

A Prefatory Note on the Final Report

February 26, 2015

From the outset, University leadership and the external review team worked to define parameters for this review that would protect the process from external pressure and ensure full transparency. In support of that goal, we offer the following description of the final steps involved in the completion of this report:

On January 18, 2015, the University contacted Elyse Summers, President and CEO of the Association for the Accreditation of Human Research Protection Programs (AAHRPP), who in turn, contacted the external review team regarding the to completion of the final report.

Specifically, the University sought clarification regarding the time frame, scheduling of a presentation to the University Senate, and whether the team planned to submit the report in draft or final form. The review team established that the report submitted would be considered “final,” and that the team was open to receiving feedback on factual matters and clarity of content. Should such issues be identified, any changes would then be added to the final report as an addendum. Submission of the final report was anticipated to be on February 16, 2015.

Early on February 18, 2015, the review team provided a draft report to Brian Herman, Vice President for Research, and William Durfee, representing the University Senate and copied Lisa Warren, Assistant Vice President, and Elyse Summers of AAHRPP. At the same time, the team informed the University that it required additional time for final editorial revision, clarification of existing text, and work on citations.

In anticipation of the original February 16, 2015 submission deadline, the review team had scheduled a call with University leadership on February 18, 2015 to discuss next steps and answer any questions the University might have. During that call, Dr. Herman indicated that the University had begun to check the document for factual errors. To clarify what constituted a factual error, he described a single example (Item #1, below). He further suggested that the University would like to provide the external review team with a list of other errors for correction. The external review team agreed to review the list and then determine if or how these would be addressed.

While awaiting the “fact check” from the University, the review team completed all editorial work. On February 23, 2015, the review team forwarded the final report in PDF to Elyse Summers at AAHRPP who later that day notified the University that the report was complete.

On February 25, the University provided the review team with a list of eleven items for the review team’s consideration.

Rather than altering the content of our final report, the review team decided to provide this prefatory note, which includes this item by item response:

1. Section 2.1., page 7: The external review team agrees that it was incorrect in stating that Dr. Olson testified in a stay of commitment hearing involving Dan Markingson on November 20, 2003. Dr. Olson’s Examiner’s Statement was provided to the court in writing. Mr. Markingson was also examined by a court-appointed psychiatrist. As this item was the one example cited

during our February 18th conference call with University leadership, the correction was included in the final report.

2. Section 2.3., page 11 and Section 2.3.4., page 14: We agree that there were telephone interviews that occurred by phone in January that are not reflected in the diagram on page 11 of this report. However, these interviews are referenced in the text, section 2.3.4 on page 14.
3. Section 2.3.2., page 14: With regard to our statement that the information provided during the interview process would not be linked to the individuals who were the source of this information, we would like to confirm that we have not done so. To the extent that individuals are named in the report, we address the University's request for clarification in item #9, below.
4. Section 3.2.1.2., page 25: With regard to Table 1, "Protocols by Medical School Department or Division Reviewed at Convened IRB Meetings," we agree that it is more accurate to say "Protocols Active in the IRB Database."
5. Section 3.2.2.1, page 27: We agree that we indicated, in error, that "As of October 17, 2014, the IRB reported that there were 11,182 active protocols." The correct date is July 30, 2014.
6. Section 3.2.3.2., pages 32 and 33: With regard to special investigations conducted under the auspices of the Executive Committee of the IRB, we indicated that "only one of the panel members had a specific background or expertise in either psychiatry or behavioral health." We agree this is incorrect. It was our intention to state that while one member of each panel had expertise in behavioral health, neither panel had expertise in psychiatry, which was the focus of the panels' review. Our conclusion is unchanged.
7. Section 3.3.1.2., page 36: We agree that our statement that "there was no specific requirement as to the timing of training" was not clear and could be seen as suggesting that there is no requirement for training before recruitment begins. That was not our intent. The sentence was a reference to the HRPP policy related to training requirements that existed prior to February 2014; these did not include a requirement that training is "current" in relationship to the submission of protocols for IRB review. In other words, for example, that training did not occur longer than 3 years prior to protocol submission.
8. Section 3.4.4.1., page 71: The final report was already revised to clarify language related to our analysis of the legal basis upon which a surrogate may be appointed to make a research decision for an individual who lacks capacity to consent in Minnesota. We agree that the authority of a health care agent under Minnesota statutes does constitute "applicable law" for some categories of research in accordance with federal research regulation. However, we maintain our view that University policies on what constitutes a "legally authorized representative" do not appear to comport with federal guidance on the topic.
9. Section 3.5., The external review team is not in a position to interpret the Minnesota Government Data Practices Act as it applies to this report. We understand that the University may be required to redact the names of faculty members that we included in our draft and final reports. We carefully considered our decision and do not believe it would be possible to rewrite the section in a manner that would effectively disguise the identity of the individuals in question

without also significantly altering the findings of the review. We believe that deleting the section in its entirety might raise questions about the integrity of the report.

10. Section 3.6.2., page 88: We note your statement that the University responded to a “whistleblower” by following appropriate policies. The section was revised prior to receipt of this comment from the University. We believe the revised section in the final report appropriately addresses this issue.
11. Section 3.6.2., page 89: We would like to note that this section was revised for clarity from the original draft. We acknowledge the University’s statement that it has apologized to the family of Dan Markingson, and we do not believe that this information alters the analysis presented in the above referenced section.

Additional note: In the course of reviewing the report to respond to items identified by the University, the team identified an inaccuracy. On page 80, the report states that, “We found no indication that investigators from the Department included supplemental methods to support comprehension and decision-making for research.” In fact, we had identified one instance in which supplemental methods were used.

February 26, 2015

President Eric W. Kaler
University of Minnesota
Via email

Re: Final report of the external review team regarding the human subjects protection program of the University of Minnesota.

Dear President Kaler,

As you may be aware, we have delivered our final report on the human subjects protections program (HRPP) of the University of Minnesota, and we look forward to discussing our conclusions with you and the Faculty Senate on March 6, 2015. With that, we will have fulfilled our charge.

The University set a high bar when it asked us to evaluate its HRPP against “best practices” and “the highest ethical standards.” We believe the report does so, and we hope that our recommendations define a pathway for achieving the ambitious goals you have established for the HRPP and the University’s clinical research enterprise as a whole. As with any report of this nature, there will be differences of opinion as to its findings and conclusions. Without question some will consider it overly critical and others insufficiently so. But we believe our work will help refocus the conversation and promote a constructive dialogue involving all members of the University community.

In the course of our work, we encountered considerable strength in both programs and people dedicated to advancing clinical research ethics. We found recent changes in IRB policy and practice to represent significant enhancements. We were left with no questions about the sincerity of University leadership in their desire to address the problems of the past by building a program in human subjects research protections that is of the highest quality. But we believe substantial change is necessary.

Our conclusions and recommendations are intended to be “forward looking.” We identified opportunities to enhance components of the HRPP with special attention to research that includes subjects at risk for impaired decision-making or who are otherwise vulnerable to coercion or undue influence. We also made recommendations to strengthen IRB review. We asserted that efforts to rethink organizational structure and lines of reporting will assist the IRB in its educational and compliance functions. We noted that appropriate investment in effort and resources will be required by the University and Medical School.

In its response to this report, the University has an opportunity to signal a change in its culture of human subjects research by creating an expectation of excellence, demanding accountability, and more effectively engaging the community. The University's willingness to commission this independent review and make public its findings reflects a clear determination to achieve excellence in clinical research ethics and it is a bold first step in that direction.

Sincerely,

Anne Donahue, JD
Melissa Frumin, MD, MS
Joan Rachlin, JD, MPH
Megan Kasimatis Singleton, JD, MBE, CIP
David H. Strauss, MD
Jeremy Sugarman, MD, MPH, MA

cc: Elyse Summers, JD
Brian Herman, PhD
Will Durfee, PhD

**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**

Final Report

February 23, 2015

Public Release Copy:

**Private data have been redacted by the
University of Minnesota on pp. 82-84
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Data Practices Act, Minn. Stat. § 13.43.**

Table of Contents

1. Executive Summary
2. Review Background, Approach, and Process Summary
 - 2.1 Background and History of the Review
 - 2.2 The External Review Team’s Approach to its Charge
 - 2.3 Review Process Summary
3. Review of the University of Minnesota’s Human Research Protections Program (HRPP)
 - 3.1 Institutional Leadership Initiatives and Their Impact on the HRPP
 - 3.2 IRB Functioning and Review Process
 - 3.2.1 IRB Membership
 - 3.2.2 IRB Review Process
 - 3.2.3 IRB Functioning as an Independent Investigative Body
 - 3.3 Review of Other HRPP Functions
 - 3.3.1 Education and Training
 - 3.3.2 Scientific Review
 - 3.3.3 Monitoring
 - 3.3.4 Engagement of Research Subjects and the Wider Community Served by the University
 - 3.4 Policies and Procedures for Assessing Capacity to Consent, Vulnerability to Coercion, Longitudinal Assessment of Capacity, Legally Authorized Representatives (LARS) and Applicable Law, and Use of Surrogate Consent
 - 3.4.1 Capacity to Consent
 - 3.4.2 Vulnerability to Coercion or Undue Influence
 - 3.4.3 Longitudinal Assessment of Capacity
 - 3.4.4 LARs and Applicable Law in Minnesota
 - 3.4.5 Use of Surrogate Consent
 - 3.5 Research Protections and the Department of Psychiatry
 - 3.6 Institutional Culture
4. Conclusions
5. Appendices

1. Executive Summary

At the request of the University of Minnesota, an external review team was asked to conduct an independent review of the University's current policies and practices that serve to safeguard the rights and welfare of participants in human subjects research with special attention to research involving individuals who may have impaired capacity to consent to research. Despite the call that the external review team evaluate *current* practices, the request for review occurs in response to longstanding criticism of the University and its Department of Psychiatry following the suicide, some ten years ago, of a young man with psychiatric illness who was a participant in a clinical trial. In this context, and as noted by University President Eric W. Kaler¹, "the intent of this review is to ensure that the University's processes for clinical research on human subjects meet or surpass the established best practices and norms and to instill confidence among faculty and the public that the University of Minnesota Research is beyond reproach."

To fulfill its charge, the external review team examined the fundamental components of the University's human research protections program. The team was granted broad access to University policies and documents related to the conduct of human subjects research. It also had the opportunity to invite and meet with personnel involved in research, research protections, and research administration.

University leadership demonstrated full and unequivocal support for the review and granted complete discretion to the external review team in defining the nature and content of the review. Among the issues the team considered paramount were the structure and function of the Institutional Review Board, research compliance monitoring activities, education of investigators in the ethics and regulation of research, University policies and practices related to consent and the inclusion of individuals with impaired decision-making, and the intersection of research and clinical care, particularly with regard to research conducted within the Department of Psychiatry. Finally, and central to process, was an analysis of the broader institutional culture and the extent to which that culture reflects the University's commitment to the ethical conduct of research.

Given the University's explicit and understandable aim to establish a human research program that is "beyond reproach," the recommendations for revisions and enhancements that are outlined in this report are often weighted in favor of strict, conservative, or protection-oriented policies and practices.

The major findings of this review are as follows:

- Institutional Review Board (IRB) leadership and members were clear in their pride of and in their commitment to the goals of human subjects protection. Recently introduced revisions of IRB policies reflect thoughtful efforts to enhance the quality of research proposals and permit more meaningful review. However, in examining IRB processes from 2011-2014, the external review team found evidence of weak and often inadequately expert review of research. The team believes this leaves the University vulnerable to criticism and its research subjects potentially susceptible to risks that otherwise would be avoidable.
- The federal human subjects regulations that lie behind and most often animate institutional policy and procedure are all but silent with regard to the protection of individuals with impaired decision-making and individuals from populations in which such impairment is likely. Nonetheless, federal guidance documents and a significant academic literature have emerged on these topics, and, absent widely agreed-upon “best practices,” these provide direction for institutions and their IRBs. The University recognizes one such set of recommendations developed by the Secretary of Health and Human Services’ Advisory Committee on Human Research Protections (“SACHRP”) and has incorporated them into its 2014 policy revisions. The University’s revised policy subsequently reflects a substantial effort to integrate these recommendations into practice. In interviews with research staff, the external review team found many examples of carefully designed procedures to assess decision-making capacity and engage surrogate decision-makers in the consent process. However, the team’s examination of research proposals and IRB deliberations at the University revealed inadequate and inconsistent attention to the process of consent, capacity to consent, the use of surrogate decision-makers, and general efforts to address vulnerability of potential research subjects to coercion and undue influence. Finally, the University’s written policies with regard to who may serve as legally authorized representative for subjects who lack capacity to consent do not appear to be fully consistent with regulatory interpretation by the federal Office of Human Research Protections.
- While there is no explicit requirement for ethics education for investigators imposed by the federal research regulations, such education is a requirement of NIH and NSF supported research and is widely considered to be a valuable element of a research protection program. The external review team noted the University’s recent introduction of policy changes that mandate additional training of IRB members. However, the broader educational policies and practices at the University fulfill minimal standards but represent a missed opportunity for a richer and more sophisticated institution-wide approach to investigator training.
- Some research subjects, by virtue of impairment or incapacity, may be unable to fully protect their own interests at the point of study enrollment and during the course of research participation. The external review team observed that inadequate attention has been paid in IRB review and in University, hospital, and IRB policies to research with these subjects. One opportunity the University could consider in order to enhance subjects protection would require

the involvement of clinical staff and others who are independent of the research team in formal gatekeeping roles. Such individuals may serve to mitigate or eliminate the conflict inherent in procedures related to recruitment, consent, and study exit. At Fairview Health Systems, where the relationship between research and clinical priorities in Psychiatry is strained and mistrust of researchers is widespread, the involvement of clinical staff in research functions as independent gatekeepers may help resolve this longstanding problem.

- In interviews, some University personnel described considerable “fatigue” related to what they considered unrelenting and unjustified criticism of the University’s human subjects protection program. In contrast, others expressed bewilderment and frustration that, in their view, the University has failed to understand and remedy problems stemming from and related to “Markingson.” Most striking was the commonly conveyed sense of doubt in leadership’s commitment to human subjects protection. The widespread characterization of a few researchers in the Department of Psychiatry as “untrustworthy” and as creating a “culture of fear” in relation to efforts to enhance the protection of research subjects was of major concern to the external review team.

In conclusion, in spite of considerable evidence of programmatic strength in many of the domains examined, the University’s efforts with regard to human subjects protections do not consistently reflect “best practices” and are not, at this point, “beyond reproach.” Many weaknesses in policy and practice were evident and require attention. Indeed, in the context of persistent internal and external criticism of University research involving populations of patients in which the likelihood of impaired consent capacity is high, the external review team believes the University has not taken an appropriately aggressive and informed approach to protecting subjects and regaining lost trust. A major objective of this report is therefore to identify areas of weakness and to suggest remedial steps that could strengthen the University’s human subjects research protections and rebuild community and institutional trust.

