



OFFICE OF THE LEGISLATIVE AUDITOR
STATE OF MINNESOTA

Protections for Human Subjects in Research Studies at the University of Minnesota Department of Psychiatry: A Preliminary Assessment of Reforms

May 19, 2016

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May 19, 2016

Members of the Legislative Audit Commission:

Last year, the Office of the Legislative Auditor issued two reports related to research studies conducted by the University of Minnesota Department of Psychiatry.

In response to those reports and another report released by a panel of outside experts, the University is in the process of implementing reforms to its Human Research Protection Program. This follow-up report is a preliminary assessment of the University's reform efforts. The University fully cooperated with our review.

Elizabeth Stawicki, JD, Director of Legal Research, conducted our review, with assistance from Joel Alter, Evaluation Manager.

Sincerely,

A handwritten signature in black ink that reads "Jim Nobles".

James Nobles
Legislative Auditor

cc: Members of the House Higher Education Policy and Finance Committee
Members of the Senate Higher Education and Workforce Budget Division

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Introduction

In response to strong and persistent criticism of certain research practices in the Department of Psychiatry, the University of Minnesota has embarked on a wide-ranging plan to reform its Human Research Protection Program. In fact, the Reform Plan goes well beyond the Department of Psychiatry and proposes changes that will affect all University research involving human subjects.

Although the University is in the process of carrying out its plan, legislators asked the Office of the Legislative Auditor (OLA) to provide a preliminary assessment of those efforts before the current legislative session ends.

Legislators also asked us to review a University-hired consultant's allegations about research practices in the Department of Psychiatry in a report that became public in February 2016. The allegations, which were the subject of news reports and legislative hearings, caused considerable concern.

Background

Last year, three outside reviews criticized research practices at the University of Minnesota's Department of Psychiatry. An outside panel of experts conducted one of the reviews.¹ Among its conclusions were the following:

- The University and Medical School's failure to develop an institutional culture that demands excellence, compliance, and accountability has resulted in persistent concern and ongoing distrust of the clinical trials activities within the Department of Psychiatry.²
- There are significant problems with core functions of the human research protections program, including IRB [Institutional Review Board]³ review, investigator education,

¹ The University brought in the outside expert panel in response to a resolution passed by the University's Faculty Senate (Resolution on *Issues Arising from the CAFÉ Study and the Suicide of Dan Markingson*, December 5, 2013). The University established the panel through an administrative agreement with the Association for the Accreditation of Human Research Protection Programs.

² Association for the Accreditation of Human Research Protection Programs (AAHRPP), *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*, February 23, 2015, 92.

³ Institutional Review Boards (IRBs) are the groups within institutions that are required to approve 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.

practices related to consent to research, and the effective coordination of administrative oversight, clinical care, and research.⁴

OLA conducted the other two reviews.⁵ We first reviewed the case of Dan Markingson, who committed suicide in 2004 while participating in a Department of Psychiatry drug study. Among our nine findings, we said that a University psychiatrist, Dr. Stephen Olson, recruited Markingson into an industry-sponsored drug study when Markingson was “extraordinarily vulnerable.” We questioned whether Markingson’s condition allowed him to give “informed consent” to participate in the drug trial. We also questioned whether Dr. Olson had a conflict of interest by serving as both Markingson’s treating physician and the head of the drug study into which he recruited Markingson. More broadly, we concluded:

...the Markingson case raises serious ethical issues and numerous conflicts of interest, which University leaders have been consistently unwilling to acknowledge. They have repeatedly claimed that clinical research at the University meets the highest ethical standards and dismissed the need for further consideration of the Markingson case by making misleading statements about past reviews. This insular and inaccurate response has seriously harmed the University of Minnesota’s credibility and reputation.⁶

Our second review examined so-called “adverse events” in a sample of industry-sponsored psychiatry drug studies the University conducted between 2004 and 2014.⁷ We concluded, “the reporting of adverse events by some study researchers has been inadequate.”⁸ More specifically, we said:

- University researchers [have] often provided the IRB with little documentation about the nature of adverse events or whether those events related to the study.⁹
- 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.¹⁰

⁴ AAHRPP, *External Review*, 92.

⁵ Office of the Legislative Auditor (OLA), Special Review, *A Clinical Drug Study at the University of Minnesota Department of Psychiatry: The Dan Markingson Case* (St. Paul, March 19, 2015). Office of the Legislative Auditor, Special Review, *University of Minnesota Department of Psychiatry Industry-Sponsored Clinical Studies: 2004-2014* (St. Paul, June 18, 2015).

⁶ OLA, *The Dan Markingson Case*, 2.

⁷ In general, an “adverse event” is a medical problem involving a study participant that arises during a clinical trial. For more information about “adverse events,” see OLA, *Industry-Sponsored Clinical Studies*, 12.

⁸ OLA, *Industry-Sponsored Clinical Studies*, 1.

⁹ *Ibid.*, 5.

¹⁰ *Ibid.*, 5.

In response to these and other criticisms, on March 12, 2015, University President Eric Kaler directed Dr. Brian Herman, Vice President for Research, and Dr. Brooks Jackson, Vice President for Health Sciences, to establish a team of experts to develop a plan to address the outside reviews' criticisms.¹¹ The University made the plan public on June 11, 2015.¹² In this report, we refer to the plan as the Reform Plan.

The Reform Plan is a complex, 73-page document that proposes a wide range of actions intended to:

- Strengthen training and education of researchers.
- Strengthen the capacity of the University's IRB to review and monitor research projects.
- Strengthen the University's conflict- of-interest policies.
- Require the University's Clinical and Translational Science Institute (CTSI) to manage the Department of Psychiatry's drug and device trials.¹³

President Kaler directed Vice President Herman to ensure all elements of the Reform Plan are complete within 12 to 18 months.¹⁴ The Reform Plan itself contains timelines for each component of the plan—most occur between 6 to 12 months. According to the University, full implementation will cost approximately \$5.5 million in one-time expenses and approximately \$2.4 million in recurring expenses.

The University has provided the Legislature with monthly progress reports. The reports divide actions (and proposed actions) into 15 separate categories, which vary widely in scope and impact. Some involve a single and limited action, such as hiring an outside advisor for the implementation process. Other proposed changes are complex and far reaching, such as overhauling the IRB's structure, membership, and review process.

