OFFICE OF THE LEGISLATIVE AUDITOR
STATE OF MINNESOTA

University of Minnesota Department of Psychiatry Industry-Sponsored Clinical Studies: 2004-2014

Special Review

June 18, 2015

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OFFICE OF THE LEGISLATIVE AUDITOR
STATE OF MINNESOTA • James Nobles, Legislative Auditor

June 18, 2015

Members of the Legislative Audit Commission:

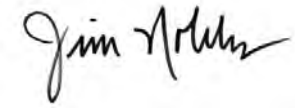
Earlier this year, the Office of the Legislative Auditor issued a report on the case of Dan Markingson, a young man who committed suicide while participating in a University of Minnesota Department of Psychiatry clinical study.

In a follow-up examination, we reviewed other "adverse events" that were reported to the University's Institutional Review Board for industry-sponsored studies conducted by Department of Psychiatry researchers from 2004 through 2014. As noted in this report, we found no evidence of other study-related deaths.

However, we think there is room for improvement in University practices for reporting adverse medical events to the Institutional Review Board. In our view, some of these events should be reported to the board in a more timely manner and with more information.

This review was conducted by Joel Alter, Evaluation Coordinator, and Elizabeth Stawicki, JD, Director of Legal Research, with assistance from KJ Starr, Ryan Moltz, and Sarah Delacueva. We received full cooperation from the University of Minnesota.

Sincerely,



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INTRODUCTION

In 2014, legislators asked the Office of the Legislative Auditor (OLA) to examine deaths related to clinical studies conducted by the University of Minnesota's Department of Psychiatry. We recently released a report on the case of Dan Markingson, who committed suicide while taking part in an industry-sponsored psychiatric drug study in 2004.[1] In this follow-up report, we present findings from our examination of University documents related to all industry-sponsored studies conducted by Department of Psychiatry researchers that were active at any time from January 1, 2004, through 2014.

According to University officials, between 2004 and 2014, the Department of Psychiatry conducted approximately 600 studies of various types; 98 were medical research that was industry-sponsored.[2] However, the University told us that 33 studies never enrolled any participants, which left 65 studies within the scope of our review. For those studies, we examined "adverse event" reports filed with the University's Institutional Review Board (IRB).[3] Generally speaking, an "adverse event" is a medical problem involving a study participant that arises during a clinical trial. More information about the scope and methods of our review, the definition of an "adverse event," and the role of the IRB is contained in the Appendix.

We limited the scope of our review primarily to industry-sponsored studies (that enrolled participants) to make the review manageable for the staff we had available and because the problems we identified in the Markingson report occurred in an industry-sponsored drug study.

In conducting this follow-up review, we had the following two objectives:

- Determine whether anyone—other than Dan Markingson—died while participating in a University of Minnesota Department of Psychiatry industry-sponsored study.

- Assess whether researchers conducting psychiatric studies at the University have adequately reported adverse events to the University's Institutional Review Board.

CONCLUSION

Based on our review, we did not identify anyone—other than Dan Markingson—who died while participating in an industry-sponsored University of Minnesota Department of Psychiatry study. However, we think the reporting of adverse events by some study researchers has been inadequate.

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[1] Office of the Legislative Auditor, Special Review, *A Clinical Drug Study at the University of Minnesota Department of Psychiatry: The Dan Markingson Case* (St. Paul, March 19, 2015).

[2] Most of the industry-sponsored medical studies examined drugs for treating mental illness. Some of the studies examined other treatments, such as stimulation devices implanted in the brain to address depression.

[3] An Institutional Review Board (IRB) is the organization that approves proposals to conduct biomedical and behavioral health research that involve human subjects. The primary purpose of an IRB is to protect human subjects from physical or psychological harm by establishing research protocols and periodically reviewing ongoing research projects. For more information about the University of Minnesota's IRB, see the Appendix.

PREVIEW OF FINDINGS

1. In the studies we reviewed, we found reports of two deaths: one was Dan Markingson's suicide; the second was a person who was screened for a research study but died before receiving treatment through the study.

2. Over time, the University of Minnesota's Institutional Review Board has narrowed the types of adverse events that clinical researchers must immediately report to the IRB, consistent with federal guidance. Researchers have considerable latitude to exercise judgment that affects how promptly they report adverse events to the IRB.

3. University researchers often provided the IRB with little documentation about the nature of adverse events or whether those events related to the study.

4. We were unable to determine how well researchers complied with IRB reporting deadlines because many of the adverse event reports lacked important details. Some serious adverse events have not been reported to the Institutional Review Board for months after they occurred.