2. Review Background, Approach, and Process Summary

2.1 Background and History of the Review

Faculty Senate Resolution

On December 5, 2013, in response to a petition asking for an investigation of the 2004 suicide of research subject, Dan Markingson, the University of Minnesota Faculty Senate approved a resolution that requested “an external review of clinical research involving human subjects at the University of Minnesota.” (See Appendix 1 for the full text)^{2,3} The resolution called for an independent inquiry that would examine the “current policies, practices, and oversight of clinical research involving human subjects,” particularly research “involving adult participants with diminished functional abilities.” The Faculty Senate made clear in its resolution that -- in contrast to the petition -- it was not seeking a new review of Mr. Markingson’s death. Instead, it suggested that there be an evaluation of the University’s *current* human research protections program (“HRPP”) including its more recent performance. The resolution asked that the inquiry focus on, but not be limited to, research involving adults with potentially impaired decision-making capacity.^{F1, 4}

Despite the charge, the resolution acknowledged that, since the time of Mr. Markingson’s death, “... individuals and groups within and outside the University have raised questions about the study [in which he was enrolled], how Mr. Markingson was recruited into it, his treatment during the study, and the circumstances of his suicide.” Although not the subject of this report, a brief summary of the Markingson case has been included for contextual purposes as that case continues to be central to so much of the criticism directed at the University’s research practices.^{F2, 5, 6}

^{F1}Although both the Faculty Senate resolution and the University’s charge used the term “diminished functional abilities,” the external review team has instead used the SACHRP/SIIDR term “impaired decision-making capacity.” Although these terms are sometimes used interchangeably, the formal definition of a “functional ability” is far broader. See, e.g., The [Encyclopedia of Public Health](#) definition, “Functional ability is the actual or potential capacity of an individual to perform the activities and tasks that can normally be expected.”² “Impaired decision-making capacity” is thus a more precise term for what we believe to be the intent of the resolution.

^{F2}Included among those who have gone on record criticizing the way in which the Markingson case was handled are bioethicists, journal editors, attorneys, researchers, and physicians from around the world, as well as a former Minnesota governor and current state legislators.

Mr. Markingson was a subject in a comparative effectiveness trial of currently marketed antipsychotic medications at the time of his death. He had been enrolled in the clinical trial one day after being placed under an involuntary court order for treatment. The principal investigator of the study was also the psychiatrist who submitted testimony in support of the involuntary court order. The Minnesota State Legislature later passed a law directly addressing the scenario that requires court approval for consent to research under such circumstances.⁷ A more complete summary of the facts of the case and subsequent investigations can be found in Appendix 2.

The Faculty Senate also noted in its resolution that “external evaluations can have the advantage of fresh perspectives not biased by familiarity with current practice, and are a way for the public to have the utmost confidence in the integrity of the research conducted at the University of Minnesota.”⁸ It was the external review team’s intention to discharge its responsibility in that spirit and with the goal of providing a useful roadmap for future conduct and oversight of human subjects research at the University.

The University’s Charge for an Independent Review

In January 2014, Eric Kaler, President of the University, endorsed the Faculty Senate’s recommendation and charged Dr. Brian Herman, Vice President for Research, with overseeing the inquiry, stating that “The intent of this review is to ensure that the University’s processes for clinical research on human subjects meet or surpass the established best practices and norms and to instill confidence among faculty and the public that the University of Minnesota research is beyond reproach.”⁹ Dr. Kaler directed that the review should be conducted “thoroughly, professionally, independently, and transparently” and that “if any deficiencies in our current practices are found, the review should include recommendations for remedying them.” (See Appendix 3 for full text)

A Request for Proposals (“RFP”) was issued by the University in March of 2014. (See Appendix 4) The RFP, among other specifications, called for “a detailed report outlining the strengths and weaknesses of current policies, practices and oversight of clinical research involving adult participants with diminished capacity to provide consent.”¹⁰

The Role of the Association for the Accreditation of Human Research Protection Programs (AAHRPP)^{F3}

On June 5, 2014 the University announced that the Association for the Accreditation of Human Research

Protection Programs (“AAHRPP”) had been awarded the contract pursuant to the RFP process.¹¹

AAHRPP is an independent nonprofit accrediting agency for human research protection programs.

AAHRPP enlisted six individuals whom it believed to be appropriate to participate in the prescribed review. Its subsequent role has been limited to logistical management (e.g., logistics of the site visit, travel, and payment). AAHRPP representatives were not involved in substantive discussions related to the review and did not have access to the team’s communications or report drafts.

External Review Team

Anne Donahue, JD, (Team Member) is a Vermont state representative, mental health consumer advocate, and member of the former Subcommittee on the Inclusion of Individuals with Impaired Decision-making in Research of the Secretary of Health and Human Services Advisory Committee on Human Research Protections, (“SIIDR/SACHRP”).

Melissa Frumin, MD, MS, (Team Member) is a neuropsychiatrist and general psychiatrist at Brigham and Women’s Hospital, and an Assistant Professor of psychiatry at Harvard Medical School. Dr. Frumin has served as IRB Chair for the Partners HealthCare IRB (Brigham and Women’s Hospital and Massachusetts General Hospital) from 2005 through the present. In her role as Chair she is responsible for the review of new protocols, as well as working at the IRB office to review amendments and data safety monitoring reports and participate in non-compliance investigations. She teaches IRB-related topics to the research staff at both hospitals.

Joan Rachlin, JD, MPH, (Team Member) served as the executive director of Public Responsibility in Medicine and Research (PRIM&R) from 1975 to 2014. During those almost four decades, she helped create the premier educational organization for those conducting and reviewing human subjects and animal research around the world. As a practicing lawyer, Ms. Rachlin worked on cases involving health law, women’s health, civil rights, criminal defense, and prisoners rights. She has taught and lectured extensively at Boston-area universities on research ethics, women’s health, and health law.

^{F3} “The external review team understood that the University has previously been accredited by AAHRPP, and learned in the course of its evaluation that the University is in the process of applying for reaccreditation, also through AAHRPP. The external review team had no discussions with AAHRPP related to this reaccreditation nor did the external team have any role in reaccreditation activities that may have been undertaken by either the University or AAHRPP in connection with the application.”

Megan Kasimatis Singleton, JD, MBE, CIP, (Team Member) is Associate Director, Human Research Protections at the University of Pennsylvania IRB. In this role she has oversight responsibility for the University's nine IRBs and their associated support staff. Her areas of responsibility include education, noncompliance, privacy, and conflicts of interest.

David Strauss, MD, (Team Member) is Associate Professor of Psychiatry and Vice Chair for Research Administration, Ethics, and Policy at the Columbia University Department of Psychiatry. He is Director of Psychiatric Research at the New York State Psychiatric Institute and oversees its 23 research divisions and 10 research centers, core research programs and research compliance functions including IRB, Institutional Animal Care and use Committee, conflict of interest, and research integrity. As a member of the SACHRP, Dr. Strauss led the development of its recommendations on the inclusion of individuals with impaired decision-making in research.

Jeremy Sugarman, MD, MPH, MA, (Special Advisor)^{F4} is the Harvey M. Meyerhoff Professor of Bioethics and Medicine, professor of medicine, professor of Health Policy and Management, and deputy director for medicine of the Berman Institute of Bioethics at the Johns Hopkins University. He is an internationally recognized leader in the field of biomedical ethics. His contributions to both medical ethics and policy include his work on the ethics of informed consent, umbilical cord blood banking, stem cell research, international HIV prevention research, global health, and research oversight.

Disclosure

The University funded this review. Members of the review team received consulting fees and reimbursement of travel costs through AAHRPP, the intermediary organization described above. The integrity of this review demanded a process that was free from bias and the appearance of bias, as well as from pressure from both the University and the many interested parties who may be seen as having a stake in the outcome of the review. During the course of the review, University leadership was clear in this message and in its corresponding behavior; apart from clarifying its charge to the review team, its only role was to serve as a conduit for information requested by the review team.

^{F4} Dr. Sugarman served as special advisor to the review team. He assisted the team with questions related to the approach to the review, accompanied the team in its site visit, and served as a reviewer of drafts of this report.

AAHRPP, as the accrediting body for the University's human subjects protection program, might also be seen as an interested party. Therefore, by design, the external review team's contact with AAHRPP was restricted to the logistics of the site visit, travel, and payment.

No member of the external review team has a personal, financial, or professional interest that would be impacted by the outcome of this work. Given the nature of the individual team member's professional careers, three of them have some preexisting connections with the University, its faculty, and/or its human subjects protections program. Each team member was confident, though, that he or she could contribute in an unbiased manner to this report and ensure the integrity of the review process irrespective of those connections. In the interest of full transparency, more detailed biographies and disclosures for each team member have been provided in Appendix 5.

2.2 The External Review Team's Approach to its Charge

In order to meet the tasks outlined by the Faculty Senate resolution and President Kaler's charge letter, the team felt it was essential to review current policies and practices and evaluate the ways in which those policies and practices are *operationalized*. The team, therefore, sought not only to identify whether the policies of the University are aligned with applicable ethical and regulatory requirements but, more importantly, to determine whether the "practice" of human subjects protections at the University paralleled those policies and is sufficiently robust and consistent. Given the limitations on resources, the external review team chose to focus on select components of the HRPP. Among the issues considered paramount by the external review team were the leadership and culture surrounding human research protections at the University, the IRB's functioning and review process, and other critical HRPP functions, including monitoring and scientific review. The intersection of research and clinical care, with regard to research conducted within the Department of Psychiatry, was another area of focus.

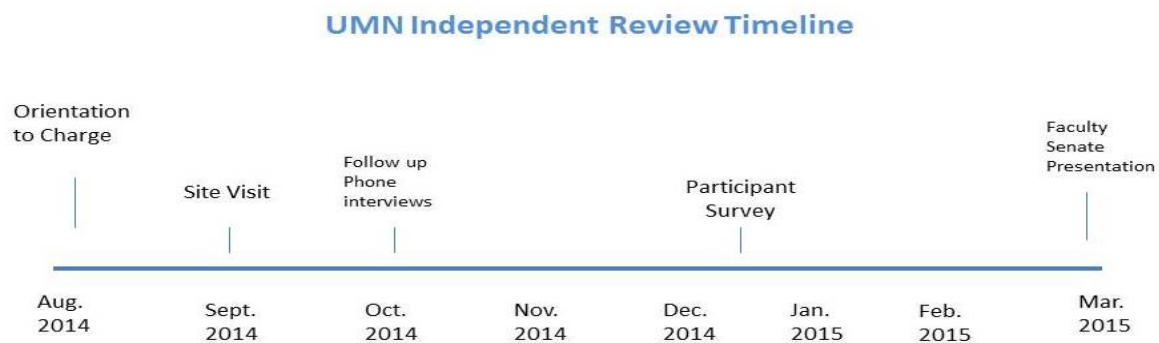
Other limitations of the team's review were the relatively short time designated for work on site and the sheer scope and volume of the University's human research activities, including the fact that many observations derive from review of records that may be incomplete, while others are based on interview data that cannot be independently validated. To mitigate some of these limitations, certain highly relevant source materials are included in appendices so as to more fully provide the background and justification for many of the statements contained herein.

The external review team is aware that this report might contain disputed facts (particularly those resulting from the team’s on-site interviews, due to their inherently subjective nature) and will be subject to scrutiny and challenge. However, the perceptions documented in this report represent specific voices of the HRPP and its stakeholders that were essential in helping the team assess research protections and efforts to enhance them. The external review team is also aware of the perception that this report would “put to bed very soon” questions about the University’s oversight of clinical research. However, this was neither our charge nor our objective.^{12, F5} The team’s goal was instead to attempt an objective assessment of key HRPP functions and thereby to provide observations and recommendations that will provide the University with the actionable information needed to make appropriate culture changes and programmatic improvements. Given the University’s explicit and understandable aim to establish a human research program that is “beyond reproach,” the recommendations for revisions and enhancements that are outlined in this report are often weighted in favor of conservative, or “protection-oriented” policies and practices.

2.3 Review Process Summary

This section will outline the key methods used by the external review team to complete its review.

Figure 1: UMN External Review Team Timeline



^{F5} Medical School Dean Brooks Jackson was a guest on Minnesota Public Radio on February 2, 2015. In the course of that interview, he noted that the issues related to Dan Markingson’s death “were being looked at by an outside group” retained by the University, and that the results were due shortly so “this should be put to bed fairly soon,” although that was neither our charge nor purpose. He also noted that he was “personally very confident that the ethics of the research [at the University] are very good.”

2.3.1. Orientation to the Charge

In order to obtain an understanding of the history and landscape at the University that gave rise to the Faculty Senate's resolution, the external review team requested an introductory conference call with Vice President Brian Herman and Professor Will Durfee.^{F6} This call was held on August 7, 2014; all members of the external review team participated.

2.3.2. Records Review

An integral component of the review process was a thorough review of HRPP documents, including relevant policies and procedures, samples of IRB documentation, and miscellaneous materials independently supplied by stakeholders. Prior to the site visit, the external review team requested an extensive list of documents both to orient it to the HRPP and to assist it in identifying a list of appropriate interviewees. As part of this initial document request, the University was asked to produce a list of active, IRB-approved protocols involving adults with potentially impaired decision-making capacity. From the protocol list developed, the external review team selected a sample of 20 protocols targeting those that recruited subjects with the potential for limited decision-making capacity for a more comprehensive examination. (See Appendix 6 for a summary of the documents examined by the external review team for these studies). It is important to note that, while the external review team considered reviewing individual research subject records from the targeted list of protocols, it was determined to be infeasible due to time constraints.

Since on-site interviews and an examination of the documents produced often led to additional requests for more documentation, the review of records was an iterative process that extended throughout the six-month duration of the team's work. Appendix 7 contains a comprehensive listing of all materials requested, including the dates on which they were requested and the dates on which they were supplied by the University. In order to ensure the confidentiality of those who independently provided the external review team with materials, this list includes only those documents *requested from the University* and a summary of the *types of materials* independently supplied by other stakeholders. The documents shared with the external review team by the University were provided via a password protected document-sharing site.

^{F6} Dr. Durfee was the Chair of the Faculty Consultative Committee at the time of the Faculty Senate's resolution and retained a role as representative of the Faculty during the course of this evaluation.

2.3.3. Site Visit

The external review team visited the University on September 8-9, 2014. The primary purpose of the site visit was to afford the team an opportunity to meet with key stakeholders, including researchers and HRPP staff, and thus to more directly evaluate the University's research and research oversight activities. Based on initial documents received by the review team in August 2014 a list of targeted interviewees was developed. In those instances where the team did not know the names of those who filled a given and relevant role, the University was asked to identify the appropriate individual(s). Notably, the external review team requested to meet with at least three or four research subjects currently enrolled in any of the studies identified on the selected 20 item protocol list referenced above. However, the University indicated that it was not feasible to arrange in-person interviews with subjects due to time constraints, so the external review team therefore considered alternate mechanisms of subject outreach prior to the site visit. Please refer to Section 2.3.5 below for a summary of follow-up measures undertaken toward that end.