Our report does not follow the format of the University's progress reports to the Legislature. Instead, we decided that it would be more meaningful to assess the University's progress by

¹¹ A 13-member team composed primarily of University senior faculty and administrators developed the plan. Two members were from outside the University—the chair, a professor of medicine from the Mayo Clinic School of Medicine, and another member, a vice president at Allina Mental Health Services.

¹² University of Minnesota, *Implementing the Recommendations of the External Review of the University of Minnesota Human Research Protection Program Work Plan*, (Minneapolis, June 11, 2015). As noted above, we refer to this document as the "Reform Plan."

¹³ The University's Clinical and Translational Science Institute is part of a national network of similar institutes supported in part by grants from the National Institutes of Health (NIH). According to NIH, the primary purpose of the institutes is to develop innovative solutions that will improve the efficiency, quality, and impact of the research that can improve the health of individuals and the public.

¹⁴ Eric W. Kaler, President, University of Minnesota, memorandum to Brian Herman, Vice President, *Implementing the work plan to improve human research participant protections*, June 23, 2015.

addressing six key concerns we identified in our two reports on the Department of Psychiatry. The concerns include the following:¹⁵

- Recruiting vulnerable people into psychiatric drug studies.
- Conflicts of interest.
- Communications with families.
- Delegating tasks to unqualified people.
- Oversight by the University’s institutional review board (IRB).
- Documentation of “adverse events.”

We assessed progress in these areas by examining University documents and interviewing 24 people involved in designing and carrying out the University’s Reform Plan. We emphasize, however, that the fluid nature of the University’s reform efforts makes it impossible for us to offer a definitive judgment on whether those efforts will be effective. The most we can offer at this stage are observations and a snapshot of a process that is complicated and incomplete.

In addition to the fact that many reforms are still in flux, the University recently appointed a new person from outside of the University of Minnesota to head its Department of Psychiatry. We anticipate that Dr. Sophia Vinogradov, who is currently at the University of California, San Francisco School of Medicine, will play a significant role in shaping and institutionalizing the reforms. Dr. Vinogradov will assume her new position at the University of Minnesota in August.

Assessment of the University’s Reforms

GENERAL ASSESSMENT

The University’s plan to reform its Human Research Protection Program is ambitious and far-reaching. The University has already carried out some reforms while many others are still in process. In fact, some reforms require significant changes in University policies and must proceed through the University’s complex governance system before they take effect. If the University accomplishes and sustains all of the proposed changes, we think it will significantly strengthen protections for human research subjects.

¹⁵ We did not reexamine one issue raised in our Markingson report because it involved the Minnesota Board of Medical Practice, not the University of Minnesota. In *The Markingson Report*, (pages 24-26), we criticized the board for its review of a complaint filed by Mary Weiss concerning Dr. Olson’s treatment of Dan Markingson. We said that the board’s review was compromised because it used a consultant to review the complaint who had numerous conflicts of interest, including a close association with Dr. Olson.

In conducting our review, we were particularly impressed with the thoughtful and positive efforts of the faculty and staff who have been working on the Reform Plan's design and implementation. Many of them told us they were troubled by what the outside reviews revealed about some of the Department of Psychiatry's research practices. They also told us that they were committed to improving the integrity of research throughout the University.

ASSESSMENT OF SPECIFIC CHANGES

1. RECRUITING VULNERABLE PEOPLE INTO PSYCHIATRIC DRUG STUDIES

Central to protecting human research subjects is ensuring that they are capable of providing “informed consent.”¹⁶ We questioned whether Dan Markingson had that ability when Dr. Olson recruited him into a drug study. Not only was Markingson mentally ill, but he also faced commitment to a state psychiatric hospital if he did not cooperate with Dr. Olson.¹⁷ The outside expert panel that examined the University's practices noted that many factors could impair a person's ability to provide informed consent, including “the fear of being subject to an involuntary legal process or perceived noncooperation, even if there is no *direct* threat of such legal compulsion, is an overwhelming barrier to voluntariness.”¹⁸

The University's Reform Plan emphasizes the need to strengthen protections for “research participants who have impaired or fluctuating capacity to consent.” The Plan proposes numerous significant actions that are well-grounded in research and good research practice. Some changes have taken place and others are in process.

The University has made the following policy changes:

- The University now prohibits researchers from recruiting patients held on involuntary 72-hour emergency holds.¹⁹ The policy also bans researchers from recruiting

¹⁶ There are at least four components to a person providing consent: “understanding information relevant to the decision; appreciating the information (applying the information to one's own situation); using the information in reasoning; and expressing a consistent choice.” Laura Dunn et al., “Assessing Decisional Capacity for Clinical Research or Treatment: A Review of Instruments,” *American Journal of Psychiatry*, 163, no. 8 (August 2006), 1323.

¹⁷ OLA, *The Dan Markingson Case*, 10.

¹⁸ AAHRPP, *External Review*, 67.

¹⁹ Minnesota law allows a law enforcement officer to “take a person into custody and transport the person to a licensed physician or treatment facility” if the officer has reason to believe the person is “mentally ill or developmentally disabled and in danger of injuring self or others if not immediately detained.” The person may be held against their will for 72 hours. To hold the person against their will past 72 hours requires a commitment order from a court. State law refers to a “72-hour hold” as an “emergency hold.” See *Minnesota Statutes* 2015, 253B.05.

hospitalized patients for 12 hours after the 72-hour hold expires (also known as the “Intent to Leave” period) and those under a commitment petition.²⁰

The Reform Plan proposes many other important changes related to “informed consent,” but they are still in various stages of development and implementation. For example:

- The Reform Plan says that the IRB must ensure all potential research participants will have access to an advocate at all times during consent discussions.

In addition, the IRB chairs are expected to approve revised informed consent policies on May 25, 2016, that include: clarifying when and how a patient’s Legally Authorized Representative may be involved in the consent process;²¹ and requiring researchers to use a validated “assessment tool” to help determine whether a person has the ability to consent to participating in research.²²

In addition, the IRB is installing a new electronic system for researchers to access approved consent, assent, and recruitment materials.²³ The hope is that the electronic system will reduce the risk of researchers using outdated consent forms; however, this part of the electronic system is expected to go live in March 2017.