5. University researchers have not always provided the IRB with information about participants who dropped out of a study because they experienced adverse events. This limited our ability—and would limit the IRB's ability—to determine the total number of adverse events that have occurred.

FINDINGS

Finding 1. In the studies we reviewed, we found reports of two deaths: one was Dan Markingson's suicide; the second was a person who was screened for a research study but died before receiving treatment through the study.

Dan Markingson is the only person we identified as having died while participating in one of the studies we reviewed, and we concluded in our March 2015 report that it was not possible to know whether Markingson's suicide was connected to his participation in a University drug study.

The other death reported in the documents we reviewed was clearly not connected to a University study. When a person was screened for a depression treatment study in April 2001, the doctor conducting the physical exam noticed that the person had difficulty swallowing. The doctor referred him to his family physician for follow-up and the physician diagnosed the patient with esophageal cancer. As a result of the cancer diagnosis, researchers withdrew the patient from the study's screening process. The patient had surgery related to the cancer on June 18,

2001, and died from complications on June 20, 2001.[4] Although the patient had signed a consent form to participate in the University study in April 2001, the patient never received the study treatment.

We reiterate that our finding is based on a review of industry-sponsored studies, which is only a portion of all studies conducted by the Department of Psychiatry between 2004 and 2014.[5] In addition, it is based on documents maintained and provided to us by the University's IRB.

Finding 2. Over time, the University of Minnesota's Institutional Review Board has narrowed the types of adverse events that clinical researchers must immediately report to the IRB, consistent with federal guidance. Researchers have considerable latitude to exercise judgment that affects how promptly they report adverse events to the IRB.

From 1999 until 2003, researchers at the University of Minnesota were required to report (1) "serious adverse outcomes" and (2) "unexpected events" involving risks to human subjects or others; these reports were supposed to be submitted "at the time they occur."[6] Researchers were asked to submit a written report of each adverse event, regardless of whether it was related to the study treatment.

Starting in 2003, the IRB required researchers to report to the IRB within ten days regarding adverse events that they deemed both serious and unexpected.[7] By applying the ten-day reporting requirement only to events that met both of the criteria, this policy change had the effect of reducing the number of adverse events that needed to be reported to the IRB promptly.

Starting in 2006, the IRB further narrowed the scope of what researchers needed to report within ten days—limiting such reporting to adverse events they deemed to be "unanticipated, serious, and at least possibly related to the research procedures." IRB staff said: "The IRB relies on the [principal investigator's] professional judgment to make this determination."[8] Adverse events that did not meet all three of these criteria were to be reported to the IRB at the time of the IRB's "continuing review" of the study, which is supposed to occur at least annually.

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[4] The patient's psychologist informed the University of the death on July 18, 2001, and the University submitted an adverse event report to the IRB on August 15, 2001.

[5] As noted in the Appendix, we also reviewed one federally sponsored study.

[6] We examined instructions the University provided to researchers between 1999 and 2014 because the clinical studies we examined in our review spanned this period. Until 2002, the University instructed researchers to report events within five working days. In 2002, this changed to within ten working days of the event.

[7] Starting in 2004, the IRB said that reports of other adverse events could be submitted by researchers periodically rather than through an individual report at the time of the event.

[8] Presentation by Moira Keane, University of Minnesota Research Subjects Protection Program Director, "From 'AE' to 'UPIRTSO:' New Practice for Reporting Unanticipated Problems to the IRB," 2006.

The IRB's policy changes mirrored federal guidance, which suggested that IRBs nationally should limit the types of adverse events they reviewed. In 2009, the U.S. Department of Health and Human Services said:

> In general, an [adverse event] observed during the conduct of a study should be considered an unanticipated problem involving risk to human subjects, and reported to the IRB, only if it were unexpected, serious, and would have implications for the conduct of the study…. An individual [adverse event] occurrence ordinarily does not meet these criteria because, as an isolated event, its implications for the study cannot be understood.[9]

The IRB instructions on adverse event reporting for 2010 through 2014 were again somewhat different from the IRB's previous requirements. During this period, the IRB required researchers to report within ten days any adverse events that researchers did not anticipate, involved new or increased risk to subjects or others, and at least possibly related to the research procedures. Thus, the criterion of "new or increased risk" replaced "serious" adverse events. Also, starting in 2014, events that met all three criteria were supposed to be reported to the IRB within five days, compared with ten days previously. Adverse events that did not meet the three criteria were to be reported in summary form, at the time of the IRB's "continuing review" of a study.