In preparation for the visit, targeted invitations, co-signed by Drs. Herman and Durfee, were electronically distributed to the selected interviewees between August 27 and August 28, 2014; interviewees were instructed to contact the external review team directly to arrange an interview time. A general outreach invitation was distributed to the broader community via University listservs to provide notice of the site visit and the opportunity for interested individuals to meet with the review team. This latter, more general, outreach effort was intended to elicit input from as many individuals as possible. All scheduling for the site visit was handled by the external review team.

The response from the targeted (i.e., pre-identified) interviewees was overwhelmingly positive; most immediately responded to the external review team. Those who did not immediately respond were sent reminders, and most of them were then agreeable to scheduling an interview. Of the pre-identified interviewees, only one did not respond to the targeted invitation; another responded but declined the interview request. Two individuals who were not identified on the targeted interviewee list saw the broader outreach notice and contacted the external review team, which then met with one of them while on site and spoke with the second individual via telephone [See Section IV for further details]. A total of 53 individuals were interviewed during the two-day site visit. All of these interviews took place at a hotel near campus so as to maximize the privacy of the interviewees, and none of the interviews were audio or video recorded. In order to further protect their privacy and promote openness, each

individual with whom the team met was promised that their names would not be linked in this report to any of the information they provided. Therefore, neither the report nor appendices link interview-generated information with its source. Two, and usually three, members of the external review team were present at each of these interviews and the entire team was present for two of them. (See Appendix 8 for a summary of the site visit interviews).

2.3.4. Follow-up Interviews

Based on the interviews conducted while on site, the external review team identified four additional interviewees with whom we wished to speak. Telephone interviews were scheduled with all of these individuals and the conversations took place between October 2014 and January 2015. In addition, one telephone call was scheduled with an individual who had contacted the team but was unable to be scheduled for an on-site interview.

2.3.5. Stakeholder Outreach

As indicated above, the external review team was committed to hearing from all relevant stakeholders. In order to accomplish this, an email account was created through which those stakeholders who were interested in sharing feedback or relevant documents with the external review team could easily and privately do so. The availability of the email account was made known to the University community through the aforementioned announcements. Nevertheless, some stakeholders contacted review team members personally.

As previously described, the external review team believes that research subjects (both current and former) and their advocates are critical informants in the process of collecting data and developing its recommendations. Therefore, the team independently sought out and scheduled a meeting with members of the Minneapolis/St. Paul chapter of the National Association of Mental Illness (NAMI). Meeting attendees included family members of former research subjects.^{F7} In addition, when early attempts to identify research subjects for in-person interviews during the external review team's site visit were determined to be infeasible, further opportunities for subject outreach were considered. Those included: 1) "snail-mailed" letters to current and former research subjects inviting them to contact the team, and 2) electronic invitations targeted to research subjects asking whether they might provide information to the team.

^{F7} Note that NAMI, a nonprofit advocacy organization, does not purport to represent the broader community of those individuals who have experienced mental illness or who have participated in research.

However, despite a continued commitment to have the perspectives of research subjects represented, the team's ability to identify and reach research participants was substantially constrained by concerns about the process through which current and former subjects could be identified and contacted, as well as by the lack of established electronic communication channels to reach the community of research subjects who had participated in, or had been approached to participate in, University research studies.

In a final attempt to afford research subjects and their family members an opportunity to provide input to the external review team, a brief online survey was developed. The survey was open for responses between December 16, 2014 and January 12, 2015. The University's HRPP leadership was asked to identify mechanisms for announcing its availability to the research subject community. (See Appendix 9 for a copy of both the online questionnaire and the dissemination strategy employed to announce the survey). A total of eighteen survey responses were received; the review team attributes the low number of responses to the time of year and the limited electronic means available to communicate the survey's availability. Subject feedback is more thoroughly discussed in section 3.3.4.2. of this report.

References for Sections 1 and 2

¹ Letter from President Eric Kaler to Vice President for Research Brian Herman re: Human Subject Research Review, Dated Jan 24, 2014. See Appendix 3 for the full text.

² Petition letter to President Eric Kaler calling for an investigation into the death of Dan Markingson, dated 10/21/2013.

³ University of Minnesota Faculty Senate resolution, dated December 3, 2013, *Issues Arising from the CAFÉ Study and the Suicide of Dan Markingson*. See Appendix 1, or access the text at:
<http://www1.umn.edu/usenate/resolutions/131205panelres.html>

⁴ University of Minnesota Faculty Senate resolution, December 3, 2013, *Issues Arising from the CAFÉ Study and the Suicide of Dan Markingson*. See Appendix 1, or access the text at:
<http://www1.umn.edu/usenate/resolutions/131205panelres.html>

⁵ See Appendix 2 for a brief summary of the events leading up to Dan Markingson's suicide.

⁶ A sampling of media stories describing the ongoing controversy can be accessed at:
<http://www.myfoxtwincities.com/story/23994239/investigators-side-effects-of-drug-study>
<http://www.minnpost.com/second-opinion/2013/11/u-m-bioethicist-latest-call-independent-look-schools-troubling-markingson-cas>
http://www.twincities.com/ci_9292549
<http://www.startribune.com/local/263745911.html>
<https://www.change.org/p/governor-mark-dayton-of-minnesota-investigate-psychiatric-research-misconduct-at-the-university-of-minnesota-2>
<http://www.minnpost.com/second-opinion/2013/12/faculty-senate-votes-inquiry-us-clinical-trial-practices>

⁷ See Appendix 17 for a summary of relevant Minnesota statutes.

⁸ University of Minnesota Faculty Senate resolution, December 3, 2013, *Issues Arising from the CAFÉ Study and the Suicide of Dan Markingson*. See Appendix 1, or access the text at:
<http://www1.umn.edu/usenate/resolutions/131205panelres.html>

⁹ Letter from President Eric Kaler to Vice President for Research Brian Herman re: Human Subject Research Review, Dated Jan 24, 2014. See Appendix 3 for the full text.

¹⁰ University of Minnesota Request for Proposal. Accessed at: <http://www.research.umn.edu/news/external-review-rfp.html>

¹¹ Press Release "University of Minnesota Hires Internationally Recognized Organization to Manage Review of Human Protections Programs" dated 6/5/2014 and accessed at:
http://www.research.umn.edu/news/documents/AAHRPP_Release.pdf

¹² See: <http://www.mprnews.org/story/2015/02/06/board-of-regents>

3. Review of the University of Minnesota's Human Research Protections Program (HRPP)

The external review team limited the scope of its evaluation to four critical questions:

- 1) Is research carried out in an environment and culture that enhances human subjects protections?
- 2) Is research at the University subject to a comprehensive review and oversight process?
- 3) Does the HRPP as a whole function in a way that maximizes human subjects protections?
- 4) Do the policies and procedures of the HRPP, specifically related to research involving adults with the potential for impaired decision-making capacity, adhere to *de minimis* ethical and regulatory requirements?

In each of the following sub-sections an introduction is provided, followed by key observations and conclusions, and actionable recommendations for improvement.

3.1. Institutional Culture: Leadership Initiatives and their Impact on the HRPP

3.1.1 Introduction

Strategic plans and announced institutional initiatives are formal articulations of an institution's priorities and its plans to ensure that those priorities are addressed. The external review team examined the University's strategic planning documents in order to understand how human subjects protections align with the institution's publically-stated priorities.

3.1.2. Observations

Strategic plans had recently been developed outlining priorities for the overall research program, the School of Medicine, and the Department of Psychiatry.^{1,2,3} All three plans were examined as part of this review, but the strategic plan for the Department of Psychiatry is discussed in brief in Section 3.5 of this report. The University's "Risk Recalibration" initiative was also reviewed.⁴

The University's Research Strategic Plan

The University's Research Strategic Plan, completed in October 2014, is titled "Five Years Forward" (*FYF*) and represents the "collective voice of the university's leadership and research community."⁵ *FYF* is an impressive blueprint for the University's research goals, as it commits to creating both a "culture of

serendipity" and a "culture of excellence." The plan includes important aims that represent a clear commitment to research, such as ensuring "high quality, state of the art research systems, capabilities and space," and "focusing knowledge and innovation on solving society's most urgent and formidable challenges." The plan also includes goals that have implications for research oversight and review processes including "reducing the faculty's administrative burden."

The four goals in this extensive strategic plan are:

1. Enhance research excellence
2. Advance transdisciplinary partnerships
3. Accelerate the transfer of knowledge for the public good
4. Promote a culture of serendipity

Within each of those four stated goals there is a notable absence of specific objectives relevant to human subject protections or research ethics more broadly.

The School of Medicine Strategic Plan

The School of Medicine also recently launched a new strategic plan titled "Strategic Vision 2025" that sets forth a commitment to achieving a culture that "demands and rewards excellence."⁶ Comparable to *FYF*, this strategic plan includes admirable research-related goals including the provision of "infrastructure support to enhance research outcomes."

The plan also recognizes that advances in clinical research are inextricably linked to the willingness of individuals to participate as research subjects and includes a specific goal of increasing clinical trial participation to achieve levels that are commensurate with the School's self-selected peers. However, the plan, similar to *FYF*, it lacks specific metrics relevant to human subjects protections as a measurement of its self-proclaimed desire to achieve "excellence" in research.

When questioned about the omission of human subjects protections as a core component of strategic planning for research, one interviewee from the Medical School acknowledged that absence and further recognized that this omission may represent a missed opportunity.

The University's "Risk Recalibration" Initiative

The "Risk Recalibration" initiative was developed by the Office of the Vice President for Research ("OVPR") and was designed to reduce administrative burden on faculty researchers.⁷ The initiative covers many aspects of research and includes plans to "strategically evaluate and manage risk related to research practices, policies and procedures," and to "support research infrastructure and practices that help faculty to focus more on research and less on unnecessary administrative tasks."

One recent change in practice implemented pursuant to this initiative is the reported elimination of the "Responsible Conduct of Research (RCR) continuing education course requirement for faculty, resulting in 3,900 hours in total annual time savings."⁸ It was hard for the external review team to understand why researcher education in ethics and responsible conduct of research would be considered an "administrative burden," especially at a time when the University's leadership should be signaling its intention to *strengthen* its protections for research subjects. Indeed, if the University feels that its existing RCR program is somehow repetitive or lacks sufficient content to merit the continuing education requirement, then the solution — especially given the challenges to the University's research program in recent years — would seem to be to enhance and improve the content of the course offerings, rather than simply eliminating the requirement altogether.

This institutional commitment to reducing administrative burden was referenced in multiple on-site and follow-up interviews with the external review team. Although the team was unable to evaluate whether the risk recalibration initiative has had any measurable impact on the way in which researchers and HRPP/IRB staff approach their responsibilities with respect to human subjects protections, it was clear that the goal of reducing administrative burden was prominent and well-publicized.⁹

3.1.3. Conclusions

As mentioned above, no readily discernible mention of research ethics and human subjects protections was found in the strategic planning documents of either the University or the School of Medicine. There *is* language about metrics, systems, and growth for research, but no explicitly stated commitment to enhancing the protection of research subjects. Moreover, the prevailing institutional message regarding University research is one of risk recalibration and *reduction* in administrative "burden," with one major

such “burden” being identified as a course in RCR education. These messages are potentially inconsistent with the University leadership’s stated goal of creating a strong and sustainable framework for supporting increased oversight of research with human subjects.

The absence of discrete objectives and metrics to measure excellence in human subjects protections is also of relevance in light of the recurrent concerns that have been raised about the adequacy of the University’s HRPP (most specifically with respect to research involving adults with potentially impaired decision-making capacity). Similarly, strategic planning documents and related initiatives such as those discussed above would have been an ideal place in which to delineate plans for the creation of a robust culture of ethics across the University's research programs.

For example, *FYF* could have called for a reexamination of *all* of the University’s policies and educational plans regarding human subject protections or research ethics education more broadly. Based on the external review team’s discussions with leadership and faculty, it is evident that the University values and supports research ethics and ethics education, but without restating and renewing that commitment in *FYF*, *arguably the most influential University document pertaining to research*, an opportunity has been lost. Such a powerful and public recommitment might have helped reverse the perception that neither the University’s wider research program nor its HRPP is as vigilant as either might be about the ethics of research.

3.1.4. Recommendations

The external review team recommends that the University, through the office of the OVPR:

1. Publicize unequivocal statements on the administration's intention to create and nurture a culture of ethics in research; the OVPR must then animate these values to life by investing in their visibility and adoption at all levels of the University’s research enterprise;
2. Convene a task force that would include research subjects, research ethicists, educators, researchers, and HRPP/IRB staff to consider ways in which ethics and ethics education on the topics of research subject protections will be integrated into practice;
3. Explore ways in which an acknowledgement of the primacy of research subject protections and ethical research could be integrated into relevant University publications, materials, and web pages;

4. Incorporate the University's stated commitment to, and plans for strengthening, research ethics and research subject protections in future strategic planning;
5. Require all departments engaged in clinical research to acknowledge this refocusing of University research priorities and craft statements reflecting their own commitment to excellence and accountability in human subjects protections.

References for Section 3.1

^{1,2,3} See *Five Years Forward* and *Strategic Vision 2025*. Accessed at:
<http://research.umn.edu/forward/index.html#.VOPsCWAtHIU>;
http://www.med.umn.edu/prod/groups/med/@pub/@med/documents/asset/med_asset_451013.pdf;
Department of Psychiatry Strategic Plan, See Appendix 7: Documents Requested by the External Review Team

⁴ See a description of the “Risk Recalibration” initiative. Accessed at:
<http://www.research.umn.edu/about/risk.html>

⁵ See *Five Years Forward*, The University of Minnesota’s Research Strategic Plan. Accessed at:
<http://research.umn.edu/forward/index.html#.VOPsCWAtHIU>;
See also Annual Report on the Status of University Research and Commercialization of Intellectual Property Five Years Forward. Accessed at: <http://www.research.umn.edu/documents/2014Report.pdf>

⁶ See University of Minnesota School of Medicine’s Strategic Plan, *Strategic Vision 2025*. Accessed at:
http://www.med.umn.edu/prod/groups/med/@pub/@med/documents/asset/med_asset_451013.pdf

⁷ A Description of the “Risk Recalibration” Initiative. Accessed at: <http://www.research.umn.edu/about/risk.html>

⁸ Dennis, E. “Rightsizing Faculty Education Requirements.” Accessed at:
<http://inquiry.research.umn.edu/tag/risk-recalibration/>

⁹ A sampling of some of the many relevant sites referring to the goal of reducing administrative burden or “risk recalibration.” Accessed at:
<http://inquiry.research.umn.edu/tag/risk-recalibration/>;
<http://blog.lib.umn.edu/asrweb/newsandnotes/2012/04/risk-recalibration.html>;
http://www1.umn.edu/ohr/prod/groups/ohr/@pub/@ohr/documents/asset/ohr_asset_494321.pdf;
<http://global.umn.edu/operations/hsp.html>;
<http://president.umn.edu/content/president-kaler%E2%80%99s-march-2013-report-board-regents>

3.2. Institutional Review Board (IRB)

The IRBs at the University oversee research at all five campuses, i.e., Crookston, Duluth, Morris, Rochester, and the Twin Cities. The University IRB also serves as the IRB of record for both the Gillette Children's Specialty Care and for Fairview Health Services ("Fairview").¹

3.2.1. IRB Membership

3.2.1.1. Introduction

There are five distinct University IRB committees: 1) Medical (meets weekly), 2) Faculty Social/Behavioral (meets monthly), 3) Student Social/Behavioral (meets monthly), 4) Continuing Review for the Medical Committee (meets monthly) and 5) Executive (meets monthly). The Executive committee is made up of IRB chairs and vice chairs of the other committees and functions as a convened IRB, but also investigates possible incidents of non-compliance, unanticipated problems, etc. The Medical IRB has a particularly heavy load with five meetings per month (weekly, new protocol panels, and a monthly continuing review panel). Given that the majority of protocols requiring full IRB review are medical in nature (e.g., those involving the testing of drugs, devices, biologics, or other interventions in the health sciences) and that these interventions usually pose greater risks, the team focused its examination on the medical IRB. The team did not look at either the Faculty Social/Behavioral IRB or the Student Social/Behavioral IRB and thus cannot comment on their policies or procedures. No one we interviewed and nothing in any of the documents reviewed suggested that any problems exist with those committees. Therefore, any observations, conclusions, and recommendations in this and other sections are not applicable to them.

