people, including mother.

C. Nov. 2003: Stephen Olson MD pursues treatment for DM, including involuntary commitment order to Fairview University Medical Center (FUMC), a University of Minnesota affiliate.

D. Olson discusses CAFÉ study with DM two days following involuntary admission to FUMC. Study is a non-inferiority trial of three antipsychotic drugs in first–episode psychosis. Sponsored by Astra-Zeneca, maker of one of the compounds, Seroquel.

E. CAFÉ study coordinator obtains informed consent, with Dr. Olson signing as witness.

COI in Minnesota Markingson Case

I. Brief overview of Minnesota Markingson case

F. Nov 2003: Mary Weiss, mother, concerned with deterioration, multiply notifies Olson and psychiatry department chairman Charles Schulz MD. Schulz was a co-I on the study and also a paid Astra Zeneca (CAFÉ Sponsor) consultant.

G. December 2003: Under a Minnesota 'stay of commitment' law, DM discharged to group home with requirement to continue aftercare agreement or be re-committed. The aftercare agreement included continuation in CAFÉ study.

H. Late 2003: One single response from Schulz reassuring Weiss that DM was in good hands.

I. April 2004: Weiss, increasingly frantic, calls coordinator expressing worry about DM's potential for killing self. Call not documented or followed up until a week later.

COI in Minnesota Markingson Case

I. Brief overview of Minnesota Markingson case

J. May 2004: In the group home bathroom, DM uses box cutter to splay open his abdomen and cut his throat to the spine. Suicide note states: "I went through this experience smiling."

K. University of Minnesota IRB notified shortly thereafter

L. UM IRB reviews consent process, notifies FDA of suicide, and requests report from Olson about this serious adverse event (SAE).

M. IRB reviews Olson's letter and concludes its review.

O. January 2007: Weiss files malpractice suit against doctors and U. Minnesota and also a product liability/negligence suit against sponsor Astra Zeneca.

P. 2007, Astra Zeneca suit dismissed - "statutory immunity."

COI in Minnesota Markingson Case

I. Brief overview of Minnesota Markingson case

Q. Judge dismissed one claim against Olson and Schulz because of Weiss' failure to provide evidence of DM's incompetence to consent to the research.

R. At deposition, Olson did not know about the following: therapeutic misconception, confirmatory bias, the Belmont Report, and good clinical practice guidelines, and how long to retain study records.

S. Olson settled for $75k. He admitted to continuing to be DM's personal doctor as well as study doctor throughout his care.

T. Pre-existing U Minn research guidelines specify that recruitment of subjects be voluntary and without penalty.

COI in Minnesota Markingson Case

I. Brief overview of Minnesota Markingson case

U. Post trial, evidence emerges of fraudulent documents, including DM's HIPAA authorization as well as an evaluation of DM's capacity to consent.

V. 2008 Minn Med Board investigates Olson. Assigned to David Adson, a colleague in Olson's department, who approved the CAFÉ study, and received $83k from Astra Zeneca in 2006. Adson recommended dismissal of Weiss' complaint.

W. 2009: Minnesota legislatures passes "Dan's Law" forbidding recruitment of research subjects who are under involuntary treatment orders.

X. 2010: Eight U Minn bioethicists raises ethics violations to University officials, as well as to U Minn Board of Regents

COI in Minnesota Markingson Case

I. Brief overview of Minnesota Markingson case

Y. 2012: Minnesota LICSW Board investigates the CAFÉ study coordinator, Jeanne Kenney and finds multiple failures to document adequately and accurately. Kenney was also found to have made clinical observations about drug response, which she was not qualified to do.

Z. Kenney ordered to 18 hours of training and to write an essay about the training's effect on her view of her CAFÉ Trial conduct.

AA. 2013: Weiss and bioethicist Carl Elliott PhD petition Gov. Mark Dayton to form independent panel to review U Minn for possible misconduct.

COI in Minnesota Markingson Case

I. Brief overview of Minnesota Markingson case

BB. Jan-Feb 2014 – AAHRPP asked to review Markingson case; report withheld by U Minn in midst of concerns about COI in the report (e.g., reviewers receiving financial support from industry related to the trial).

CC. Nov. 2014: FDA investigates Olson and finds no evidence of misconduct or significant violation of protocol /regs. FDA reviewer never spoke to Weiss or Group Home staff.