In addition to narrowing the types of adverse events that must be reported immediately, the IRB has also given researchers more discretion in determining what must be reported. For example, until 2004, IRB policy required any serious adverse event (such as a hospitalization) to be reported immediately. Today, a hospitalization would have to be immediately reported only if the principal investigator judged that it (1) was unanticipated, (2) reflected a new or increased risk to subjects or others, and (3) was at least possibly related to the research procedures.

If a researcher determines that a patient's hospitalization for thoughts of suicide are a part of the patient's underlying mental illness (and not triggered by a study medication), the event may be deemed anticipated and is not required to be reported to the IRB within days of the event. Likewise, if a clinical trial's patient consent form tells study participants that suicidal thoughts are a possible side effect of the medication being studied, the researcher may determine that a hospitalization for suicidal thoughts is anticipated and wait to report the event until the IRB's annual review of the study.

In some studies, the principal investigators' judgments may be informed by the findings of a "data and safety monitoring board," which is an independent group of experts that advises study investigators. However, such boards are not required for all studies.[10]

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[9] U.S. Department of Health and Human Services, *Guidance for Clinical Investigators, Sponsors, and IRBs: Adverse Event Reporting to IRBs—Improving Human Subject Protection* (Washington, DC, January 2009), 3.

[10] Federal regulations require plans for research studies to, "when appropriate," make provisions for monitoring the data collected to ensure the safety of research subjects. Sometimes this occurs through the establishment of a "data and safety monitoring board." We did not determine how often the University of Minnesota establishes such boards for psychiatric research studies.

Finding 3. University researchers often provided the IRB with little documentation about the nature of adverse events or whether those events related to the study.

During industry-sponsored studies, researchers generally report adverse events to sponsors using a sponsor-designated form. The IRB also has its own forms for researchers to use—one for reporting unexpected, study-related events that must be reported within five days, and one for reporting other types of adverse events as part of annual "continuing reviews" for each study.

Generally, the sponsor and IRB forms have provided researchers with opportunities to describe the event that occurred. Sometimes, however, researchers have relied on letters rather than standard forms to report adverse events, leaving out key details that are specified in the forms. Also, in past years, the IRB asked researchers to report about "anticipated" adverse events in spreadsheets, and it did not specify what details of the events the spreadsheets should address.

We reviewed 88 instances where researchers informed the IRB of an adverse event. In a majority of these cases, the IRB records did not contain a detailed, standalone report of the individual event from a researcher. Rather, the study's principal investigator usually briefly described the event in a letter to the IRB or in an annual "continuing review" report to the IRB. These brief descriptions often lacked key details—such as whether the event was study-related. In addition, we found that about 17 percent of the adverse event records never said when the event had occurred.

In 2014, the IRB created a form for researchers to use when annually reporting on "anticipated" adverse events that are not required to be reported to the IRB within five days.[11] This new form may help the IRB obtain more complete information on adverse events. The new form—along with the IRB's detailed form for events that must be reported within five days—asks researchers to report the date of the adverse event. IRB forms also ask researchers to indicate whether, in their judgment, the event was anticipated, whether the event was related to participation in the study, and whether the event represents a new or increased risk to participants. However, it is worth noting that the forms do not ask researchers to explain how they arrived at these judgments. One of the forms says, "The IRB will make the final determination regarding whether this event meets the regulatory definition of [an unanticipated problem involving risk to subject or others]," but it would be difficult for the IRB to independently make such determinations without knowing the basis for the researchers' judgments.

Finding 4. We were unable to determine how well researchers complied with IRB reporting deadlines because many of the adverse event reports lacked important details. Some serious adverse events have not been reported to the Institutional Review Board for months after they occurred.

[11] Before 2014, University researchers had little IRB guidance for how to report adverse events as part of "continuing reviews," which are sometimes called non-UPIRTSOs. On the other hand, the IRB has—for many years—had forms for researchers to report "unanticipated problems involving risks to subjects or others" (UPIRTSOs).

Current IRB policy requires researchers to report to the IRB within five working days those adverse events that, in the researchers' judgments, meet all of the following criteria:

- Unanticipated by the researchers,
- Related to the study, and
- Pose new or increased risk to the study participants or others.

Adverse events that do not meet all of these criteria should be reported at the time the IRB conducts a "continuing review" of a study (typically annually).

We found wide variation in the amount of time it took researchers to notify the IRB of adverse events. Some researchers informed the IRB the same day while others took more than 300 days. This wide range could be consistent with IRB policy, which has required some events to be reported within days, while allowing other events to be reported over a longer period of time.