3.2.1.2 Observations

As per the federal regulatory requirements for IRB composition, "each IRB shall have at least five members, with varying backgrounds to promote complete and adequate review of research activities commonly conducted by the institution."² (Please note that the foregoing citation applies to the additional direct quotes from 45CFR46 in this section). In addition, "the IRB shall be sufficiently qualified through the experience and expertise of its members" and must possess "the professional competence necessary to review specific research activities." Finally, "if an IRB regularly reviews research that involves a vulnerable category of subjects, such as children, prisoners, pregnant women, or handicapped

or mentally disabled persons, consideration shall be given to the inclusion of one or more individuals who are knowledgeable about and experienced in working with these subjects.”

The University’s policy on IRB membership incorporates these requirements and states that “typically, at least one IRB panel member has primary professional expertise in a scientific field relevant to the type of research reviewed by that panel, and at least one member has primary concerns in a nonscientific field.”³

The complete list of IRB members can be found on the University’s website.⁴ The quorum for the medical meeting is five members and attendance at meetings is based on nine member slots, pulled from a pool of 37 potential members, and includes physician scientists, other scientists, and non-scientist members. Although there is a large pool of 37 members from which to draw, most Medical IRB members attend sporadically, resulting in there being only between five and seven members at many meetings. The average Medical IRB member attended approximately six out of the 26 meetings held between January and July 2014. The review team did not identify or receive a policy regarding IRB member attendance, although that is not to suggest one does not exist.

At the request of the external review team, the IRB created a listing by medical school department or division the 933 protocols reviewed at a convened IRB meeting in the previous year (October 1, 2013 through September 30, 2014). Eight departments or divisions in the medical school generated approximately 50% of the protocols submitted for convened IRB review. The greatest number of protocols originated from adult hematology, oncology, and transplant (145), followed by psychiatry (85), and cardiology (60).

Table 1: Protocols by Medical School Department or Division Reviewed at Convened IRB Meetings from October 1, 2013 through September 30, 2014 with Corresponding Committee Expertise

Medical School Departments/Divisions	Number of Protocols	MD or PhD members with specific expertise in the field
Adult hematology, oncology and transplant	145	0
Psychiatry	85	1
Cardiology	60	0
Surgery	46	0
Pediatric blood/marrow transplant	45	1
Pediatric hematology	44	1
Pediatric endocrine	34	0
Neurology	31	0

As shown in Table 1, general expertise did not correlate with the types and volume of research protocols submitted to the IRB. Of note, there were no individuals on the IRB during this time period with expertise in adult hematology, oncology and transplant, cardiology, surgery, or neurology, although those fields taken together represented over 300 protocols. There was only one psychiatrist on the IRB, despite the fact that the Psychiatry Department submitted 85 protocols for review during the time period examined.

Based on IRB minutes from January through July 2014, the psychiatrist on the IRB roster attended only four of 26 Medical IRB meetings at which new protocols were reviewed. Thus, at 22 of the 26 meetings at which new IRB protocols were reviewed, there was no member present with an expertise in psychiatry. Further, while in attendance at these meetings, the psychiatrist recused himself from reviewing four new protocols or changes in protocols in order to avoid a potential conflict of interest (COI) or the appearance of a conflict. The recusal in these situations left the IRB without expertise in psychiatry, and in three of the four recusals an IRB staff member was required to join the meeting in order to maintain a quorum.

When an IRB lacks a member with relevant expertise in a given area, federal regulations permit it to “invite individuals with competence in special areas to assist in the review of issues which require expertise beyond or in addition to that available on the IRB.”^{5,F1} Despite the many situations in which psychiatry protocols were reviewed without a psychiatrist present, no other expert was called upon to

provide supplemental review. Instead, the external review team was told that experts were rarely brought in for consultations.

The external review team was told by some of those interviewed of a relatively recent policy change that eliminated the compensation previously available to members of the Medical IRB (unless the faculty member's department had specifically budgeted compensation). This is quite predictably an impediment to attracting and retaining qualified IRB members. It should be noted, though, that IRB chairs continue to receive compensation.

3.2.1.3 Conclusions

The IRB is, by its very charge, at the core of an HRPP. Its importance as the independent body charged with ensuring that any research it approves is both ethically and scientifically sound cannot be underestimated.

This makes it all the more concerning that the Medical IRB does not routinely have the requisite number of members or expertise at its meetings to properly handle the number of studies it reviews. Specifically, as described above, based on its review of several sets of meeting minutes and associated protocols, it was clear to the external review team that the membership of the Medical IRBs did not include sufficient members with the scientific expertise necessary to adequately address the research being reviewed at corresponding meetings. This departure not only contravenes the University's own policy of having at least one member with "primary professional expertise in a scientific field relevant to the type of research reviewed by that panel," but also prompts concern about the quality of review. Members who have expertise in the fields from which the protocols are drawn are uniquely suited to raise questions about study design, risks, inclusion criteria, etc. They can also educate the other members of the IRB on clinical and scientific aspects of the protocol so that other members' votes are informed. In light of the deficiencies discussed in the scientific review process as noted in Section 3 (c) (ii) of this report, the lack of sufficient expertise to fulfill this role is more concerning.

^{F1} Additionally, the regulations contemplate the use of consultants or experts in "special areas" which "require expertise beyond or in addition to that available on the IRB." Consultants are not to be used, though, as a substitute for the requirement that an institution's IRB include members that possess the expertise needed to "promote complete and adequate review of research activities commonly conducted by the institution." <http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.html>; section 107(f).

While the external review team believes that the University values its IRB, it does not adequately support them by ensuring that a sufficient number of members are present at meetings to handle the volume of protocol review. Further, the “roving” nature of IRB quorums, with majorities of IRB members failing to attend each meeting, predictably leads to a lack of continuity, consistency, and sustained attention to systemic issues. The failure to have either adequate number of IRB members, or adequate expertise, during IRB deliberations raises profound questions about the IRB’s ability to conduct a robust and reliable protocol review.

3.2.1.4. Recommendations

In light of these observations, the external review team recommends that the University:

1. Implement guidelines regarding IRB meeting attendance in order to ensure that a larger, more critical mass of members are present at each meeting;
2. Broaden the membership of the Medical IRB to ensure that it includes individuals with expertise reflecting the nature and volume of the University’s research;
3. Consider providing compensation, or alternate incentives (e.g., released teaching time, reduction of other responsibilities, consideration during promotion, etc.) to foster and support qualified faculty participation on an IRB.

3.2.2. IRB Processes and Functioning

3.2.2.1. Introduction

As of October 17, 2014, the IRB reported that there were 11,182 active protocols. Of these “active” protocols, 6,772 (approximately 60 %) qualified for exemption. Of the 4,410 non-exempt protocols in which continuing IRB oversight was warranted, 2,664 were medical (60%), 1,134 Faculty Social and Behavioral (26%), and 612 Student Social and Behavioral (14%). The external review team examined IRB processes and functioning by examining complete sets of minutes from January-June 2014 for each IRB. It also reviewed IRB policies and procedures, IRB application forms and review tools, IRB rosters (including the resume for each member), and IRB documentation related to specific reviews. (See Appendix 7 for a complete set of all documentation requested and reviewed). Additionally, the external review team’s site visit included interviews with HRPP and IRB leaders and staff, IRB members, and IRB Chairs.

3.2.2.2. Observations

As in our review of the IRB meetings, in which we focused on the medical IRBs, the external review team focused its examination on biomedical research proposals. At the weekly Medical IRB meetings for new protocols, between January and June 2014, there were 26 IRB meetings that included the review of 127 new biomedical applications, along with a number of other reviews, addressing changes in protocols, responses to deferrals and requested changes, and continuing review applications.

In the majority of the minutes from meetings at which new biomedical research proposals were reviewed, the team found little discussion of the risks and benefits to subjects. Requests for “Changes in Protocol,” for example, which primarily involved modifications of the inclusion/exclusion criteria--changes that may increase or decrease risks to subjects--were almost always approved without any documentation of related discussion. Instead, most of the changes required by the committee were to address administrative issues, e.g., misspellings, adding standard language to consent forms, etc. Even in those protocols where more substantive changes appear to have been made (e.g., an increase in monitoring of liver function tests, or revisions based on new requirements from the Data Safety Monitoring Board or Data Monitoring Committee), the minutes contain few details regarding either the nature of the changes or the reasons they were made. Without adequate documentation indicating that such important background information was, in fact, discussed, the external review team was not able to ascertain whether or not a thorough and meaningful discussion about the protocol’s risks and benefits took place. Without such documentation, and since supplemental information (e.g., on site interviews) did not contradict the impression that the discussion on many protocols was scant, it is unclear whether an adequate review had occurred.

Additionally, informed consent and protocol violations were noted in the minutes but not described in any detail. When a “deferred” or “response to stipulations” (i.e., a response to the required changes) application was on the agenda, the minutes did not reflect any discussion that might have taken place about either the details or sufficiency of the changes made by the principal investigator, thereby making it impossible for the external review team to determine how the committee came to the decision to approve the proposed modification(s).

Another area of concern encountered by the team related to “controverted issues.” A controverted issue usually means that there are questions, or at times disagreements, requiring a more extended

discussion about a given protocol.⁶ Examples of controverted issues include concerns about placebos, payment to subjects, recruitment methods, risks, etc. In each set of minutes received by the team there is a section titled “Discussion of Controverted Issues Summary.” Most of the minutes reviewed, however, stated that “there were no controverted issues,” even on those occasions when the required changes would seem to have warranted a more substantive discussion and where the IRB correspondence to the study teams indicated that “controverted issues” *had* in fact been discussed. Accordingly, the minutes did not completely or accurately appear to represent what occurred during the IRB meetings.

The external review team also observed that there were many agenda items that might have been approved in an expedited, administrative manner, e.g., a change in research staff, a new recruitment advertisement, etc., but that were instead brought to the full IRB. The inclusion of these items on the meeting agenda suggests that certain administrative items that do not require full committee review (i.e., as they do not typically impact the criteria for IRB approval) may be unnecessarily consuming valuable time that could be better spent dedicated to issues requiring more substantive discussion.

In addition, the length of time allotted for IRB review was alarmingly inadequate given the number of complex items scheduled for review on many of the IRB agendas reviewed. The team reviewed the minutes from meetings dedicated to the continuing review of already approved protocols from January through June 2014. The team requested the number of continuing review submissions and the specific length of time allotted for each meeting for July through September 2014. A summary of the data provided is listed below in Table 2.

Table 2: Continuing reviews and meeting duration (July through September, 2014)

Meeting Date	Continuing Reviews (#)	Length of Meeting (minutes)	Average time for the review of each protocol (minutes)
July 30, 2014	57	180	3
August 27, 2014	37	190	5
September 24, 2014	46	150	3

Though some continuing reviews are straightforward and could conceivably require only five minutes, the sheer number of action items raises questions about the depth and thus quality of reviews.

3.2.2.3. Conclusions

The review process, as documented in the minutes, does not reflect a meaningful discussion of the risks and benefits of research protocols and the necessary steps taken to protect human subjects in the face of scientific or ethical concerns. Although some discussions were included in the minutes, most of the minutes stated that there were “no controverted issues.” In fact, the majority of required changes were restricted to administrative issues despite. Very occasionally, some required changes were “controverted” and the IRB correspondence to the study teams indicated that “controverted issues” *had*, in fact, been discussed. However, the minutes nonetheless stated that there were no controverted issues. Accordingly, the minutes reviewed by the team did not appear to completely, accurately, or consistently represent what occurred during the IRB meetings.

While required discussion may have occurred, it was not appropriately documented, and the protocols, minutes, and agendas provided to the external review team did not therefore consistently reflect an in-depth review by the IRB. Thus, the inadequate documentation of review and the sheer volume of research being reviewed, combined with the membership issue described in section 3.2.1., suggest that the IRB review process may be unacceptable, and that it often contravenes the IRB’s own policies and procedures.

3.2.2.4. Recommendations

In light of these observations, the external review team recommends that the University:

1. Revise the format of the convened IRB meeting minutes to include a meaningful summary of the study, any controverted issues that are discussed, their resolution, and documentation to support the IRB’s rationale for requesting modifications to the study;
2. Consider whether certain actions may not warrant convened IRB review and therefore may not require discussion at the convened IRB meeting, freeing up time for the discussion of more complex and challenging protocols;
3. Consider developing a system for evaluating the appropriate number of action items per convened meeting agenda with consideration of the expertise of those present and the planned length of the agendas;

4. Consider making arrangements for the University's IRB staff to attend IRB meetings at peer institutions so as to better assess best practices and to determine ways in which the University's IRB can be improved.

3.2.3. The IRB as an Independent Investigative Body

3.2.3.1. Introduction

Perhaps one of the most challenging but critical functions of an IRB is addressing incidents of researcher noncompliance when they arise during the conduct of human subjects research. The federal regulations explicitly require that institutions have "written procedures for ensuring prompt reporting to the IRB, appropriate institutional officials, and the department or agency head of (i) any unanticipated problems involving risks to subjects or others, or any serious or continuing noncompliance with the federal regulations or the requirements or determinations of the IRB; and (ii) any suspension or termination of IRB approval."^{7,8} Institutions have flexibility in the development of these procedures to best suit their own research programs.