2. CONFLICTS OF INTEREST

Conflicts of interest are a persistent concern in research involving human subjects, and they were clearly a concern in the Markingson case.²⁴

Dual-Role Conflicts:²⁵ This conflict occurs when a patient’s treating physician attempts to recruit the patient into a research study the physician is involved in directly. We highlighted this conflict in our report on the Markingson case.

²⁰ The Legislature is currently considering a bill with language that mirrors the policy adopted by the University. If enacted, state law would not allow a patient to participate in a clinical drug trial during an emergency hold unless the patient was already in the trial. As we noted in our report on the Markingson case, in 2009, the Minnesota Legislature enacted legislation that, with some exceptions, prohibits a person under a civil commitment order from participating in a psychiatric drug study. If a court is asked to allow an exception, the law prohibits the person’s treating psychiatrist from also being the psychiatrist conducting the drug study. The law is commonly referred to as “Dan’s Law.”

²¹ A Legally Authorized Representative is an individual or entity (such as a judicial body) authorized by law to grant permission on behalf of a prospective participant for their participation in research activities.

²² See University of Kentucky Impaired Consent Capacity Policy, <https://www.research.uky.edu/ori/ORIForms/62-Impaired-Consent-Capacity-Policy.pdf> or The MacArthur Competence Assessment Tool for Clinical Research.

²³ We explain the new electronic system in more detail on page 14.

²⁴ In addition to the two conflicts we address in this section, in a later section of this report we discuss another conflict we raised in our Markingson report related to the IRB review of Markingson’s suicide.

²⁵ The dual-role conflict relates to the concept also known as “therapeutic misconception.” The concern developed several decades ago when research showed that patients often do not understand the difference between treatment and research. For more information see, *What is Therapeutic Misconception?* at <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2082641/>.

We noted that Dr. Olson was serving as Markingson’s treating physician when he recruited Markingson into a research study—called the “CAFÉ” study—for which Dr. Olson was the study’s principal investigator (lead researcher) at the University of Minnesota. We said:

Rather than continue to treat Markingson with the antipsychotic medication he initially prescribed (and later claimed had been effective), Dr. Olson discussed with Markingson the idea of participating in the CAFÉ study, which meant Markingson would be randomly assigned one of the three study medications. Dr. Olson now had two potentially conflicting roles in Markingson’s life—researcher and treating physician.²⁶

Others who reviewed the Markingson case also found Dr. Olson’s dual roles troubling. For example, a consultant who reviewed the case for the Board of Medical Practice said the fact that Dr. Olson was both Markingson’s treating psychiatrist and the principal investigator on the research study was “not ideal” and “open to criticism as possibly constituting coercion.”²⁷

The Department of Psychiatry has adopted a policy that addresses the “dual-role” conflict (or, as it’s also called, the “therapeutic misconception” issue).

In April 2016, the Department of Psychiatry’s faculty endorsed a new department policy that requires a person other than the treating physician to answer questions about a study and obtain a participant’s consent. The policy says:

To mitigate issues of therapeutic misconception when a study investigator is also the treating clinician of a potential study participant, the investigator/clinician should not be involved in the consenting process. Questions about the study should be answered by another study team member not involved in the potential participant’s clinical care. Potential participants should be given the option to see another clinician, not involved with the study to discuss treatment options before deciding to participate in the study.²⁸

While the new policy does not prohibit a department psychiatrist from being a patient’s treating physician and principal study investigator, it acknowledges the potential for a conflict and establishes a process to reduce the risk to a patient. We think it is particularly noteworthy that the department faculty initiated the change in policy. Moreover, the Director of Research at the Department of Psychiatry, Dr. Kelvin Lim, told us that the policy emerged from extensive faculty discussions about a wide range of ethical concerns.

Financial Conflicts: We found that Dr. Olson’s dual role conflict was compounded by a financial conflict. The pharmaceutical company, AstraZeneca, paid for the CAFÉ study and prorated its payments to the University based on the number of research subjects

²⁶ OLA, *The Markingson Case*, 12.

²⁷ OLA, *The Markingson Case*, 13.

²⁸ Kelvin O. Lim, MD, Professor and Vice Chair for Research to Mark S. Paller, MD, Interim Head, Department of Psychiatry, *Department of Psychiatry Dual Role Consenting Policy*, April 25, 2016.

Dr. Olson enrolled and retained in the study.²⁹ We also reported that the head of the Department of Psychiatry, Dr. Charles Schulz, had received significant consulting fees from AstraZeneca while a co-investigator in the CAFÉ study.³⁰

The University's internal review procedures and governance structure have slowed efforts to address financial conflicts of interest.

Currently, once a researcher's outside income reaches \$5,000 over the past 12 months, a University conflict-of-interest panel reviews whether there is a conflict that needs mitigation.³¹ If one is needed, that mitigation plan must be in place before the IRB will approve the study to move forward.

Under the University's latest proposed policy, researchers would no longer be able to accept **any** personal consulting fees from a company while conducting a study sponsored by the same company, barring compelling circumstances. Any consulting (or speaking fees) would go to the University generally, not toward the researcher's salary. The ban would run from the time the IRB approves the study until participant enrollment closed and the primary study results have been published. A conflict review panel could allow the researcher to receive consulting fees from the same company only if it finds "compelling circumstances."³²

Given the nature of these changes, the proposal must go through several layers of the University's governance process, including the Faculty Senate. The Senate is an advisory body to the President's Policy Committee concerning administrative policies.

In addition, on January 20, 2016, the Service Employees International Union filed a petition with the Minnesota Bureau of Mediation Services to represent all instructional employees on the University's Twin Cities campuses. In response, the Bureau issued a *Maintenance of Status Quo Order* requiring the University "to preserve existing

²⁹ OLA, *The Markingson Case*, 15.

³⁰ *Ibid.*, 18.

³¹ The University's policy, *Individual Conflicts of Interest*, says that each Conflict Review Panel will consist of both voting and nonvoting members. Voting members will be faculty and professional academic and administrative staff and community members whose appointments to the panel have been approved by the University's Senior Vice Presidents. Nonvoting members may include representatives from the Office of Institutional Compliance, Office of Technology Commercialization, Sponsored Projects Administration, Human Research Protection Program, Office of Research Education and Oversight Programs, and Office of the General Counsel.