However, we were unable to conclusively determine the extent to which researchers complied with the IRB's standards for timely reporting. The deadline for reporting a particular event depends partly on whether the researcher deems the event to be unanticipated and related to the study treatment—but, as noted in Finding 3, researchers' reports of adverse events sometimes had little discussion of the event. Weak documentation made it difficult for us to know whether an event was considered to be anticipated, or whether the event was related to the study treatment.

Also, as noted in our discussion of Finding 3, 17 percent of the adverse event reports we reviewed never listed the date when the medical problem occurred. As a result, it is impossible for University officials or external reviewers to comprehensively determine the timeliness of researchers' reporting practices.

We identified 73 adverse events in University records that included both the date the event occurred and when the researcher reported it to the IRB. For 26 percent of these events, researchers reported the medical problem to the IRB within ten days. In another 51 percent, researchers did not report to the IRB for at least two months. In some cases that took months to report, researchers said patients experienced only minor problems, such as an instance of a shortness of breath. But we also found eight hospitalizations that researchers did not report to the IRB for at least six months.

An example of a study with relatively prompt reporting was one that reported 13 hospitalizations from 2000 to 2005. Researchers reported most of these hospitalizations to the IRB within one week. There was only one hospitalization that took longer than 30 days to report.[12]

[12] The relatively prompt reporting in this study occurred despite the fact that only two of the hospitalizations were deemed by the researchers to be possibly related to the study treatment.

Some other studies had less prompt reporting of adverse events. In one study of medications for schizophrenia, IRB members expressed concerns about a study participant who was hospitalized due to worsening symptoms of schizophrenia. The researcher did not report the case to the IRB until ten months later. IRB reviewer notes included comments such as: "Why was this [adverse event] reported to us so late? Reported to sponsor but not us!" The study's principal investigator responded to the IRB: "This event was not reported in a timely manner due to study staff error."[13]

In addition, IRB records showed that two people who received surgical implants in 2012 to address depression were hospitalized for post-surgical infections. In neither of these cases did the researcher submit detailed adverse event reports to the IRB. Rather, because these events were classified as anticipated events, limited information on the events was submitted to the IRB as part of a "continuing review" spreadsheet months after the events occurred. We did not see any indication that the IRB discussed these incidents or how to prevent similar problems in the future.

Finding 5. University researchers have not always provided the IRB with information about participants who dropped out of a study because they experienced adverse events. This limited our ability—and would limit the IRB's ability—to determine the total number of adverse events that have occurred.

Federal regulations require IRBs to conduct "continuing reviews" of research projects at least once a year. This provides an opportunity for the IRB to check on the study's progress and ensure that researchers are taking adequate measures to protect study participants.

Prior to a "continuing review," the IRB requires the study's principal investigator to summarize the research study's progress by answering questions on a form. One of those questions asks researchers to list how many participants have withdrawn from the study.[14] We observed that researchers sometimes mentioned withdrawals that occurred due to expected or unexpected adverse events, yet they indicated elsewhere on the form that no adverse events had occurred or provided no detailed reports for these events. Examples included the following:

- For a study of an antipsychotic medication (olanzapine), four patients withdrew from the study because of what the principal investigator described as side effects or an inability to tolerate the medication. Based on the records we reviewed, the researcher never submitted adverse event reports to the IRB about these cases.

[13] Stephen C. Olson, M.D., Principal Investigator, letter to Patrice Webster, Executive Assistant, Institutional Review Board, September 12, 2003.

[14] Withdrawals can occur for a variety of reasons. For example, people might choose to withdraw from a study if they become concerned about the study's risks, experience expected or unexpected side effects, or have difficulty fitting study-related appointments into their schedules. Also, some people might fail to comply with study requirements, for example, if they move out of state or fail to take the medication as required.

- For a study of an antipsychotic drug (quetiapine), the researcher's annual reports over a four-year period identified 12 people who withdrew from the study because they could not tolerate the study medication or what the researcher described as "adverse events." The reports contained minimal information on the nature of these problems and no information on exactly when they occurred. Based on the records we reviewed, the researcher did not submit to the IRB a detailed adverse event report for any of these instances.

- In an annual report on a clinical trial for an anti-anxiety drug (paroxetine), a researcher said that one person in the study withdrew due to "adverse events: somnolence, dizziness."[15] This occurred after the patient took the study medication for three days. However, the IRB records contained no separate report from the researcher on the details of this event (including when it occurred), and there is no indication that the IRB reviewed this incident as an adverse event.

- In a study of a medication for mood disorders (lamotrigine), the researcher's annual reports over a two-year period said one person withdrew from the study because "he received no benefit"; two others withdrew after they developed rashes; and one person withdrew after reporting "mood swings." IRB records contained no separate reports from the researcher on the details of these events.