In alignment with these federal regulatory requirements, the University's IRB has policies and procedures to address noncompliance.⁹ The IRB policies not only address the requirement that researchers report incidents of noncompliance to the IRB, but also outline the IRB's processes for handling these incident reports once received. One unique feature of the IRB's policies for addressing noncompliance is the creation of "Investigative Committees" to handle allegations or concerns about noncompliance when the need arises. According to IRB policy 408, if there is an incident of noncompliance where "the facts about non-compliance are contested, it appears that more extensive information will be needed, or if the matter is serious enough to lead to possible termination of the study by the IRB" an Investigation Committee may be formed to address the alleged incident of noncompliance.¹⁰

The IRB's Executive Committee is charged with delegating a three person Investigative Committee (IC) comprised of IRB members with expertise relevant to the allegation and area of study, to conduct the investigation. The IC is then responsible for "reviewing relevant materials related to the noncompliance allegations, providing the investigator an opportunity to respond to allegations, interviewing witnesses as needed and preparing a report of its conclusions and recommended actions."¹¹ To assist the IC in the discharge of its responsibilities, it may "draw on the resources of the institution, including the institution's Post-Approval Review Program (PAR) (responsible for internal monitoring and auditing of

approved studies) or external consultants to assist in the review of issues that require additional material verification mechanisms or expertise beyond or in addition to that available on the panel.”¹² The IC’s findings are advisory to the Executive IRB, which is ultimately responsible for determining what, if any, corrective action measures should be required in response to the allegations of noncompliance.

3.2.3.2. Observations

Two ongoing internal investigations utilizing designated ICs came to the attention of the external review panel. Both investigations were initiated by complaints related to research in the Department of Psychiatry. One investigation was prompted by a complaint from a research subject (“Investigation 1”); and the second was prompted by a series of complaints related to Department of Psychiatry research that was conducted within the facilities of Fairview (“Investigation 2”). In this section, the external review team will comment only on its observations related to the *process* of these two investigations. During its site visit, the external review team met with each of the two active ICs to better understand the processes they used to conduct these investigations. Additionally, the external review team received copies of the final report from Investigation 1 and the draft report of Investigation 2 (as of the date of the submission of this report, the IRB Executive Committee had not completed its review of the Investigation 2 report).

As required in the IRB’s standard operating procedures (SOPs), each of the two ICs was comprised of three IRB members.¹³ Although each investigation was focused on research within the Department of Psychiatry, only one of the panel members (the Chair of the Faculty Social and Behavioral IRB) had a specific background or expertise in behavioral health. Additionally, although the IRB’s standard operating policies (SOPs) permit the involvement of internal or external consultants with relevant expertise to assist with the investigations, there is no evidence that consultants were engaged in either of the two investigations. Following the issuance of the final report of Investigation 1, the Vice President for Research determined that the allegations of noncompliance required further investigation by an external review body with “expertise in psychiatric clinical research.”¹⁴

It was evident to the external review team that the effort spent by the IRB members in each of these investigations was significant. The external review team is aware that each IC pursued several of the permissible investigative methods specified by the IRB’s policy, including review of documentation, correspondence with investigators, and, in the case of Investigation 2, engaging in extensive interviews.

The team was made aware that the IC for Investigation 1 did not meet with the complainant, other than via telephone, and instead focused its review primarily on relevant clinical and study-related records. During its evaluation, the external review team learned of a general concern regarding the lack of transparency of IC findings, particularly as they relate to following-up with complainants to inform them of the progress and outcome of the investigations, as demonstrated in the example from Investigation 1, above. According to the IRB's policy covering these ICs, it does not routinely publicly disseminate their findings.

3.2.3.3. Conclusions

While the stated procedure for investigating incidents of research noncompliance as outlined in the University's IRB policies is commendable, the quality of any investigation into such incidents rests largely on the resources available to ensure that it can be fully and effectively carried out. It is concerning that any IC may lack sufficiently relevant expertise to conduct an adequate investigation. The external review team was particularly concerned that, given the nature of the complaints, neither of the active investigations to which it was privy during this evaluation had members with relevant expertise in psychiatry, although, as noted above, the chair of the social/behavioral panel is an expert in behavioral health issues.

While the IRB's policies permit the use of internal or external resources, where warranted, to assist with the work of an IC, it was surprising that this option was not exercised for either of the investigations evaluated by the external review team. Based on the need for a continued examination of IC1, it would seem that valuable time and resources might have been preserved if the need for external expertise had been identified at the outset of the investigation, rather than at its conclusion.

While the work and dedication of the IRB members who serve on these two ICs should in no way be minimized by these observations, it is important for the University to re-consider whether the IRB membership is best equipped to conduct future investigations of this nature. At the very least, the external review team suggests that at least one or more non-IRB member(s) be added to each future IC to expand the expertise of these committees and ensure some measure of impartiality as many of these investigations may relate back to the oversight responsibilities of the IRB.

Finally, while the external review team concurs that it is often appropriate and in alignment with standard institutional practices for investigating and responding to incidents of noncompliance to consider the findings of such inquiries privileged and confidential, in light of the concerns expressed to the team regarding transparency and follow-up with complainants, the University's practices in this regard should be reevaluated and revised if deemed appropriate.

3.2.3.4. Recommendations

In light of these observations, the external review team recommends that the University:

1. Reconsider the reliance on IRB membership to staff ICs looking into incidents of noncompliance;
 - a. Consider whether one or more non-IRB individuals might also be appointed to the ICs;
 - b. If the University will continue to draw only from IRB membership to formulate these Panels, expand the IRB membership to ensure sufficient expertise to meet this charge, a recommendation that was independently made in the foregoing section;
2. More rigorously make use of other internal resources (such as the PAR Monitoring Program discussed in section 3(C)(iii) below) and external resources to supplement the work of the ICs;
3. Evaluate the mechanisms through which IC findings and any corrective action required are disseminated, particularly with regard to follow-through with complainants.

References for Section 3.2

¹For institutions covered by UMN IRB see: About the IRB. Accessed at: <http://www.irb.umn.edu/about.html#VObHsvnF98F>

²For the requirements regarding IRB members with required knowledge, see 45CFR46107(c) IRB membership accessed at: <http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.html>

³UMN policy on IRB membership. Accessed at: <http://www.research.umn.edu/irb/membership.html#.VN-k-od0zIU>

⁴UMN listing of Active Committee members. Accessed at: http://www.research.umn.edu/irb/membership.html#.VN_I3ld0zIU

⁵For the requirements regarding individuals with competence in special areas see: 45 CFR 46.107(f), IRB Membership. Accessed at: <http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.html>

⁶For the operational definition of the term “controverted issues” see: 45 CFR 46.115(a), IRB records. Accessed at <http://www.hhs.gov/ohrp/archive/humansubjects/guidance/45cfr46.html>

⁷For the requirements regarding investigator noncompliance see: 45 CFR 46.103. Accessed at: <http://www.hhs.gov/ohrp/archive/humansubjects/guidance/45cfr46.html>

⁸For guidance on reporting incidents/noncompliance to OHRP, see: OHRP Policy and Guidance. Accessed at <http://www.hhs.gov/ohrp/policy/advevntguid.html>

⁹UMN Policy on IRB noncompliance. See Appendix 7 for a list of those documents requested and reviewed by the External Review Team

¹⁰IRB policy on forming an IRB investigation. See Appendix 7 for a list of those documents requested and reviewed by the External Review Team

¹¹IRB policy on IRB Investigative Committees. See Appendix 7 for a list of those documents requested and reviewed by the External Review Team

¹²IRB policy on the use of PAR. See Appendix 7 for a list of those documents requested and reviewed by the External Review Team

¹³Membership of the IRB Investigative Committees for Investigation 1 and Investigation 2. See Appendix 7 for a list of those documents requested and reviewed by the External Review Team

¹⁴IRB Investigative Committees Final Report of Investigation 1 and Draft Report of Investigation 2. See Appendix 7 for a list of those documents requested and reviewed by the External Review Team

3.3 Review of other HRPP Functions

An effective HRPP engages University leadership, departments, and individuals across the institution to ensure that human subjects protections are considered at each stage of study development and implementation and within the broader hierarchy of institutional activities. The external review team focused on the following components of the HRPP: 1) Education and Training, 2) Scientific Review, 3) Monitoring, and 4) Engagement of Research Subjects and the Community. An evaluation of each of these core functions is provided below.

3.3.1. Education and Training

3.3.1.1. Introduction

Ethical and scientifically responsible researchers and staff are the building blocks of a high quality research program. The medical ethicist, Henry K. Beecher, MD, noted that “the presence of an intelligent, informed, conscientious, compassionate, and responsible investigator offered the best protection for human research subjects.”¹ Therefore, educating all parties involved in the conduct and oversight of research about the applicable principles and requirements is critical to ensuring that the research achieves the highest ethical and scientific standards. One measure of an institution’s commitment to human subjects protections is the way in which it educates its research community about these standards.

3.3.1.2. Observations

Prior to February 2014, education in human subjects protections, via a variety of endorsed programs, was a prerequisite for all individuals engaged in human subjects research at the University. There were no specific requirements as to the timing of this training in relationship to the date of protocol submission to the IRB, though, and while continuing education in human subjects’ protections was “encouraged” according to IRB policy, it was not mandatory.²

Within the past year, the University has made a few significant changes to its requirements for education pertaining to human subjects research. In February 2014, the University refined its requirements for human subjects training to require that all individuals engaged in human subjects’ research at the University complete basic human subjects training through the CITI program.³ Accompanying this change was a new *continuing* education requirement: Specifically, all individuals engaged in human subjects research must now re-certify their training every three years.⁴ In addition, in

January 2015, the University purchased a site license for PRIM&R's E-ROC online learning platform and plans to require this training for all IRB members.⁵

In addition to changes in these basic educational requirements, the University also instituted a new CITI course requirement in February 2014 for individuals who wish to serve as sponsor-investigators.^{F1} Documentation of successful completion of this tailored training is required as part of the IRB submission process whenever a University researcher plans to serve as a sponsor-investigator.^{6, 7} Beyond the basic CITI requirements, though, there are currently no human subjects protections training requirements for investigators, including those working with high-risk or vulnerable populations. An HRPP may supplement its basic courses by providing optional targeted trainings to the research community.

During on-site interviews, it was reported that IRB-led training aimed at the research community is primarily focused on the administrative aspects of the IRB application process, including any updated requirements. This training is most frequently directed towards research coordinators or student researchers. The external review team was otherwise unable to identify any advanced level training opportunities that currently exist for principal investigators, other researchers, or research staff. Of a reported 56 IRB-led trainings targeted to the research community between January 2011 and October 2014, only three were identified to include topics beyond "IRB Basics" and only four were identified that specifically targeted faculty researchers.⁸ Time and resource constraints have reportedly limited the number of advanced level trainings the IRB is able to offer to the research community, among them the lack of a position within the IRB dedicated specifically to researcher education and training.

It is clear that significant efforts are being devoted to orienting the University student researcher and research coordinator community to IRB processes and application requirements. However, the external review team's on-site interviews with researchers and institutional leaders demonstrated critical knowledge gaps about University policies related to specific areas of human subjects research, including study monitoring and requirements related to scientific review. Notably, at the time of this review, a

^{F1} Sponsor Investigators "The category of investigator defined by FDA regulations with additional responsibilities related to the conduct of investigational trials with drugs or devices." See 21 CFR 50.3 (f)

current copy of the HRPP's policies, which typically serves as the primary point of reference for institutional requirements related to human subjects research, was not publicly available on the IRB's website despite the fact that they are essential to ensuring the research community's compliance.⁹ The lack of advanced level training in human subjects protections is of particular concern with regard to investigator noncompliance. The external review team examined documentation related to several incidents of investigator noncompliance, including in IRB minutes, determination letters, and letters reporting the noncompliance and any required corrective action measures to external oversight entities. Based on the documents examined, even when investigators demonstrated a lack of understanding of the regulatory and ethical requirements related to human subjects research, the corrective actions implemented by the IRB with regard to re-training were primarily limited to a requirement that noncompliant team members retake the basic CITI training course. Of the materials examined, none of the recent management plans instituted by the IRB in response to an incident of noncompliance included a requirement for advanced level training.^{10, 11}

This absence of advanced level training seems to coincide with recent efforts to reduce the "burden" of continuing education in the area of responsible conduct of research ("RCR"). In order to serve as a principal investigator on a sponsored project at the University, researchers are required to complete an RCR course.¹² As described previously in section 3A, while the basic RCR requirement remains intact, continuing education in RCR was recently eliminated as part of the "Risk Recalibration" initiative.¹³ To support this change, the University cited a study conducted by the institution's Research Education Office which revealed that RCR continuing education requirements were "no longer needed given the broad range of educational opportunities and requirements that have been implemented at the U."¹⁴ The external review team, however, did not find evidence of this "broad range of educational opportunities and requirements" in the area of human subjects protections sufficient to support any reduction in educational requirements for researchers and research staff.

3.3.1.3. Conclusions

It is essential that individuals at all levels of the human research protections program be knowledgeable about the ethical principles, as well as the specific regulatory, policy, and procedural requirements related to human subjects research. A reconsideration of the methods currently used to communicate these requirements to the broader University community should thus be undertaken with an eye

toward developing a more interactive, meaningful, and sustainable educational program. While some improvements have already been implemented (or are in the process of being implemented) in the area of basic human subjects protections training, it is critical that training in human subjects protections not fall prey to the decision to “right-size” educational requirements in the wake of ongoing institutional efforts to reduce the administrative burden placed on researchers.¹⁵

While education and training have tangible costs, limited resources should not be used as an excuse for failing to provide a robust set of advanced educational offerings that includes ethical principles and their application. Advanced level trainings should allow for in-depth exploration of specific topics in human subjects protections. The introduction of the sponsor-investigator training requirement is one example of such advance level training. For research involving adults with the potential for limited decision-making capacity, advanced level training sessions might cover topics such as establishing capacity to consent or how to engage legally authorized representatives (LARs) in the consent process.

3.3.1.4. Recommendations

In light of these observations, the external review team recommends the following with regard to education and training of the University’s research community:

1. Conduct an evaluation of the resources of the HRPP specifically dedicated to the education and training of the research community to ensure that appropriate resources are in place to offer basic *and* advanced training opportunities in human subjects’ protections;
2. Create opportunities for advanced training in human subjects protections for all individuals involved in human subjects protections including investigators, IRB members and staff, research personnel, and clinical staff on units that conduct research;
3. Evaluate whether additional mandatory training requirements, comparable to the new mandatory training for sponsor-investigators, should be implemented. Careful attention should be given to areas of research that are considered to be “high-risk,” including those involving vulnerable populations such as individuals with the potential for limited decision-making capacity;
4. Institute a more substantive requirement for advanced level training for investigators and research teams when a determination has been made by the IRB of serious or continuing noncompliance, and develop a mechanism for ensuring compliance with this requirement;

5. Evaluate the mechanisms through which HRPP policies and procedures are communicated to the broader University research community in order to ensure that all its members are knowledgeable about and have ready access to the policies and procedures related to human subjects research;
6. Create expectations for the involvement of research departments and centers in the development of educational programs tailored to the nature and context of their research activities;
7. Consider ways to involve the University's Center for Bioethics in the educational programs focusing on human subjects research;
8. Consider efforts to engage the local community of patients and prospective subjects with programs on the ethics of research and the University's HRPP; and
9. Upgrade and professionalize education in, among other subjects, the responsible conduct of research and research ethics.