³² A Conflict Review Panel could choose to consider the extent to which the individual could influence the design, analysis or outcomes of the study; the extent to which the individual's personal remuneration or equity may be influenced by the outcomes of the study; the magnitude of the remuneration or equity and its relation to the research study; the degree of risk for the human participants in the study; the relationship between the activity that results in the personal remuneration or equity and the product, device or technology being evaluated in the study; the extent to which the study would be unable to proceed without the individual's participation because of a unique expertise or skill of the individual; and any other factor deemed relevant.

conditions and promote a free and fair environment for the resolution of [the] question of representation.”³³

The leader of the group working on conflict of interest reforms told us that he understands that the President’s Policy Committee will wait to take any action on the policy until the union organizing process is resolved. Consequently, even if the Senate approves the new policy, the earliest it would take effect would be fall 2016. If the faculty votes to unionize, the policy change may have to wait until a collective bargaining agreement takes effect.

3. COMMUNICATIONS WITH FAMILIES OF RESEARCH PARTICIPANTS

We found the University’s treatment in 2003 and 2004 of Markingson’s mother, Mary Weiss, so troubling that we highlighted it as a concern in our Markingson report.³⁴ We noted that Ms. Weiss wrote letters and made telephone calls to provide Dr. Olson and his study coordinator, as well as Dr. Charles Schulz (chair of the Department of Psychiatry at the time), with information about her son’s condition. Frustrated with a lack of response, Ms. Weiss finally asked the study coordinator: “Do we have to wait until he kills himself or anyone else before anyone does anything.”³⁵

Given what we learned about the University’s treatment of Mary Weiss, we said:

We think [Ms.] Weiss’ observations should have been taken more seriously. When a family member takes the time to compose a letter to the treating physician and the head of the department, common courtesy requires an acknowledgement that the letter was received and a response, even if brief.

The study team should have built a more open and collaborative relationship with Mary Weiss. While she was not a medical professional schooled in psychiatry, she was Dan’s mother and knew her son’s history from birth. She was also in a position to offer an outside perspective given that she drove him to and from his appointments. Even if the team ultimately ruled out her concerns, it should have explained the reasons why so that she knew that those caring for her son had heard her and considered her observations.³⁶

³³ Bureau of Mediation Services, State of Minnesota, MAINTENANCE OF STATUS QUO ORDER, Service Employees International Union, Local 284 and The University of Minnesota, Unit 8 (BMS Case No. 16PCEO644), January 20, 2016.

³⁴ OLA, *The Dan Markingson Case*, 17.

³⁵ *Ibid.*, 17.

³⁶ *Ibid.*, 18.

These are the current policies the University has in place for handling complaints related to human subject research:

- Researchers must list on consent forms the “Subject Advocate Line” (telephone), which the Human Research Protection Program (HRPP) monitors.³⁷ A member of HRPP Post Approval Review staff is supposed to respond to all calls to the Subject Advocate Line and manage any problems reported through that mechanism.
- HRPP staff members work with complainants in a confidential manner to document and log questions, concerns, or complaints. Each staff member is authorized to correct problems to the limit of his/her authority. If the problem requires higher level problem solving, expert consultation may be sought or it may be characterized for the IRB Committee, institutional officials or the Institutional Official as directed by the Executive Director.

Given the time constraints we faced in conducting this follow-up review, we were unable to evaluate how well these policies are followed.

The outside expert panel acknowledged the University’s policies for handling research-related complaints but said the University needed to go further. In its February 2015 report, the expert panel said:

The availability of channels for reporting complaints and concerns about research or unsatisfactory research experiences is an essential component of a human research protection program and of self-regulation more broadly.... The University has developed several such communication channels. However, the ultimate effectiveness of any reporting mechanism requires an institution to receive and respond to information in a fair, confidential, and comprehensive manner, and to ensure both that complainants will not be at risk of retaliation and that they believe that to be the case.³⁸

The Reform Plan recognized the need for improvement and made several suggestions, but much is still in process.

For example, the Reform Plan made several recommendations, including:

- When a research study results in death, disability, or injury, the University must have a system for response to research participants and families that is prompt, empathetic, and informative. The study’s principal investigator must be an integral part of this process and should receive training on these types of discussions.³⁹

³⁷ In order to reduce confusion for subjects, studies connected to the Fairview Health System are permitted to use the Fairview Patient Help Line and Gillette Children’s Health Specialty are permitted to use their Research Office.

³⁸ AAHRPP, *External Review*, 88.

³⁹ University of Minnesota, *Reform Plan*, 30.

- The University should develop and require investigators to distribute a handout (such as a small card) at study enrollment to research participants, family members, and legally-authorized representatives regarding where and how to provide confidential feedback or share concerns about the research procedures, including the mechanism for handling reported concerns. This is in addition to information provided on the informed consent form.⁴⁰

The University says it is still working on a response system to participants and families when a death, disability or injury occurs. The group working on this issue is expected to issue a final report on June 30, 2016.

In addition, we were told that some researchers are providing their own cards to research participants and their families. Nevertheless, we are troubled that the group working on this project has not finalized or implemented a uniform card. A member of the workgroup told us that there have been discussions over language. The last version (third) we viewed was directed at research participants; we have not seen a draft designed specifically for families.

We are encouraged, however, by the Community Oversight Board's composition. The Reform Plan recommended that the Community Oversight Board have a member whose family members have participated in medical research, who themselves were subjects in medical research, or served as surrogate decision-makers. The board includes two members who fit the Reform Plan's definition.

4. DELEGATING TASKS TO UNQUALIFIED PEOPLE

We noted in our Markingson report that a state regulatory board found Dr. Olson's study coordinator, a social worker, performed tasks beyond her competency, and that she made significant mistakes.⁴¹ As a result, the Board of Social Work entered into an Agreement for Corrective Action with the coordinator. While the board only had jurisdiction over the study coordinator as a social worker, we said the board's findings suggested that Dr. Olson inappropriately delegated tasks to his study coordinator and failed to adequately supervise her.⁴²

The Reform Plan does not propose specific qualifications or training requirements for research study coordinators. It does propose improvements in training generally for all people involved in research involving human subjects. Most of the changes are still in the development process.

⁴⁰ *Ibid.*

⁴¹ OLA, *The Dan Markingson Case*, 23-24.