- In a study of an antipsychotic drug (bifeprunox), a participant went to the emergency room three times for various symptoms, and the participant withdrew from the study due to his concerns that the drug may have caused these problems. The principal investigator did not report these emergency room visits as adverse events in his annual report to the IRB on this study.[16]

It was unclear to us why researchers reported such limited information on adverse events that led patients to withdraw from research studies. Better reporting of such events could help the researchers evaluate the study medications, and it might help the IRB ensure that other research subjects are adequately protected. These events should either be reported to the IRB as "unanticipated problems involving research subjects or others" (UPIRTSOs), or they should be reported in a comprehensive manner in the "Non-UPIRTSO Adverse Event Log" that the IRB asks researchers to complete.

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[15] Somnolence means to be drowsy or sleepy.

[16] IRB staff told us that the IRB policy at the time of this study required researchers to (1) report within ten days those events the researcher deemed serious, unanticipated, and possibly related to the study; and (2) report annually on other events the researcher deemed to be serious. The latter would be reported as part of the IRB's annual "continuing review" process for each study. In fact, however, the IRB policy said that non-serious events "should be reported [to the IRB] in summary form" at the time of the annual review. Thus, even if the primary investigator in this case deemed the symptoms that brought the research participant to the emergency room to be not serious, the policy appears to have required their inclusion in the study's annual report.

RECOMMENDATIONS

As part of its efforts to ensure that human subjects in psychiatric research are protected from harm, the University's Institutional Review Board reviews the information on adverse events reported by researchers leading clinical trials. The IRB can then independently assess the information and consider what steps, if any, should to be taken. To fulfill this role more effectively, the IRB should receive more complete and timely information than it has received in past years. We offer the following recommendations.

1. **The Institutional Review Board should consider options for ensuring more prompt IRB review of events that would be classified by federal regulations as "serious adverse events."**

In the files we reviewed, there were many reports of serious adverse events, as defined in federal regulations. For example, we saw evidence of 42 hospitalizations, usually for suicidal thoughts or worsening symptoms of mental illness. Researchers classified only four of these events as being possibly related to the study in which the person was enrolled—thus, under current IRB policies based on federal guidance, researchers would not have to report most of these hospitalizations to the IRB within five days.[17]

A primary responsibility of the IRB is to ensure that human research subjects are not placed at undue risk. Even if a clinical trial's principal investigator believes that a serious adverse event was unrelated to a study drug or procedure, or that the event was an anticipated one for someone with a particular condition or receiving a particular treatment, an independent assessment of the researcher's judgment might reach a different conclusion. In our view, the IRB should consider options for ensuring more timely reporting of serious adverse events. These options include:

- **Requiring the reporting of all—or at least more types of—serious adverse events to the IRB within five days**. The IRB, consistent with federal guidance, now requires researchers to immediately report serious adverse events only if they are deemed unexpected and related to the research procedures. Requiring researchers to immediately report additional types of serious events to the IRB would give the IRB the opportunity to independently review the events soon after they occur. This might provide stronger oversight of patient safety; it would also increase the number of adverse events for the IRB to review.

  A five-day time frame for reporting serious adverse events to the IRB would be closer than current IRB practices to the requirements of state law for reporting serious incidents to the state's Ombudsman for Mental Health and Developmental Disabilities (one day). The ombudsman has authority to conduct independent investigations of certain adverse events, just as the IRB has authority to review events that occur in the University's clinical trials. State law requires state and local health, education, and human services

[17] For some of the hospitalizations, the principal investigator's report to the IRB did not explicitly address whether the event was related to the study.

agencies and facilities subject to state licensure to report deaths or serious injuries to the ombudsman within 24 hours of their occurrence.[18]

We recognize that the University's implementation of this option would go beyond what is federally required. Federal guidance has stated that "only a small subset of adverse events" should be considered unanticipated problems, which require prompt reporting to the IRB.[19] The federal guidance has aimed to ensure "timely, meaningful" review of these events "while reducing unnecessary burden."[20] We agree that requiring the IRB to immediately review all **non-serious** adverse events would be burdensome and not very meaningful, but we think prompt review of **serious** events should be considered by the IRB—at least for studies overseen by the Department of Psychiatry.[21]

- **Requiring more frequent IRB "continuing reviews" for studies that might pose greater risk to research subjects.** Continuing reviews are supposed to occur at least once a year, and documents we reviewed in IRB files suggested that most have occurred at roughly annual intervals. But if a research study seems especially risky, or if it has large numbers of adverse events reported at the time of continuing reviews, the IRB should consider requiring the principal investigator for that study to submit continuing review forms more frequently—such as every six months. This would give the IRB a chance to more promptly review events classified by the principal investigator as "expected" or "unrelated to study procedures."