References for Section 3.3.1

¹ Beecher, H. Ethics and Clinical Research, NEJM, 1966. Accessed at:
<http://www.hhs.gov/ohrp/archive/documents/BeecherArticle.pdf>

² University of Minnesota IRB Policy 801: Researcher Education and Training Dated 1/4/2011

³ University of Minnesota IRB Policy 801: Researcher Education Requirements Dated 5/23/2014

⁴ University of Minnesota IRB Policy 801: Researcher Education Requirements Dated 5/23/2014

⁵ Please see a description of the course at <http://www.primr.org/eroc/>

⁶ IRB: Biomedical Application Updates. Accessed at: <http://research.umn.edu/irb/biomedical.html>

⁷ University of Minnesota IRB Policy 801: Researcher Education Requirements Dated 5/23/2014

⁸ List HRPP training activities 2011-2014: See Appendix 7 for Documents Requested by the External Review Team

⁹ See IRB website at: <http://www.research.umn.edu/irb/>

¹⁰ Convened IRB Minutes related to reports of noncompliance. See Appendix 7 for Documents Requested by the External Review Team.

¹¹ IRB Reports of noncompliance to federal agencies. See Appendix 7 for Documents Requested by the External Review Team.

¹² See University of Minnesota: Institutional Review Board: Training. Accessed at:
<http://www.research.umn.edu/irb/training.html>

¹³ Office of the Vice President for Research, Risk Recalibration. Accessed at:
<http://www.research.umn.edu/about/risk.html>

^{14,15} Dennis, E. "Rightsizing Faculty Education Requirements," dated March 25, 2014. Accessed at:
<http://inquiry.research.umn.edu/2014/03/25/rightsizing-faculty-educational-requirements/>

3.3.2. Scientific Review

3.3.2.1. Introduction

The scientific review of protocols is essential to help ensure that the risk/benefit ratio of the research is favorable and that the study is designed in a way that is both scientifically and ethically sound. The HRPP has a specific policy requiring documentation of scientific assessment for biomedical protocols involving greater than minimal risk.¹ This policy, in effect since 2007, requires that at the time of submitting an application for greater than minimal risk research to the IRB for review, documentation of scientific assessment must be provided. The policy defines four acceptable methods for scientific assessment, two of which permit reliance on external peer review (Methods 1 and 2). The other two methods for scientific assessment rely on internal review mechanisms. Method 3 permits reliance on a locally constituted peer review body that is responsible for awarding funding or granting permission to utilize resources to conduct the review; examples include the University's Cancer Protocol Review Committee, the Clinical and Translational Science Institute (CTSI), or a departmental peer review committee. The fourth and final method permits investigators to request a scientific assessment through the HRPP.

In order to conduct an assessment of this process, the review team requested copies of scientific review documents for a sample of protocols. Scientific review documents were supplied for 32 studies of which 30 utilized the departmental peer review process permitted under Method 3 as the chosen method of scientific review. Given the preponderance of those choosing departmental peer review (Method 3) and the fact that the other methods of scientific review utilized at the University largely rely on well-established peer review channels (e.g., National Institutes of Health, National Science Foundation, etc.), the external review team focused its inquiry on the use of departmental peer review under Method 3.

The HRPP policy on scientific assessment identifies some basic requirements for an appropriate departmental level scientific review, including a minimum of two reviewers and a process that documents the review methods, discussion, and review outcome. The policy also provides a sample scientific assessment form that outlines the specific criteria to be assessed by the scientific review committee (See Appendix 10 for a full list of Method 3 scientific review requirements). The external review team utilized these guidelines in performing its assessment.

This section of the report discusses the following issues related to department level peer review as a permitted mechanism for scientific review at the University: 1) the quality of scientific reviews utilizing Method 3, 2) conflicts of interest in the scientific review process, and 3) the integration of scientific review into the IRB review process.

3.3.2.2 Quality of Scientific Reviews utilizing Method 3

3.3.2.2.1 Observations:

As noted above, the external review team examined the scientific review documents of 30 protocols that relied on the use of departmental peer review (Method 3). A summary of the findings is provided in Table 3 below.

Table 3: Scientific Review Findings for 30 Protocols

Time Period	# of Reviewers			Reviews with comments	Checklist only	IRB minutes available	IRB considers Scientific Assessment comments	Number of Protocols Reviewed by Subordinate
	1	2	3*					
2007-2014	5	17	8	23	7	21	4	5

*The scientific review included 3 reviewers or was performed by the local Cancer Protocol Review Committee (CPRC) or Clinical and Translational Science Institute (CTSI)

Of the scientific review documents examined, there was only a *single* documented scientific reviewer for five studies, in clear violation of the University’s policy requiring a minimum of two reviewers for all departmental level review.² The 25 remaining had at least two reviewers and of those, eight had three or more reviewers.

Twenty-three of the scientific review documents examined included only non-specific statements and thus provided insufficient evidence that a substantive scientific review had been conducted. For example, one reviewer observed that...“The study is well designed and clinically important...No change

needed,” and another indicated that “This appears to be a well-designed study that will contribute helpful information to guide clinicians in the future. Methods are appropriate.” Seven reviews were limited to a checked box or signature on the standardized form referenced above with no commentary that outlined the review process or outcome. In fact, only one of the scientific review documents we examined contained substantive commentary.

3.3.2.2.2 Conclusions

Although HRPP policy clearly delineates the expectations for scientific reviews that are conducted at the departmental level (i.e., a minimum of two reviewers and a process that documents the review methods, discussion, and review outcome), it is clear that these requirements are often inconsistently or incompletely applied. As indicated above, several of the scientific reviews conducted at the departmental level failed to include the requisite number of reviewers and, more importantly, the majority of reviews provided to the team lacked substantive assessments on which the IRB could rely.

According to the University’s IRB website “the purpose of scientific assessment is to encourage the development of scientifically sound medical research....To justify the inclusion of human subjects in research, and to assess the balance between any risks that may be imposed upon human subjects with the utility of the outcomes of the investigation, an assessment is required to evaluate the scientific question and appropriateness of the methods planned to answer the scientific question.”³ Despite this acknowledgement of the importance of scientific review, the review team found inadequate evidence that the IRB, or the HRPP more broadly, has mechanisms in place to ensure that departmental level scientific assessments are not only performed, but are sufficient in quality to meet the stated goals. While the HRPP policy does indicate that protocols will not be assigned to an IRB for review absent documentation of an appropriate scientific assessment, it does not comment on how the IRB should assess the scientific review documents submitted to ensure that the process utilized: 1) meets all requirements set forth in the policy in terms of number of reviewers and the process used, and 2) contains sufficient documentation related to the assessment on which the IRB may rely.

3.3.2.2.3 Recommendations:

In light of these observations, the external review team recommends the following related to the quality of scientific review conducted under Method 3:

1. Carefully consider the impact on the IRB's overall ability to conduct an appropriate risk-benefit analysis when the evaluation of study merit is delegated to the department;
2. Carefully consider whether a robust review at the department level is feasible for each department, taking into consideration the size of the department, reporting relationships, and the volume of research;
3. If the University chooses to maintain a department-based process for scientific review:
 - a. Ensure the applicable policies delineate departmental and IRB responsibilities regarding the assessment of study design;
 - b. Develop guidelines for careful scientific review and ensure that the *de minimis* requirements are adhered to when department-level scientific review is used.

3.3.2.3 Conflict of Interest

The ability of an institution to address conflicts of interest in research is central to its ability to establish and maintain the public trust. It is essential, *and required* for publicly funded research, that institutions identify, review, and manage significant financial interests that have the potential to create a conflict.⁴ Recent changes to federal regulations have required increased disclosure of investigator financial interests, and there is a growing expectation that disclosure and management of institutional—as well as investigator—financial interests are necessary to promote confidence in research.^{5,6}

While the predominant focus in the realm of conflict of interest rests on regulation and management of the interests of *investigators* who are involved in the design, conduct, or reporting of the research, there are other situations that create bias or the appearance of bias, and thus pose a threat to research integrity. The Association of American Medical Colleges (“AAMC”), in its December 2001 report on conflicts of interest noted that “A Dean of Research, for example or a department chair, or a laboratory director, might have a financial interest in research being conducted by someone over whom they have direct authority” and goes on to say that “these research examples should be of special concern and receive strict scrutiny.”⁷

3.3.2.3.1 Observations

In light of the foregoing observations related to the apparent lack of rigor and consistency in departmental-level scientific review, the external review team determined that it was important to evaluate the ways in which conflict of interest is addressed in these processes. Notably, the HRPP policy

for scientific assessment does not define who may appropriately serve as a reviewer, and it does not specify that individuals with a conflict of interest should be excluded as a reviewer.⁸ Despite the absence of any **requirements** related to conflict of interest in scientific review within the HRPP policy, the external review team observed that for studies that rely on Method 4 and request that a scientific assessment be performed by the HRPP, the scientific reviewer to whom the protocol is assigned is specifically asked to identify any conflicts of interest. Method 4 utilizes an electronic system to facilitate reviews; in the event that a potential conflict or other “interest” is identified, the reviewer must click the “Recuse due to conflict” button, thereby terminating his or her role in the review process.⁹

However, the external review team did not see evidence that the “template reviewer forms” for departmental level scientific assessments completed under Method 3 include this same requirement.¹⁰ Of the 30 protocols examined for scientific review, five cases were identified where the scientific review was completed by a subordinate faculty member for research in which a department chair was the principal investigator. In these cases, a conflict of interest exists and the risk of bias in the review is significant.

When HRPP representatives were asked to document, as part of the external review team’s requests, how they ascertained whether or not a scientific reviewer had a potential conflict of interest before being enlisted to examine a protocol under Method 3, the response received stated that “Under Method 3, departments and units are responsible for identifying, addressing, and mitigating any conflict of interest in the scientific assessment process.” The response went on to indicate, “While the IRB’s evaluation of the effect of a leadership role has not been consistently documented, it clearly recognizes that scientific assessment of protocols should be completed by individuals who are not in a position subordinate to the principal investigator.”¹¹ The IRB expects departments to discharge this responsibility, but the team found no formal documentation that they have done so. Moreover, the IRB has not specifically challenged scientific reviews emerging from small departments, or Method 3 scientific reviews of protocols of individuals who hold a leadership role.

3.3.2.3.2 Conclusions

The absence of a clear statement in the HRPP policy on scientific assessment prohibiting individuals with a conflict of interest from serving as a scientific reviewer needs to be addressed and remedied. At a minimum, the current version leaves the University open to the perception that no sufficient safeguards

exist to ensure that the review and approval of human subjects research is unbiased. While not every researcher elects to utilize the departmental review option (i.e., Method 3) for scientific assessment of protocols, it is critical that mechanisms exist to ensure that scientific reviews are free from bias or undue influence that could raise doubt about the integrity of review.

In order for the IRB to rely on the scientific review conducted at the departmental level, the charge given to the departments to identify and manage conflict of interests in the scientific review process must thus be clear. Departments performing scientific assessments must be held responsible for ensuring that the scientific reviewers appointed to department level review committees do not have any conflicts. As part of its acceptance of the scientific review submitted by a given department in support of a research protocol, the IRB should verify compliance with these requirements.

3.3.2.3.3 Recommendations

In light of these observations, the external review team has the following specific recommendations:

1. Revise the HRPP policy on scientific review and related guidance on the IRB's website to state that individuals with a conflict of interest or conflict of commitment may not serve as a scientific reviewer. Conflict of interest should be operationally defined in these documents;
2. Revise the template titled "Departmental Scientific Assessment Form" (used pursuant to Method 3) to ensure that this form includes a statement defining potential conflicts of interest and affirming that individuals with such a conflict of interest may not serve as a scientific reviewer;
3. Consider whether additional protections are needed to ensure that scientific reviews of research proposed by senior faculty are not reviewed by subordinates. Given these concerns, the University should determine whether department-based review is feasible for individual departments.

3.3.2.4 Integration of Scientific Review into the IRB Review Process

3.3.2.4.1. Observations

As noted above, HRPP policy requires that for all greater than minimal risk medical research, appropriate documentation of scientific review must be provided at the time of IRB submission. This

policy suggests that the IRB believes the scientific assessment is critical in order for the IRB to make a determination as to whether the criteria for IRB approval of a research protocol have been met. While the HRPP policy clearly indicates that the IRB remains responsible for assessing whether a research project meets the criteria for approval for research with human subjects, it also notes that the purpose of the scientific assessment is to evaluate items such as: 1) whether the inclusion of human subjects is justified, 2) whether the risk/benefit ratio is balanced, and 3) whether the methods planned are appropriate to answer the scientific question.¹²

Presumably, the scientific review would then produce sufficient information to inform the IRB's assessment and documentation of the way in which the IRB incorporated this information into its determinations, as evidenced in the discussions from the IRB meetings. However, a review of medical IRB minutes that corresponded to 21 of the protocols for which scientific assessment documents were provided, showed little evidence that the merits of scientific design had been discussed in relation to the study risks and benefits. In fact, there was no evidence in those minutes examined to indicate that the scientific review had been either evaluated or discussed. In the meeting minutes for the initial review of four studies, only once did the minutes confirm that the IRB had concerns related to the scientific review; the lack of substance in the scientific review documents as noted above may explain the lack of discussion about these documents in the IRB meeting minutes. While it is possible that sufficient documentation about the scientific review *was* made available to the IRB and that the scientific reviews *were* adequate and sufficiently discussed, there is insufficient documentation to support this. The lack of documentation raises concerns as to whether IRB systematically reviews the scientific assessment documents accompanying the IRB submission and carefully determines whether they contain sufficient information upon which the IRB can rely.

3.3.2.4.2. Conclusions

The review process, as documented in the minutes, does not reflect a meaningful discussion of the risks and benefits of research protocols and the necessary steps taken to protect human subjects in the face of scientific or ethical concerns. It appears that, although the University's medical IRBs purport to rely on scientific review at the departmental level, there is inadequate evidence to suggest that the scientific reviews provide sufficient detail to inform the IRB's assessment of a protocol. Instead, the team found, at least based on the evidence it reviewed, that a portion of departmental scientific reviews lacked sufficient substance to be relied upon by the IRB. While the HRPP policies seem to recognize the

importance of scientific review, there is little evidence that departmental level scientific reviews are incorporated into or used to inform IRB decision-making.

3.3.2.4.3. Recommendations

1. Develop a mechanism for systematically incorporating scientific reviews into the IRB review process to ensure that scientific concerns impacting the criteria for IRB approval are sufficiently addressed;
2. Require that the IRB meeting minutes specifically document the IRB's review of the scientific assessment documents and any substantive concerns raised in the course of this review.