⁴² *Ibid.*

The Reform Plan says:

The team [that developed the Reform Plan] strongly believes that appropriate training of investigators is at the core of creating and embracing a culture where research can be conducted that meets the highest ethical standards.⁴³

According to the officials we interviewed, enhanced training, specifically aimed at the Department of Psychiatry, will be under the control of the University's Clinical and Translational Research Institute (CTSI). Specifically, CTSI's Associate Director told us that the Institute is helping the University develop curricula that will provide additional training specifically designed for researchers who work with people whose abilities to make decisions are impaired.⁴⁴ He also told us that the University is developing training for principal investigators specifically on how to oversee their study coordinators.

While most of the efforts to enhance training are in process, Dr. Steven Miles, M.D., Professor of Medicine and Bioethics at the University, has developed and is teaching a class that addresses 15 topics related to research on human subjects. The class is not required but designed so that anyone interested can selectively participate in presentations and discussions that are of interest. Dr. Miles told us that most of the people who have been attending—about 40—are faculty level; some of whom are on the IRB or in the Office of Vice President for Research.

Dr. Miles told us that, in preparing the class, he gained a renewed understanding of just how complex and challenging it is for researchers to know all of the requirements they must follow. He said:

I think that the federal regs themselves, having now read them all, are actually an obstruction to good research because they're so poorly and incomprehensibly written.... I finally wound up translating them into English.... If people can't read the regs, then they have no idea what the regs are telling them to do. And to make it worse, you've got, for example, data safety monitoring, which is how unexpected problems in research are identified, [but] there's a separate version on the common rule for each of the 23 NIH Institutes. No researcher can handle this [since] each of those variants is written in Sanskrit.⁴⁵

We think Dr. Miles' comment shows the need for training and retraining. The world of medical research that involves human subjects is extraordinarily complex. Obviously, the research itself is complicated and requires high levels of expertise. In addition, as Dr. Miles emphasized, the regulatory requirements are not only complex but also challenging to understand and apply.

⁴³ University of Minnesota, *Reform Plan*, 7.

⁴⁴ Researchers are required currently to complete three hours of online training; trainees must receive another six hours per year. See <http://www.irb.umn.edu/basic.html>.

⁴⁵ OLA interview with Dr. Steven Miles, M.D., Professor of Medicine and Bioethics, University of Minnesota, April 7, 2016.

5. OVERSIGHT BY THE UNIVERSITY'S INSTITUTIONAL REVIEW BOARD

A strong and active Institutional Review Board (IRB) is essential to the University's reform efforts. As an IRB member handbook says, an IRB "is a committee whose primary responsibility is to protect the rights and welfare of research subjects and to function as a kind of ethics committee focusing on what is right or wrong and on what is desirable and undesirable."⁴⁶

An IRB accomplishes its mission primarily through its reviews of research proposals and follow-up monitoring. In addition, an IRB can investigate allegations about a research study or a study team member.

We criticized the University's IRB for its review of Dan Markingson's suicide. We noted that the IRB did not review his medical records, did not seek information from anyone other than Dr. Olson, and did not review information about Markingson's suicide. When we talked last year to the IRB Chair (who is not the current Chair) about the Markingson case, she told us that the IRB cannot ensure that a researcher is following the strict letter of the law or ethics principles. She told us, "The general consensus is really trust your investigators."

The University has implemented and will continue to implement a wide range of changes to strengthen the oversight capacity of its IRB. In addition, the University is in the process of establishing a new Research Compliance Office to investigate certain allegations about research projects, a function previously performed by the IRB.

We think the following four changes are particularly significant:

Expansion of the IRB's Membership and Structure

The University is in the process of revamping its IRB approval process to increase the number of IRB members, panels, and expertise. One of the problems with the current IRB system was that it has been understaffed. According to University officials we interviewed, it was difficult to get people to participate because IRB members were overworked, unpaid, and received no recognition from their department or the medical school for serving on an IRB.

Instead of having four medical panels focused on a particular topic, there will be eight panels with a variety of experts on each of them. If some projects require special expertise and none of the panels have appropriate experts, the University will supplement the panels with a roster of consultants or people within or outside the University who can serve as objective reviewers. Serving on an IRB will also be recognized as a service to the University and members will be paid.

Creation of a Research Compliance Office

In 2015, the University Vice President for Research created the Research Compliance Office (RCO) to consolidate the University's oversight of research compliance with pertinent regulations. Previously, such oversight occurred in various parts of the University—depending

⁴⁶ Robert Amdur and Elizabeth A. Bankert, *Institutional Review Board Member Handbook* (Sudbury, MA, 2011), 5.

on where funds for the research came from, or whether the research involved humans, animals, biosafety, or other areas of focus. The RCO has also assumed responsibility for some investigations—known as “for-cause” investigations—that the IRB previously conducted.⁴⁷ In addition, the RCO will track the ongoing compliance of research projects with regulations and develop accountability measures for approved projects. The University expects to approve policies and procedures for this office in July 2016.

Use of an External IRB

Since we issued our reports last year, the University has outsourced the oversight of 12 psychiatry studies involving human subjects. Previously, the University’s IRB reviewed the research protocols for these studies and provided ongoing oversight. In 2015, the University entered into an agreement with a private IRB (known as Quorum). For studies selected by the University, Quorum has independently examined the research protocols. In 2015, Quorum recommended that one study the University’s IRB had already approved be discontinued, due to what it considered an inadequate study protocol submitted by the principal investigator.

Electronic IRB Tracking of Research Studies

The University is investing approximately \$5 million in a new system to make its entire IRB submission, approval, and review process electronic. Part of the expense is to acquire software packages known as Huron Toolkit and “Click® IRB Software.”⁴⁸ The University expects the new system to streamline the current process which University officials characterize as extremely inefficient and ill-suited for the volume and complexity of research the Human Research Protection Program oversees.⁴⁹

IRB staff and reviewers will start using some elements of the Huron Toolkit in July 2016. But some elements that researchers will use, such as standard operating procedures (SOPs), templates, worksheets, and an investigator manual, will not be available until the end of the year, about three months before the Click® system officially launches in March 2017.

⁴⁷ “For-cause” investigations examine concerns about research compliance in response to a specific allegation. These investigations are not part of routine monitoring of compliance with regulations; they may reflect cases in which researchers have not adequately addressed compliance problems or in which University officials want more information on a particular problem.