DD. March 2015: Office of Legislative Auditor, State of Minnesota: " . . . we concluded the case involves serious ethical issues and numerous conflicts of interest . . . .We are especially troubled by the response of University leaders . . . They have made misleading statements about previous reviews and been consistently unwilling to discuss or even acknowledge that serious ethical issues and conflicts are involved.

COI in Minnesota Markingson Case

I. Brief overview of Minnesota Markingson case

EE. March 2015: State Auditor formally reprimands U Minn for research safety negligence & the defensive, reputation-defending posture, inability to acknowledge errors, and take responsibilities for deficiencies.

FF. May 2015: University plans to overhaul institutional safeguards.

GG. June 2015: U Minn President Eric Kaler announces research ethics reforms, including exclusion of any consulting fees for investigators from sponsors of clinical research. The 75 page plan, led by Mayo Clinic physician Dr. Wm. Tremaine, also specified other safeguards for oversight and assurances of voluntary consent to participation.

COI in Minnesota Markingson Case

II. Panel Questions:

What went wrong?

How to prevent these in our institution?

COI in Minnesota Markingson Case

III. Dr. Reisch:

Perspective from biostatistician

COI in Minnesota Markingson Case

IV. Dr. Brown:

Perspective from a clinical investigator

COI in Minnesota Markingson Case

V. Mr. Wright: IRB perspective

COI in Minnesota Markingson Case

VI. Dr. Sadler – conclusions and do's and don'ts

A. **Don'ts**:

1. Enroll subjects eligible for/ under involuntary treatment

2. Ignore power analysis considerations with high-dropout study populations

3. Ignore family concerns before, during, after study.

4. Don't 'offload' sole responsibility for research ethics considerations to the IRB

5. Alter study documents or fraudulently create them

COI in Minnesota Markingson Case

VI. Dr. Sadler – conclusions and do's and don'ts

A. **Don'ts**:

6. Assign data-safety monitoring/case review to individuals with financial interests from the same sponsor(s) as the study.

7. Assume a defensive, cover-up posture when addressing research errors and institutional violations

COI in Minnesota Markingson Case

VI. Dr. Sadler – conclusions and do's and don'ts

B. **Do's:**

1. Be knowledgeable about and review the relevance of Federal rules, state laws, and university policies when planning a new clinical research protocol.

2. Minimize or avoid conflicts-of-duty regarding personal care of patients vs. enrollment of your own patients as research subjects.

3. Document the decision-making capacity of subjects at risk for impairment; use one of many validated instruments available

COI in Minnesota Markingson Case

VI. Dr. Sadler – conclusions and do's and don'ts

B. **Do's**:

4. Be wary of industry-sponsored noninferiority trials

5. Listen to, promptly address, and document concerns voiced by a subject, and with subject permission, family concerns.

6. Examine your protocol for situations where clinical practice obligations could undermine the conduct of the research, and plan ahead.

7. IRBs should have a low threshold for audits involving AE deaths of non-terminally ill subjects.

COI in Minnesota Markingson Case

VI. Dr. Sadler – conclusions and do's and don'ts

B. **Do's:**

8. Take your research-regulation and research ethics training seriously, understand the key terms and procedures relevant to your studies.

9. Assign truly independent DSMC members and case reviewers

10. Train, supervise, and monitor your study coordinator about domains appropriate for her/his decisionmaking and domains outside her/his decisionmaking authority or competence.

COI in Minnesota Markingson Case

VI. Dr. Sadler – conclusions and do's and don'ts

B. **Do's**:

11. Institutions: be open and responsive to good-faith concerns about research safety and research errors.

12. Get research ethics consultation and listen to your friendly neighborhood bioethicist.

COI in Minnesota Markingson Case

Questions and discussion?

References and links

General resources for CAFE Trial and documentation:

www.circare.org/dw/ACA_**Kenney**-13622-11082012.pdf

Minnesota LICSW Board investigation of Jeanne Kenney:
www.circare.org/dw/ACA_**Kenney**-13622-11082012.pdf

Report of Minnesota Legislative Audit Commission:
www.auditor.leg.state.**mn**.us/sreview/**markingson**.pdf

Association for the Accreditation of Human Research Protection:
http://news.sciencemag.org/education/2015/03/human-subjects-protections-under-fire-university-minnesota

Response of U Minnesota:

http://www.startribune.com/dan-markingson-case-finally-yields-real-reforms-at-the-u/304830391/