References for Section 3.3.2

¹ University of Minnesota IRB Policy 904: Scientific Review and Resource Assessment

² University of Minnesota IRB Policy 904: Scientific Review and Resource Assessment

³ See Institutional Review Board, Guidance & FAQs: What Every Research Needs to Know: Scientific Assessment. Accessed at: <http://www.research.umn.edu/irb/guidance/scientific.html>

⁴ Responsibility of Applicants for Promoting Objectivity in Research for which Public Health Service Funding is Sought and Responsible Prospective Contractors, 42 CFR Part 50; Subpart F; 45 CFR Part 94 Accessed at: http://grants.nih.gov/grants/policy/coi/fcoi_final_rule.pdf

⁵ Responsibility of Applicants for Promoting Objectivity in Research for which Public Health Service Funding is Sought and Responsible Prospective Contractors, 42 CFR Part 50; Subpart F; 45 CFR Part 94 Accessed at: http://grants.nih.gov/grants/policy/coi/fcoi_final_rule.pdf;

⁶ See 42 CFR Part 50; Subpart F; 45 CFR Part 94

⁷ *Protecting Patients, Preserving Integrity, Advancing Health: Accelerating the Implementation of COI Policies in Human Subjects Research*. A Report of the AAMC-AAU Advisory Committee on Financial Conflicts of Interest in Human Subjects Research, Feb, 2008, pp. 31. Accessed at: <https://members.aamc.org/eweb/upload/Protecting%20Patients,%20Preserving%20Integrity.pdf>

⁸ University of Minnesota IRB Policy 904: Scientific Review and Resource Assessment

⁹ See Appendix 10

¹⁰ See Appendix 10

¹¹ See Appendix 7 for Documents Requested by the External Review Team: Response provided in relationship to a request for a description as to how conflicts of interest are managed for the scientific review process

¹² See Institutional Review Board, Guidance & FAQs: What Every Research Needs to Know: Scientific Assessment. Accessed at: <http://www.research.umn.edu/irb/guidance/scientific.html>

3.3.3. Monitoring and Oversight

3.3.3.1. Introduction

Monitoring of approved research serves an important function in protecting human subjects by ensuring investigator compliance with IRB and other requirements and expectations. It may also be used to ensure adherence by the IRB to regulatory mandates and institutional policy. A monitoring program contributes to the human protection program's ethical mandate, and when appropriately integrated with IRB review, provides data valuable to the continuing review process. Federal regulations permit broad discretion (but provide little guidance) with regard to research monitoring. As a result institutions can determine the design, scope, and conduct of monitoring of IRB-approved research, as well as the nature and authority delegated to these programs within the institution's organizational structure.

As part of this review, the external review team obtained program descriptors, policy documents, and review tools of several distinct research monitoring or audit functions at the University. In 2011, the University re-structured its research monitoring program to create "Post-Approval Review" (PAR) (See Appendix 11 for a description of the program and its associated policies).¹ All routine human subjects research monitoring is conducted in accordance with the PAR program under the auspices of the HRPP and the Academic Health Center Clinical Trials Monitoring Program (AHC) or conducted within the Clinical and Translational Sciences Institute (CTSI). The AHC/CTSI Clinical Trials Monitoring Program focuses on FDA and GCP compliance related to investigator initiated clinical trials and conducted 177 reviews in the prior year. These reports were not reviewed by the team.

3.3.3.2. Observations

PAR

PAR's three monitoring components together describe a well-conceived tracking structure. PAR identifies and seeks to address through reports to the IRB, any issues of concern with the conduct of the protocol on the part of the investigative team, as well as any identified shortcomings in the IRB review and approval process. It similarly identifies and seeks to address evidence of problematic communication between the IRB and the investigator. PAR staffing is described as 1.5 FTE at present.²

The annual number of protocols monitored since the program's launch is provided in the table below.

Table 4: Number of PAR reviews per year:

Year	Number of PAR Reviews
2011	15
2012	32
2013	166
2014	106

The University provided the review team with the templates/audit forms used by the PAR program (see Appendix 12). For the list of 20 protocols the team initially selected for review, copies of any available PAR reports were provided. Additionally, several additional PAR reports were provided in response to subsequent document requests of the external review team (see Appendix 7). The external review team evaluated several PAR reports and the associated tools utilized to complete those reports. The reports revealed a detailed and comprehensive review process. Furthermore, these findings reflected a thorough, sophisticated, and substantive examination of both the design and planned implementation of the human research protocol in question. There was also evidence of careful attention to consent and surrogate consent procedures, parental permission, investigator compliance with IRB reporting requirements, and sponsor-investigator responsibilities, among others.

Among the observed deficits in the PAR program was the absence of live consent monitoring (or at least the absence of any *description* of live consent monitoring) by which select consent discussions between an investigator and a prospective subject are observed and assessed by a research monitor. Moreover, although it was assumed that the PAR monitoring program prioritized protocols for review based on a risk assessment, there was no clear explanation of the manner in which these risk-based assessments was performed. While there is some documentation in the IRB minutes acknowledging the review of and response to monitoring findings, the lack of substantive commentary in the IRB meeting minutes, as discussed previously does not permit the panel to assess the adequacy of IRB handling and follow-through of monitoring reports and data.

Additionally, in the small sample of PAR reviews examined by the external review panel, a concerning number of findings pointed to shortcomings in the initial IRB review of research. How these issues were addressed by the IRB was not evident from the materials received. This could be of particular concern given the fact that the HRPP Director oversees both the monitoring function and the IRB.

Although the external review team found evidence of a robust PAR monitoring program, the feedback received during on-site interviews was at odds with these initial conclusions. In fact, during the site visit, we repeatedly heard monitoring cited as a primary area of deficiency and one that had the potential to pose the greatest institutional risk, as the reviews were thought to be infrequent and of poor quality. Although efforts were reportedly underway to increase staffing and resources for monitoring efforts, some high-level staff members expressed their concern that monitoring efforts had not yet achieved the desired standard. Notably, there were specific reports about the lack of monitoring of the research conducted at Fairview (as well as the lack of communication about the need for monitoring) despite the fact that the monitoring function for human subjects research conducted at Fairview is the responsibility of the University under the Master Agreement between the two institutions.³

Specific examples of challenges in monitoring that were cited during the on-site interviews included: 1) the lack of a centralized database for reporting and tracking adverse events, unanticipated problems, and subject complaints that would permit the compilation and reporting of data fundamental to monitoring efforts, 2) the lack of clear communication channels for reporting results of monitoring efforts to department chairs or other institutional leaders with research oversight responsibilities, and 3) the difficulty of rebuilding the monitoring program following the relatively recent (approximately 2012) dismantling of the Office of Research Affairs (ORA), which had previously been responsible for several important aspects of the HRPP, including monitoring,⁴ and 4) the lack of clearly identified policies and procedures for ensuring responses to and follow-through of deficiencies identified through monitoring efforts related to the IRB review processes.

3.3.3.3. Conclusions

A review of PAR policies, procedures, review tools, and a sample of reports of findings reveals an impressive and potentially valuable tool to promote compliance with human subject protection priorities, including those related to the inclusion of subjects with impaired consent capacity and the use of legally authorized representatives.

It is not clear, though, that monitoring has been used effectively to address concerns about research at Fairview. This is particularly relevant given the concern expressed during on-site interviews that the monitoring efforts (or the communication about those efforts) at Fairview were limited, such that Fairview personnel were not engaged in or even aware of monitoring activities.

While the actual monitoring activities appear to be thorough in most cases, the institutional perceptions related to monitoring suggest that there is a need for significant improvements to increase awareness of the program and its activities. Educational initiatives related to the functions of the PAR program may be warranted to help promote this awareness and might be coupled with publication of PAR policies, including the methods used to conduct a “risk-based” selection of protocols to target for review.

Even the most effective monitoring activities cannot, though, ultimately replace thoughtful and diligent initial review of research by the IRB. While the monitoring function is indeed essential to ensuring the protection of human subjects, the observed sense that monitoring was a primary area of deficiency seems displaced in light of the program’s apparent strengths and other concerns raised in this report.

3.3.3.4. Recommendations

1. Efforts to expand monitoring conducted through the PAR program and/or via the application of its methods to other HRPP monitoring efforts should be considered. Specific emphasis should be placed on increasing PAR monitoring efforts for research conducted at Fairview with an active dialogue with the Fairview staff so that they can be actively engaged in the process;
2. PAR should track and measure IRB follow-through on its findings and recommendations and report these to research leadership including department chairs and the Dean of the Medical School;
3. PAR should regularly share summary reports of its findings with department chairs and other institutional leaders charged with research oversight responsibilities to ensure that key areas of investigator and programmatic noncompliance can be readily identified and addressed.
4. Deficiencies in IRB review processes/functioning should also be addressed through existing reporting and supervisory hierarchies, and not be addressed solely within the more limited authority of the IRB and Office of the Vice President of Research;
5. In the context of ongoing concerns about problems related to subject recruitment and consent in psychiatric studies, PAR should include live consent monitoring of such studies in its repertoire of subject safeguards;
6. Separate reporting chains for IRB review and Post-Approval Review should be considered.

References for Section 3.3.3.

¹ See Post Approval Review Description in Appendix 11

² See Appendix 7 for Documents Requested by the External Review Team

³ See Appendix 7 for Documents Requested by the External Review Team; Copy of agreement with Fairview Health Systems

⁴ See Appendix 7 for Documents Requested by the External Review Team; Description of former monitoring program

3.3.4. Engagement of Research Subjects and the Wider Community Served by the University

3.3.4.1. Introduction

Engagement of research subjects and the broader community is an essential component of an institution's HRPP. Developing mutually respectful relationships with community members and ensuring that the voice of research subjects is heard are ways in which the ethical conduct of research can be advanced. In an era of "patient centered outcomes research"¹(PCORI) and "community-based participatory research"²(CBPR) where research subjects are increasingly seen as partners rather than as simply participants, there is also the parallel expectation that an HRPP will have mechanisms for soliciting and responding to concerns and interests of the research subject community. The University does, in fact, have a policy addressing Community-based participatory research.³

As noted previously (See section 2.3.5.), the external review team understood that research subjects (both current and former) and their advocates are key stakeholders and would thus be key informants in the review process. The team therefore sought to understand how the University engages the research subject community and responds to its feedback.

3.3.4.2. Observations

The external review team requested information about any and all mechanisms used by the University to encourage *ongoing* communication with subjects, including those established for situations in which research subjects want to lodge a complaint or concern. The team learned that there is a range of options by which subjects in University research can register their concerns, including a section of the IRB website prompting them to submit complaints to the IRB.⁴ In addition, "UReport" is an anonymous channel by which anyone can report violations of the University's policies, rules, regulations, or other laws.⁵ Finally, should subjects have questions or concerns about their participation in research, they are instructed, in a section of the consent form, to either contact the IRB office, or for research conducted at Fairview, to call the Fairview Research Administration Helpline.⁶ While the University thus has channels to receive and respond to research subject complaints and concerns, none seems to provide a systematic means for facilitating bi-directional communication between the University and the broader community of current or future subjects. (See "Stakeholder Outreach," section 2.3.5, on page 14 of this report).

As discussed previously in Section 2.3 the lack of existing channels available to communicate with the research subjects community (among them, a standing community advisory board) was evident in the challenges faced by the external review team when we sought to solicit research subject feedback to inform this report. The team did have two opportunities to obtain feedback, first through its discussions with representatives of the local National Alliance for the Mentally Ill (“NAMI”) during the site visit and secondly through the brief online survey made available to research participants and their family members between December 16, 2014 and January 12, 2015.

During its meeting with several members of NAMI, representatives shared their feedback on research conducted by the University’s Department of Psychiatry, all of it positive. One member brought written comments from her son, a research subject, who was unable to attend. Several individuals spoke highly of the Department Chair’s participation in an annual NAMI dinner where he provided an update on the latest research efforts. Those with whom we met cited this annual appearance by the chair as a positive reflection of the Department’s desire to create a relationship with the NAMI community.

As noted in section 2.3 of this report, in December 2014, the external review team launched a short online survey targeted to research subjects and their family members. While the total number of respondents (18) was too small from which to draw any conclusions from the data, the majority reported that their experiences with research at the University were positive. Notably, approximately half of the participants (10) were subjects themselves and the other half (8) were family members of an individual who had participated in a University research study (8).⁷ This stratification suggests that future efforts to engage this community may need to be broadly targeted to both research subjects and their family members, and alternatives to internet-based efforts may need to be considered. This may be particularly true for efforts to engage adult research subjects with limited decision-making capacity.

The external review team does not wish to suggest that the University has no mechanisms in place to engage the research subject community. In fact, during the site visit, there was evidence of several strategies for engaging the community, including community consultation activities led by researchers in emergency medicine and efforts to introduce University research to the community by setting up a “Driven to Discover” building at the Minnesota State Fair.⁸

3.3.4.3. Conclusions

While it is not particularly uncommon for a HRPP's contact with research subjects to occur primarily when there are complaints or concerns, the external review team is of the opinion that, for an institution working to restore public trust and in many ways *change* the public perception related to its research oversight, standard channels for communicating with subjects may simply be insufficient. The frustrations the external review team experienced when attempting to meet with, or otherwise solicit feedback from subjects, suggests that there are many opportunities for improvement in the University's efforts, and thus ability, to engage and communicate with this core constituency. Successful efforts directed at engaging the research subject community (e.g., community engagement regarding emergency research) should be amplified, systematized, and strengthened. Such directed efforts would send a clear message to research subjects and potential subjects that the University not only *wants* research subject feedback, but is actively working to obtain it, evaluate it, and implement programmatic changes based on the feedback received.

3.3.4.4. Recommendations:

In light of these observations, the external review team has the following recommendations:

1. Establish accessible and reliable electronic and non-electronic channels (in addition to existing complaint mechanisms) for facilitating sustained communication among research subjects, their family members and other advocates (within the permissible bounds of the Health Insurance Portability and Accountability Act (HIPAA)), researchers, research team members, and HRPP/IRB administration;
2. Develop mechanisms to regularly solicit, evaluate, and respond to research subject feedback;⁹
3. Partner with researchers to incorporate mechanisms for soliciting feedback regarding the research subject experience so that it can be secured contemporaneously with the individual's agreement to participate in research;¹⁰ For example, the HRPP might afford research subjects an opportunity to complete a research subject satisfaction survey at the end of study participation, or add an option to the University's template consent form asking subjects if they would agree to be contacted by the HRPP about their experiences as a research subject. Contact information for individuals who agree to this option could then be shared with HRPP officials and, post-participation, these individuals could be surveyed about their experiences. Data from these evaluations could be used to assess the research subject experience more broadly and would afford the HRPP a road map for developing programmatic changes that are directly responsive to the expressed needs of the research subject community;

4. Include members of the research subject community on relevant research related committees, task forces, and/or educational programs as another means by which researchers, research staff, research administrators, and University leadership can form relationships with them and thus more directly solicit their input on community priorities and areas of community concern; and,
5. Consider systematic approaches to express appreciation for subject participation, develop mechanisms to share research findings, and where appropriate, individual research results with subjects as a method of demonstrating partnership, showing respect and building trust.