Again, these options would go beyond the minimum standards established by federal guidance, and they would require more IRB review than now occurs. In our view, however, these options could be implemented in ways that do not have a significant impact on the IRB's workload.

2. For adverse events that must be reported to the IRB within five days, the IRB should ensure that the researcher provides a detailed, standalone report rather than mere notification.

It is important for the IRB to have a thorough understanding of adverse events as it determines ways to protect human subjects in research studies. We saw instances in which principal investigators submitted detailed reports on adverse events to a study's industry sponsor but did not send comparable information to the IRB. A detailed, prompt report is especially important for those adverse events for which the IRB requires reporting within five days. For this purpose, principal investigators should use the form that has been developed by the IRB, rather than simply notifying the IRB of the event in a letter.

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[18] *Minnesota Statutes* 2014, 245.94, subd. 2a.

[19] U.S. Department of Health and Human Services, "Guidance on Reviewing and Reporting Unanticipated Problems Involving Risks to Subjects or Others and Adverse Events," http://www.hhs.gov/ohrp/policy/advevntguid.html, accessed May 20, 2015.

[20] *Ibid.*

[21] If there is concern that requiring researchers to report all serious events to the IRB would place an undue burden on the IRB, another option would be to require all serious events to be reported for those studies that are not subject to review by an independent data and safety monitoring board.

3. IRB forms for reporting adverse events should give researchers an opportunity to explain their judgments about whether the event was anticipated, was related to participation in the study, or presented new or increased risks to participants.

The IRB should critically review the researcher's conclusions about the adverse event. For example, even if a researcher asserts that an event was unrelated to a patient's participation in a drug study, the IRB should review the researcher's documentation and consider whether it agrees with the researcher's conclusion.

APPENDIX

In this appendix, we provide more details about (1) the scope and methods of our review, (2) what is meant by the term "adverse events," as used in clinical research, and (3) the role of the University's Institutional Review Board in reviewing adverse events.

Scope and Methods

In 2014, we asked the University of Minnesota for copies of "adverse event" reports related to psychiatric research that was active during or after January 2004. ("Active" studies included (1) those authorized by the IRB on or after January 1, 2004, and (2) those authorized by the IRB prior to 2004 that were not officially terminated by the IRB prior to January 1, 2004.) In subsequent discussions with University officials, we refined the scope of this request because University officials said more than 600 studies by the Department of Psychiatry were active on or after January 1, 2004. This included more than 500 medical research studies and more than 100 social science research studies. Because Dan Markingson's death occurred in a medical study sponsored by a pharmaceutical company, we asked the University in July 2014 to limit the study documents it provided to us to those that the University's Institutional Review Board (IRB) had identified as having "business and industry" sponsors.

As the IRB retrieved these records, it found that 98 such studies had been active during or after 2004. The IRB determined that no subjects were ever enrolled at University of Minnesota sites in 33 of the 98 studies.[22] There are various reasons that an IRB-authorized study may have had no enrollments. For example, the University may have had difficulty recruiting research subjects or negotiating a contract with the study sponsor; the sponsor may have relied on data from other locations and closed the study before enrollment of subjects began at the University of Minnesota; or the study may have been too new to have enrolled any subjects as of 2014.

At our request, IRB officials reviewed the records of the 65 industry-sponsored studies by the Psychiatry Department that had at least one person enrolled. Specifically, IRB staff searched for documents related to "adverse events" at sites directly managed by University of Minnesota researchers. (The nature of "adverse events" is discussed below.) In 41 of these 65 studies, there

[22] We did not request data from the IRB that would have allowed us to independently determine the total number of individuals who participated in each study.

were no reported adverse events, according to the IRB.[23] Consequently, we focused primarily on 24 industry-sponsored psychiatric studies that were active on or after January 1, 2004, enrolled at least one person, and reported at least one adverse event to the University's IRB.

In addition, our office requested information about one additional study from the University—called the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study. That study, unlike the others we reviewed, was funded by the National Institute of Mental Health rather than by industry. We requested records for the CATIE study because it bore some similarities to the study in which Dan Markingson died. The two studies were conducted at similar times, and they both focused on medications to treat schizophrenia. In addition, information we obtained from the University suggested there had been a significant number of adverse events reported in the CATIE study. Overall, with the CATIE study, we reviewed records from 25 Psychiatry Department clinical trials, ranging in length from a few months to several years.