⁴⁸ Click®, also made by Huron Consulting Group, is the electronic mechanism (portal) for researchers and IRB staff and members to communicate, submit, and review documents.

⁴⁹ The Program receives approximately 10,000 unique submissions annually. According to an official in the program, under the current system, “[S]ubmissions are e-mailed to our office. Each e-mail and all attachments must be downloaded to PDFs and details about the submission must be added by staff into our database (a system implemented in 2005). Each submission and all subsequent communication must also be added to our document routing system and the online file sharing site reviewers use to access materials. Our database feeds minimal information to a system transparent to researchers. They are able to check basic status information but little else. They may be able to see that a submission is under review but they are unable to view the documents or communication related to that review.”

6. DOCUMENTATION OF “ADVERSE EVENTS”

Federal regulations pertaining to research involving drug studies define an adverse event as “any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.”⁵⁰ Adverse events can also occur in non-drug clinical trials, such as those investigating medical devices.

In a 2015 report, we reviewed industry-sponsored clinical studies the Psychiatry Department conducted between 2004 and 2014. We found that University researchers often provided the IRB with little documentation about the nature of adverse events they reported.⁵¹ Sometimes researchers relied on letters rather than standard forms to report adverse events, leaving out key details that they are supposed to explain. Researchers often did not discuss whether a reported adverse event related to the research study, and 17 percent of the adverse events we reviewed did not indicate when the event occurred.

Deficiencies with adverse event reporting made it difficult for us to determine how well researchers complied with IRB reporting deadlines. We expressed concern that some serious adverse events—such as hospitalizations of research subjects—were not reported to the IRB for months after the event occurred. We recommended some changes to University policies for reporting adverse events in psychiatric clinical studies.

The IRB’s policies, procedures, and forms—including those related to adverse events—are scheduled for review and revision by June 30, 2016. The University, however, has taken a couple of noteworthy actions regarding adverse event reporting since we issued our report.

Revision to Adverse Events Reporting Form

In May 2015, the University revised a form for reporting adverse events to the IRB. The form now asks researchers to explain whether the event was unanticipated and whether it related to the research. Prior to this revision, the form did not request such explanations.

As noted earlier, in 2015, the University transferred some of its psychiatric research studies to a non-University institutional review board, known as Quorum. Studies under Quorum’s review use Quorum’s forms and policies for reporting adverse events; these forms and policies differ in certain respects from the University’s forms and policies. Thus, it is important to consider that changes in the University of Minnesota’s IRB policies and practices will only affect studies that are subject to the IRB’s oversight, not studies that are subject to Quorum’s oversight and review.

Efforts to Ensure More Complete Reporting of Adverse Events

The University has—through presentations and newsletters—tried to improve understanding about which adverse events researchers must report to the IRB. A University official told us that—for the University as a whole, for the period from October 1, 2015, to March 23, 2016—researchers studying human subjects reported to the IRB a sharply higher number of adverse events compared with a similar period one year earlier.

⁵⁰ 21 *CFR*, sec. 312.32(a).

⁵¹ OLA, *Industry-Sponsored Clinical Studies*, 8, 11.

Assessment of Consultant's Allegations

When we began planning our follow-up review earlier this year, we intended to focus solely on the issues we raised in our 2015 reports. In February 2016, however, a report by a University-hired consultant made serious allegations about the Department of Psychiatry's human subject research program. The allegations produced alarming headlines, and legislators asked OLA to assess the validity of the allegations.

Background

In July, the University's Clinical and Translational Science Institute (CTSI) hired a consultant to assess the status of research studies at the Psychiatry Department. CTSI located the consultant through a staffing agency.

CTSI wanted an experienced person to make an independent assessment of research studies being currently conducted at the department—their status, feasibility, and projected end dates. CTSI also wanted the consultant to identify concerns over the quality and completeness of study documents and regulatory files. In addition, to help CTSI develop a plan to manage the Psychiatry Department's clinical research portfolio, the Institute asked the consultant to recommend which studies to close, which studies to remain open, and which staff to retain.

According to the consultant, she interviewed at least 50 people in the Department of Psychiatry, including faculty, research study staff, graduate students, and volunteers, and reviewed more than 100 studies. The consultant met with members of CTSI periodically to relay her observations.

The consultant provided CTSI with a final report at the end of December 2015.⁵² In February 2016, media stories highlighted the report's conclusions and allegations. For example, a *StarTribune* headline read: "Review finds lapses at University of Minnesota psychiatry department; Review suggests ethics problems revealed after a 2004 suicide haven't been resolved."⁵³

The consultant's report contained a wide-range of criticisms and this overall conclusion:

...the standard research practices in the Department of Psychiatry demonstrate a profound lack of knowledge about how to conduct clinical research and an intentional lack of adherence to requirements set forth by the U of M IRB and state and federal regulatory agencies.⁵⁴

⁵² Jan Dugas, "University of Minnesota Department of Psychiatry Assessment Report," December 31, 2015.

⁵³ Jeremy Olson, "Review finds lapses at University of Minnesota psychiatry department: Review suggests ethics problems revealed after a 2004 suicide haven't been resolved," *StarTribune*, February 11, 2016.

⁵⁴ Dugas, *Psychiatry Assessment Report*, 26.

University officials responded by saying that the Reform Plan was addressing many of the issues raised in the consultant's report. But, they also disputed the report's more serious findings.

OLA Review

Given the serious and public nature of the allegations, several legislators asked OLA to assess the validity of the consultant's most concerning allegations. In response, we interviewed the consultant and examined her work papers. We also followed up several times through e-mail and telephone conversations, seeking clarification and additional information.

We were unable to verify the consultant's allegations we reviewed.

- First, interview documentation was inadequate. The consultant based many findings on interviews, but she conducted them alone and did not record them. In addition, we were unable to locate detailed interview notes in the consultant's work papers.
- Second, some of the report's conclusions were general and imprecise. As a result, we were unable to determine which specific studies had the problems cited in the report, and what specific regulations or best practices were violated.
- Third, it was unclear to us how much the consultant conducted follow up research to verify certain allegations that came out of interviews.

Given these deficiencies and our time limitations, we focused on two specific allegations in the consultant's report: inadequacies with obtaining parental consent, and unqualified research staff "operating" MRI machines.