We examined the number and nature of adverse events reported to the IRB in these cases, but we did not evaluate other aspects of these cases. In contrast to our review of the Markingson case, we did not review patient recruitment into the studies. We also did not interview study subjects' family members; our review was based largely on University records.

Adverse Events

Federal regulations pertaining to experimental drugs define an adverse event as "any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related."[24] Adverse events can also occur in non-drug clinical trials, such as those investigating medical devices.

Federal regulations define a "serious" adverse event or reaction as:

- Death,
- A life-threatening adverse event,
- Inpatient hospitalization or prolongation of existing hospitalization,
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or

[23] IRB staff initially determined that 28 of the 65 studies enrolled subjects but had no reports of adverse events that occurred at sites managed by the University. They provided our office with records from the remaining 37 studies. In our review of the 37 studies, we identified another 13 studies that did not have reports to the IRB of adverse events that occurred at University sites. For one of the studies we classified as having no reported adverse events, the principal investigator filed annual reports showing the percentage of patient evaluations in which various types of anticipated side effects (such as nausea or muscle aches) were identified. However, these reports provided no information on the individual events.

[24] 21 *CFR* 312.32(a).

- A congenital anomaly/birth defect.[25]

Federal regulations state that other medical events may be considered serious when, based on medical judgment, they may jeopardize the research subject and require medical or surgical intervention to prevent one of the outcomes above.

Federal regulations also require research institutions to have procedures for promptly reporting unexpected problems to institutional review boards. Specifically, the regulations require the reporting of "unanticipated problems involving risks to subjects or others," often called UPIRTSOs.[26] According to current IRB policy, an event is unanticipated if it is not part of the patient's underlying disease, is not described as a potential risk in the study's patient consent form, or is not in the Investigator's Brochure for the study.[27] The University of Minnesota's IRB requires researchers to report a UPIRTSO to the IRB within five working days of determining that the event qualifies as such. The IRB requires other types of adverse events (called non-UPIRTSOs) to be reported in a spreadsheet at the time a study undergoes a "continuing review" (at least once a year) by the IRB.

While regulatory bodies have adopted specific definitions of adverse events, serious adverse events, and UPIRTSOs, we use the term "adverse events" in this report to broadly describe the full range of patient-related health events that were reported by University researchers to the IRB. We observed that this generic term is commonly used by University researchers when reporting both expected and unexpected medical problems involving research subjects to the IRB. We found that the lack of detail submitted by researchers regarding some adverse events would not allow them to be categorized by the IRB or others based on their seriousness or whether they could have been anticipated.[28]

Institutional Review Board (IRB)

Institutional Review Boards are the groups within institutions that are required to review applications to conduct biomedical and behavioral health research that involve human subjects.

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[25] *Ibid.*

[26] 45 *CFR* 46.103 (5).

[27] University of Minnesota IRB, "Guidance & FAQs: Investigator Requirements for Reporting Problems and Other Events to the IRB," http://www.research.umn.edu/irb/guidance/ae.html#.VTVYMuFZ-So, accessed April 17, 2015. The Investigator's Brochure is a document prepared by the sponsor of a research study that summarizes what is known about the product being investigated.

[28] University of Minnesota researchers are obligated to report various other types of "events" to the IRB that we did not examine, including the following: (1) reports of adverse events in IRB-authorized studies that occur at study locations not under the direct control of University of Minnesota researchers; (2) instances in which there are deviations from the research protocols approved by the IRB; (3) research or publications that identify new risks in approved studies that may affect subject safety; (4) federal audits, inspections, or inquiries; (5) unresolved complaints by research subjects; (5) incarceration of subjects enrolled in studies not authorized to involve prisoners; (6) actions by the state medical board or hospital staff affecting approved studies; and (7) suspension or premature termination of approved studies by the research sponsor or others.

A primary purpose of an IRB is to protect the rights and welfare of human subjects by reviewing and evaluating research protocols and periodically reviewing ongoing research projects.

The University of Minnesota established its IRB in the early 1970s. It has jurisdiction over research conducted at all of the University's campuses, as well as at Fairview Health Services and Gillette Children's Specialty Hospital. The IRB has about 60 University-appointed members that represent University faculty, staff, students, Fairview Health Services, and the community. It has several committees that review University research, plus an executive committee comprised of the chairs and vice-chairs of the subcommittees. Proposed research projects that would involve human subjects must apply to the IRB for approval. The IRB reviews proposed research protocols and methods of obtaining the informed consent of participants; it also reviews proposed changes to protocols and informed consent. Adverse events must be reported to the IRB by the principal investigators of IRB-approved research studies. The IRB reviews the events and considers whether the events justify actions to protect human subjects—such as changes in research protocols or the information provided to current or future research participants.

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June 15, 2015

James Nobles, Legislative Auditor
Office of the Legislative Auditor
State of Minnesota
Room 140 Centennial Building
658 Cedar St.
St. Paul, MN 55155-1603

Dear Legislative Auditor Nobles:

Thank you for your draft report dated June 10, 2015 and the recommendations therein. The University's response to each recommendation is listed below.

We appreciate that your office made a number of changes based on our comments in response to the draft report, including clear notation of the fact that our current practices follow regulatory guidelines. As you know, the University of Minnesota Board of Regents recently adopted the recommendations put forth by an Implementation Team (http://discover.umn.edu/news/vision-leadership/u-m-board-regents-endorses-plan-strengthen-human-research-protections), appointed by President Kaler (http://research.umn.edu/advancehsr/documents/workplan-final.pdf).

Recommendation 1:

The Institutional Review Board should consider options for ensuring more prompt IRB review of events that would be classified by federal regulations as "serious adverse events".

We believe we should not change the current reporting practices of serious adverse events (SAEs) for studies done under an IND/IDE that are industry or NIH sponsored and are externally monitored. Having a different set of reporting requirements especially for multicenter studies is especially problematic and significantly cumbersome.

If the reporting plan for internal serious adverse events includes required reporting to a monitoring entity other than the IRB (e.g. the research sponsor, a coordinating or statistical center, an independent medical monitor, or a data and safety monitoring board or committee), the IRB will evaluate:

- The type of data or events that are to be captured for the monitoring entity
- The entity responsible for monitoring serious adverse events
- The time frames for reporting to the monitoring entity
- The frequency of assessments of data or events captured

- Definition of specific triggers or stopping rules
- The procedure and time frames for reporting any findings to the IRB

This will be accomplished by revising Section 12 of its biomedical application to require applicants to more completely identify the safety reporting plan for internal events.

Requiring reporting of all – or at least more types of – serious adverse events to the IRB within five days.

If the reporting plan for internal events **does not** include required reporting to a monitoring entity (as identified above), or the IRB does not find the plan makes adequate provision for monitoring the data collected to ensure the safety of research participants, the IRB will require the investigator to report all serious adverse events to the IRB within five days. Events that must be promptly reported are defined as any adverse event that:

1. Results in death
2. Is life-threatening (places the research participant at immediate risk of death from the event as it occurred)
3. Results in inpatient hospitalization or prolongation of existing hospitalization
4. Results in a persistent or significant disability/incapacity
5. Results in a congenital anomaly/birth defect
6. Based on appropriate medical judgment, may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the other outcomes listed above.

Requiring more frequent IRB "continuing reviews" for studies that might pose greater risk to research subjects.

The IRB can – and does – require more frequent continuing reviews for studies that might pose greater risk to research subjects. A more frequent schedule can be defined at initial review and approval of the research or at any point during the conduct of the research.

The IRB will, under the plan outlined above, receive information it can evaluate to consider requiring a more frequent than annual continuing review as follows:

1. For studies that have a monitoring entity other than the IRB, investigators will be required to submit statements or reports from the monitoring entity as they are received (these must be submitted within five days under current IRB policy) describing study-wide adverse events, interim findings, any recent literature reviewed; the date of the review; and the monitoring entity's assessment of the information.
2. For studies that do not have a monitoring entity, the IRB will receive prompt (within five days) reports of all serious adverse events.

Recommendation 2:

For adverse events that must be reported to the IRB within five days, the IRB should ensure that the researcher provides a detailed, standalone report rather than a mere notification.

The IRB will address this recommendation in one of two ways:

- By revising the current Report Form to ask specific questions when the event reported is an adverse event, or
- By preparing an additional form, modeled after a typical business and industry sponsor serious adverse event form, that would be required when the event reported on the current Report Form is an adverse event

The IRB could make specific exemptions for five-day reporting for certain types of commonly expected and/or unrelated SAEs.

Recommendation 3:

IRB forms for reporting adverse events should give researchers an opportunity to explain their judgments about whether the event was anticipated, was related to participation in the study, or presented new or increased risks to participants.

A revision to the Report Form made in May, 2015 adds a requirement for the investigator to "provide an explanation of the most significant factors/considerations the investigator relied upon to draw these conclusions".

In addition to responding to recommendations, one error in the draft report was noted. On page 3, line 15, the date of the report should be March, 2015 (not 2014).

Sincerely,

Brian Herman

Brian Herman, Ph.D.
Vice President for Research