Obtaining Parental Consent

The consultant alleged that a Department of Psychiatry researcher said in an interview that she had enrolled children in clinical trials with only the parents' verbal permission (obtaining written consent later, sometimes by e-mail).

The consultant's account of the interview is as follows:

She [the researcher] approaches children hospitalized at the Fairview Riverside Hospital to see if there [sic] would be interested in participating in a study before talking with the parents. If the child agrees to participate, she will then contact the family. If the parent is not available at the hospital, she will obtain consent by telephone or email. "It is not a concern when the parent signs the form as long as they say yes, we start enrolling. If we wait, they may not be interested." This is a major violation of CFR Part 50: Protection of Human Subjects.⁵⁵

⁵⁵ Dugas, *Psychiatry Assessment Report*, 18.

We conducted a recorded interview with the researcher, and she disputed the consultant's version of their interview. The following is a transcription of our interview with the researcher (edited only to improve readability):⁵⁶

Researcher: I'm 100 percent certain I did not say that. I'm certain she took sentences out of context. So I can tell you what we do. We have a form, which is a permission to contact that is extended to the parents. The parents fill out that information. We call the parents, screening the suitability of the child with the parent on the phone because there a number of things the child can't have before going into an MRI. For example, they can't have braces, they can't be left handed, they can't have any extraneous metal body.

OLA: ...So you don't go to the child first?

Researcher: We eventually have to ask permission from the child because we can't involve a child in research without their consent. But yes...

OLA: So a parent gives permission to contact and then you ask the child?

Researcher: We talk to the parent always. So we screen the child with the parent on the phone.

OLA: Are you seeing children who are in your care?

Researcher: They are not in my care because...I am not a clinician; I am a full time researcher....

OLA: So how does a child come into your world?

Researcher: What happens is the clinician puts the permission to contact in the sheet they receive upon entrance. So the parent sees the sheet that describes the research and if they wish to be contacted they fill it out, and then that clinician sends that permission to contact form to us.

OLA: And then you call the parent?

Researcher: Then I call the parent.

OLA: So then if the parent says ok on the phone....

Researcher: Then we set up the first appointment where they come in, in person.

OLA: It sounds like it's a two-step process with the parents, permission to contact the child after you have the parent's consent to contact the child. Then it's a second step that you need to get the parent's permission for the child to be enrolled in the study.

⁵⁶ OLA Interview with researcher, April 11, 2016.

Researcher: Correct. So if I were to summarize this is how it goes: form goes into file. Family/parent sees form. [If] interested, fills in information. [The] clinician who receives that file e-mails or faxes those forms to us, then we call the parent at their home, explain the research to them – what does it entail, what doesn't it entail. And then if they're willing to participate, we set up a first session. And then during that first session, we explain the research again, and then we have a consent form, and parents and child, you would have the forms in front of you. I would have the form in front of me. We would read it, explain it, and sign it. And it's only after that, that we start such procedures. There is absolutely nothing done with a child before a signature and a date by a parent and a piece of paper. I have never, and I don't know of anybody here that has ever done that.

Since the consultant did not record her interview with the researcher, we cannot know how the above responses compare with what the researcher told the consultant.

Unqualified Staff Operating MRI Machines

The consultant alleged that principal investigators “were delegating non-medical non-licensed and non-credentialed study coordinators to conduct MRIs on study participants.”

First, it is important to note that an MRI system creates images by using a high-powered magnet and radio waves, not radiation. Second, while extremely safe with properly trained staff, MRI machines can cause injuries, such as burns and projectile injuries, if staff members do not have appropriate training.⁵⁷

We followed up on the consultant's allegation about unqualified staff operating MRI machines by interviewing the Associate Director of the University of Minnesota's Center for Magnetic Resonance Research (CMRR) as well as the Center's Lab Manager and Safety Officer. They told us that the consultant never contacted them or the Center's director about claims that untrained researchers were conducting MRIs.

We e-mailed the consultant to ask her who she spoke with at CMRR, and she said it was the “acting CMRR manager.” We could not find an acting CMRR manager on the website. So, we followed up with the consultant and she e-mailed us that it was the same person as the Executive Director of the University's Human Research Protection Program. The director of the program, however, told us she never had a position at CMRR, and CMRR confirmed this.

Next, we looked into training. The associate director told us there are essentially two separate areas of training for conducting MRI scans: expertise and safety. The amount of expertise required depends on what the scan is for: (1) a diagnosis, such as a tumor; or (2) research, such as mapping a part of the brain. The training for each is very different. If *diagnostic*, a technologist must have broad knowledge in different patient populations, diseases, body parts,

⁵⁷ Projectile injuries can occur when objects that have magnetic properties such as ink pens, wheelchairs, or oxygen canisters are pulled into the MRI scanner at rapid velocity. “Preventing Accidents and Injuries in the MRI Suite,” *The Joint Commission*, Sentinel Event Alert, Issue 38, February 14, 2008.

and scanning techniques. The technologist needs to understand how the doctor will use the image. Learning to conduct diagnostic scans takes more time and credentials.

Conducting scans for *research* does not require the same level of expertise because the scans focus on one area of the body, for example brain function, and typically require only understanding of one kind of scan technique. Researchers typically have more training on a particular body part they are studying compared to a technologist who performs diagnostic scans.

Regardless if diagnostic or research, however, those who conduct MRI scans must have the same level of *safety* training because they are in the presence of a powerful magnet. CMRR policies follow guidelines set by the American College of Radiology, which are considered a best practice in the field.⁵⁸ In addition to safety training, CMRR requires research scanners to undergo its MRI operator training and project-specific training. The Lab Manager and Safety Operator told us that CMRR had updated its operator training in the past few weeks partially in response to the consultant's allegations. In the past, CMRR relied on the principal investigators to ensure that their staff completed the operator training. Now, CMRR independently verifies that each researcher has completed the operator training.

We do not know exactly what caused the consultant to have concerns about the involvement of psychiatric research staff with MRI scans. Based on our research and interviews, we were satisfied that CMRR appropriately manages the use of its MRI machines.

Contract Management Concerns

The University brought in a consultant to address complex and sensitive issues at a time when the Department of Psychiatry was under intense scrutiny. Given this situation, affording the consultant independence to find and report problems was important, but that still left room for appropriate—even necessary—contract management that we found lacking.

For example, the University did not directly vet and hire the consultant; officials used a staffing agency to select her. In fact, the University did not have a contract with the consultant that defined her duties and responsibilities. Of particular importance, the University did not specify the consultant's responsibility to verify findings and maintain detailed source documents. Nor did the University specify the consultant's obligation to follow up on issues by meeting with University officials and providing them with additional information after she finalized the report.

Because it did not have a written, detailed contract with the consultant, the University itself was left without the information it needed to verify and follow up on the consultant's findings. We received the following response to questions we asked the University about the consultant's report:

Because many of the [consultant's] observations were general without study identifying information, we asked [the consultant] to meet with us to provide us with additional information and documents to enable us to identify the studies, PIs [Principal

⁵⁸ See ACR Guidance Document on MR Safe Practices: 2013, *Journal of Magnetic Resonance Imaging*, 37:501-530 (2013).

Investigators] or staff involved in her observations in order to take corrective action, but she refused to accommodate that request.⁵⁹

The University's effort to bring in an outside consultant was well intentioned, but inadequate contract management significantly diminished the report's usefulness.

Concluding Comments

As we said at the beginning, the University's plan for improving its Human Subject Research Protection Program is ambitious and wide-ranging. We conclude our assessment by noting that the plan calls on the University to "cultivate a culture of ethics." For example, it says:

The work plan presented here signifies an awareness that reforms are needed and offers a roadmap for improving culture. Culture is an attribute of a community, not an institution. Institutions' policies, procedures, practices, and leadership creates and sustains the ethical culture for its activities. Sustaining an ethical culture for research with research participants will require institutional time and resources. More importantly, it will require personal commitments and an understanding that cultural reform is necessary if health research is to be able to keep its promise of creating better knowledge to serve human health.⁶⁰

As with other proposals in the Reform Plan, we cannot judge at this stage whether the University will succeed in its efforts to "cultivate a culture of ethics." We simply observe that the Plan's authors—mostly University senior faculty and staff—concluded that a shift in culture is needed.

A "culture shift" in any program or organization is a complex undertaking. Some elements of the shift will be clear and tangible; others will be less visible. As the Reform Plan says, "[it] will come from fostering University-wide conversations, better educating research investigators, and setting standards that commit the U of M to an ethical culture of accountability that is a national model for others to emulate." In other words, it will be incremental and take time.

We conclude by encouraging research investigators and others who interact with patients—particularly patients with mental illness—to ensure that the culture shift puts a priority on the needs and interests not only of patients but also their families. Thus, we were encouraged that even before assuming her new position at the Department of Psychiatry, Dr. Sophia Vinogradov, met with Mike Howard, a long-time friend of the Markingson family.⁶¹

⁵⁹ Brooks Jackson, Dean of the Medical School and Vice President for Health Sciences, Memorandum to James Nobles, Legislative Auditor, February 18, 2016.

⁶⁰ University of Minnesota, *Reform Plan*, 16.

⁶¹ Jeremy Olson, "University of Minnesota's new psychiatry head seeks to heal wounds with families," *StarTribune*, April 7, 2016.

Appendix A: Individuals OLA Interviewed⁶²

- Joanne Billings, MD, IRB Chair, Assistant Professor, Department of Medicine
- Michelle Biros, MD, IRB Vice Chair, Interim Department Head and Research Director, Department of Emergency Medicine
- Laura Brod, Chair, Board of Regents Audit and Compliance Committee
- Jill Cordes, Director, Research Administration, Fairview Health Services
- Jan Dugas, Consultant, Department of Psychiatry Assessment Report
- Will Durfee, Professor, Mechanical Engineering
- Debra Dykhuis, Executive Director, Human Research Protection Program
- Milton “Mickey” Eder, Assistant Professor, Department of Family Medicine and Community Health
- Michael Garwood, Associate Director, Center for Magnetic Resonance Research, Professor, Department of Radiology
- Jeramy Kulesa, Safety Officer, Center for Magnetic Resonance Research
- David Ingbar, MD, Professor, Department of Medicine, Pulmonology and Critical Care
- Dean Johnson, Chair, Board of Regents
- Kelvin Lim, MD, Professor, Department of Psychiatry, Vice Chair for Research
- Steven Miles, MD, Professor, Bioethics, Center for Bioethics, Professor, Department of Medicine
- Lori Nesbitt, Consultant, Compass Point Research Report
- Mark Paller, MD, Interim Head, Department of Psychiatry, Executive Vice Dean, Medical School
- Timothy Schacker, MD, Professor, Department of Medicine
- Beth Thomas, MD, Interim Chief Medical Officer and co-chair, Fairview Health Services
- Sarah Waldemar, Director, Research Education and Oversight
- Pamela Webb, Associate Vice President for Research
- Susan Wolf, JD, Chair, Consortium on Law and Values in Health, Environment and the Life Sciences
- Lynn Zentner, Director, Office of Institutional Compliance

⁶² We interviewed two other individuals who asked that we not name them in our report. We also spoke briefly by telephone with the incoming head of the University of Minnesota Department of Psychiatry, Sophia Vinogradov, MD.

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May 18, 2016

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

Dear Legislative Auditor Nobles:

Thank you for providing us a report of your assessment titled, "Protections for Human Subjects in Research Studies at the University of Minnesota Department of Psychiatry: A Preliminary Assessment of Reforms". We are pleased with OLA's recognition that the University's plan to reform its human subject research protection program is ambitious, far reaching and once implemented will significantly strengthen protection for human research subjects.

We are proceeding at a pace that signifies the high priority the University places on this activity while ensuring the meaningful engagement of our most knowledgeable faculty and staff. The implementation plan's deadlines for completion for the 14 different work groups is 12-18 months, and we are pleased that in all areas you affirmed the work group activity is on time and on target according to the original timeline. Our inclusive and consultative process requires significant input from a numerous University constituencies.

Over the past year, the University has made significant efforts to enhance the culture of ethics for human participant research. A full set of our efforts can be found at:

http://www.research.umn.edu/advancehrp/documents/WorkTeams_ProgressSummary.pdf

We appreciated the opportunity to provide this response.

Thank you and warm regards,



Brian Herman
Vice President for Research