References for Section 3.3.4.

¹Patient-Centered Outcomes Research Institute (PCORI). Accessed at:
<http://www.pcori.org/about-us>; <http://www.pcori.org/content/what-we-do>;

² Community-Based Participatory Research (CBPR). Accessed at:
http://en.m.wikipedia.org/wiki/Community-based_participatory_research

³ See University of Minnesota Policy 508; community-based participatory research

⁴ Reporting Research Complaints and Concerns.” Accessed at:
<http://www.irb.umn.edu/report.html#.VOlvdFnF-gY>

⁵ University of Minnesota UReport. Accessed at:
<https://secure.ethicspoint.com/domain/media/en/gui/9167/index.html>

⁶ Fairview Research Administration Helpline. Accessed at:
<http://www.fairview.org/Research/ResourcesandInformation/FairviewResearchResources/ResearchAdministration/index.htm>

⁷ See Appendix 9: Online Survey Questions and Dissemination Strategy. See also “Stakeholder Outreach,” section 2.3.5, on page 14 of this report.

⁸ Driven to Discover, University of Minnesota Research at the State Fair. Accessed at:
<http://www.statefair.umn.edu/d2d-building.html>

⁹ “Assessing Research Participants’ Perceptions of their Clinical Research Experiences,” Kost, Lee, and Henderson, Clinical Translational Science, 2011 December: 4(6):403-413.

¹⁰ One noteworthy example of such a system is the Harvard Clinical and Translational Science Center (“Harvard Catalyst”) Research Subject Advocacy (“RSA”) Program, which has “reengineered subject advocacy, distributing the delivery of advocacy functions through a multi-institutional, central platform rather than vesting these roles and responsibilities in a single individual functioning as a subject advocate. The program is process-oriented and output-driven, drawing on the strengths of participating institutions to engage local stakeholders both in the protection of research subjects and in advocacy for subjects’ rights.” A Distributed Model: Redefining a Robust Research Subject Advocacy Program at the Harvard Clinical and Translational Science Center, Clinical and Translational Science, Volume 7, Issue 4, pages 329–335, August 2014

3.4. Selected Policies and Procedures Related to Research with Individuals Who May have Impaired Decision-Making Capacity

Introduction

Pursuant to its charge,¹ this section addresses research with adults who may have impaired decision-making capacity. Given the breadth and complexity of that topic, though, the external review team confined its inquiry to five topics related to informed consent: (a) the assessment of capacity to consent, (b) susceptibility of subjects to coercion in the context of involuntary hospitalization, (c) longitudinal assessment of capacity, (d) Legally Authorized Representatives (LARs) and applicable law in Minnesota, and (e) the use of surrogate consent.

The team requested and was provided with a list of all protocols active during the past three years that posed more than minimal risk and that included subjects from diagnostic groups that may include adults with impaired decision-making capacity. In order to identify the requested protocols, the University's information technology department conducted a search of study titles using key words. The team then selected a cross section of 20 protocols (from among the 89 studies identified) for a more intensive review. In addition, the corresponding IRB minutes were also reviewed, along with any and all materials related to scientific review (at least in those cases where departmental scientific reviews had been conducted) or continuing review. Finally, any available internal or external audit documents relating to the 20 protocols were also examined.

In an effort to enhance IRB review and oversight of research involving adults with impaired decision-making capacity, the HRPP recently revised several of its relevant policies. At the time of the team's site visit in September, 2014, many of these policies, as well as the associated forms and IRB review guides, had been rewritten, some substantially.² In fact, the announcement of new requirements pertaining to potential subjects whose decision-making might be impaired (and the revised forms accompanying them) directly coincided with the team's site visit. The external review team therefore requested all protocols that were submitted pursuant to these new policies during the months of September through December, 2014, and 24 additional protocols were subsequently shared with and assessed by the team (Please see Appendix 13 for a complete listing of the categories of protocols as well as for copies of the related policies, tools, and information reviewed by the team).

While on site, the team met with several individuals involved in and/or familiar with research involving the targeted population, and asked them about the application of the University's policies and procedures related to informed consent. Some of those interviewed provided supplemental departmental materials or other documents upon request and these were similarly examined. The team paid careful attention to the most recent policy revisions in an effort to ascertain whether they adequately addressed the concerns that prompted this external review. The team also tried to determine whether the IRB's review of protocols *after* the adoption of the new policies reflected increased and improved oversight.^{F1}

3.4.1. Capacity to consent

3.4.1.1. Observations

The majority of protocols examined by the team predated the above-referenced 2014 consent policy revisions. These earlier protocols contained little or no information about the consent process and virtually no details as to how capacity would be assessed, regardless of whether a targeted population was likely to include prospective subjects with impaired decision-making capacity and regardless of the level of risk.^{F2} The corresponding IRB meeting minutes similarly failed to reflect a review of these issues by the IRB.

Likewise, a number of practices described in the examined documents reflected a departure from recognized standards designed to support autonomous decision-making (with appropriate protections) for those who cannot make decisions for themselves regarding participation in research. For example, the team noted the arguably inappropriate use of a LAR when the subject's disability was *physical* rather than related to consent capacity. In one such protocol, the IRB required the addition of a signature line for surrogate consent because "some subjects may not be able to sign their name when enrolling in this trial." In still other cases, the internal policy was to "err on the side" of obtaining consent by a LAR, even when the individual may be able to make a consent decision on his or her own.

^{F1} Individual protocols referenced in this report are not identified by specific citations in order to avoid singling out either protocols or investigators because the work is being referenced in order to illustrate a broader point.

^{F2} Several of the Department of Psychiatry protocols examined by the team did not appear to give serious consideration to evaluating the risks involved in the research, suggesting, for example, that having a subject change medications for schizophrenia, for example, presented no risk "over and above that to which they would normally be exposed" because switching medications is seen as a "common practice" among the population.

Among the newly released IRB policies and procedures was one titled “Adults Lacking Capacity to Consent” (Policy 506).³ The new policy states that “prospective adult subjects with impairments to functional abilities are presumed to be capable of providing consent unless there is substantial evidence otherwise.” This major change eliminated the requirement that a researcher must proactively ensure that prospective subjects possess the capacity to consent to participate in research. While the University’s IRB reported having had discussions about the important balance between protection and autonomy when discussing and enacting these revisions, the external review team questions whether the new approach aligns with current guidance and best practice.

Guidance from the Office for Human Research Protections (OHRP), for example, notes that “the informed consent process should ensure... that prospective subjects or their legally authorized representatives adequately understand the research so that they can make informed choices.”⁴ The process of obtaining consent for research thereby requires the researcher to *affirmatively* establish that a prospective subject understands the risks and benefits of the proposed study, as well as the available alternatives to participation. Recommendations from the *Secretary’s Advisory Committee on Human Research Protections (SACHRP)* similarly established this as a requirement, while recognizing that the threshold for “understanding” and the methods necessary for its assessment should be tailored by the IRB in relation to the associated degree of research risk, the nature and degree of subject impairment, the complexity of the decision to be made, and other considerations.⁵ Therefore, University policy, which *assumes* capacity to consent to research absent “substantial evidence” to the contrary, is inconsistent with the principles underlying the OHRP guidance.

As part of the 2014 policy changes, the IRB now requires a new “Appendix I,” a specific section of the IRB application that must accompany all IRB submissions whenever individuals with potentially impaired decision-making capacity are targeted or may be included in a protocol.⁶ The new forms prompt responses from investigators, and a checklist for the IRB reviewers highlights topics specifically relevant to the targeted population. However, a review of the meeting minutes recorded following the adoption of these newly created forms suggests that they are limited in their ability to inform the IRB’s protocol review and decision-making. In the documents received, for example, one reviewer responded, “how can I assess this?” in response to the question, “Does the process to assess capacity provide reasonable assurances that the evaluator’s judgments will be impartial?” Therefore, even with these new tools,

additional work is necessary to educate investigators and the IRBs' members about attendant expectations regarding consent, enhancements to the consent process, and the assessment of capacity.

The external review team was encouraged by examples of some effective processes related to the assessment of capacity that came to its attention during the site visit. One protocol shared with the team by a study coordinator, for example, involved a minimal risk study for older individuals that included a staged assessment for capacity as well as the opportunity for subjects to select a surrogate in advance, in anticipation of the potential for future loss of capacity. Participants who declined to designate a surrogate and later lost capacity were excluded from further participation. While the research protocol using this method was approved, the coordinator reported being unable to get a more general endorsement of the method from the IRB.

3.4.1.2. Conclusions

The timing of this external review coincided with the release of new policies and procedures related to research involving individuals with the potential for limited decision-making capacity. While many of the policy enhancements have begun to have a positive impact as they relate to the assessment of capacity, the external review team has some remaining concerns about them. Specifically, the external review team found it worrisome that the revised policy eliminated the previous structure that made it mandatory to affirmatively establish a prospective subject's ability to consent.^{F3} The team is also concerned that the new standard requiring "substantial evidence" of the need to assess consent capacity may in fact leave the institution vulnerable should investigators or research staff fail to assess consent capacity in those cases where it *is* needed. Additionally, while the revised tools (and corresponding appendices) required for protocols that may involve individuals with limited decision-making capacity are likely useful, they are limited in their ability to fully capture all of the relevant elements needed for the IRB to assess whether the protections afforded by the consent process are adequate and appropriate.

^{F3} 506, *Prospective Subjects and Capacity to Consent*, revisions to version dated July 7, 2011, was edited as follows: "This policy describes the requirements concerning review of research that involves adults lacking decision-making capacity who could be vulnerable to coercion in regard to autonomy, but are not specifically protected by a Subpart of 45CFR 46 and 21CFR56 and present conditions that may affect the criteria for approval of research. The policy provides guidance on how to determine and document whether non-exempt human research involving adults lacking decision-making capacity can be approved. to ensure that the capacity to make consent decisions is assessed and considered when enrolling prospective participants in research." Policy 506 was then retitled "Adults Lacking Capacity to Consent."

It is recommended that in assessing the appropriateness of the methods used to assess capacity to provide informed consent, the required methods be customized on a continuum to help ensure that more rigorous methods are used when the degree of subject vulnerability is likely to be greater and when the risks of research are higher.⁷ While the reworked Appendix I⁸ prompts the investigator to provide information pertinent to such methods, the team found little evidence that the IRB is engaged with investigators in the process of crafting or reviewing these methods.

Opportunities for stronger processes for protecting potentially vulnerable subjects are broadly available in the wider research community and were, as described above, observed by the external review team in some protocols. However, studies examined by the team seldom showed the IRB to be engaged in a substantive discussion of the potential tools that might be utilized in an assessment of consent capacity. These could include, among other practices: 1) the use of a decision tree that outlines the different potential requirements for assessment of consent capacity, starting from a universal informal subject assessment for consent capacity for all subjects and moving to more formal and validated independent assessments when impairment is more likely to be present, capacity fluctuations are likely, anticipated benefits are fewer, and foreseeable risks are greater;⁹ or 2) the use of independent consent monitors to oversee and assist with the assessment of capacity. In the protocols reviewed following the implementation of the new policy changes, the external review team found no evidence that these types of tools had been considered or implemented, suggesting that more attention, education, and a reconsideration of certain sections of the new policy are needed.

3.4.1.3. Recommendations

In light of these observations, the external review team has the following recommendations:

1. Policies, guidance, application and review forms, and the IRB review process itself, should be redrafted and/or restructured for clarity and consistency to ensure that they will be appropriately used to prompt consideration of the methods used for assessing capacity to consent;
2. The IRB should ensure that its review includes a substantive assessment of the scope and appropriateness of protocol-specific procedures that address the capacity to consent in light of the subject population being approached;
3. Revised policies on legally effective informed consent should:
 - a. provide the means for verifying decision-making capacity and voluntariness in all protocols as preconditions for all human subjects research;

b. reject the standard that presumes capability by establishing a test of “substantial evidence otherwise” for adults with impairments.

4. The IRB must provide adequate review and oversight of its policies to ensure that they:

a. align subject screening or other protections with the degree of risk involved in a study or the level of risk of impairment in a targeted or enrolled population;

b. promote the use of strategies to support or enhance subject decision-making, including the advance selection of a surrogate decision-maker by a subject who may later lose decision-making capacity;

3.4.2 Vulnerability to Coercion or Undue Influence

3.4.2.1. Observations

Federal regulations require that an investigator “shall seek such consent only under circumstances that...minimize the possibility of coercion or undue influence.” Further, “When some or all of the subjects are likely to be vulnerable to coercion or undue influence, such as ...mentally disabled persons, additional safeguards have been included in the study to protect the rights and welfare of these subjects.”¹⁰ Neither University policies nor practice distinguish between vulnerability to coercion or undue influence when it could occur with subjects who are limited in their understanding of the research. This area of concern is heightened in psychiatric setting situations where there is a prospect of civil commitment (i.e., involuntary hospitalization), since that threat can increase a prospective subject’s vulnerability to coercion or undue influence.

Despite a history that includes legislative intervention by the State to protect subjects perceived to be in potentially coercive situations^{F4} (i.e., those under a stay of an involuntary mental health commitment order), the external review team found no evidence that the University, Fairview, and its investigators have taken steps to ensure a broader understanding of the implications of this very fraught situation. When patients with severe behavioral disorders are in the medically unique circumstance of facing legal compulsion to receive treatment against his or her will, that prospect can affect their decision-making.

^{F4} These issues include findings that the patient may benefit because other treatment options have been ineffective; that the treating psychiatrist is not the psychiatrist conducting the drug trial; and that the court determines that the patient is competent to choose and is freely choosing to participate, the compulsion of the stayed commitment is not being used to coerce the person to participate, and that a reasonable person may choose to participate. 2014 Minnesota statutes 253B.095(e)] See Appendix 17

Simply put, the fear of being subjected to an involuntary legal process for perceived noncooperation, even if there is no *direct* threat of such legal compulsion, is an overwhelming barrier to voluntariness. Yet none of the studies examined by the external review panel referenced, or distinguished among potential subjects based upon, civil commitment status, apart from verifying compliance with the state law.

Nor did anything in either the newly revised HRPP policy or the supporting implementation materials provide for an assessment, for example, of whether or how the recruitment or consent process would introduce safeguards to protect against the inherent coercion of being held for involuntary treatment, even (or even *more so*) on an emergency basis. Of note, the September, 2014, revisions to Appendix I add the requirement that plans, if any, to avoid seeking consent during periods of greater than normal impairment be documented, but they fail to specify that this could include circumstances when an individual is being held for involuntary treatment.¹¹

The above problem, i.e., the risk of coercion or the appearance of coercion, is further exacerbated when the principal investigator is also the treating physician and thus has the power to initiate the individual's involuntary confinement. We found only a single instance where consideration of the dual and potentially conflicting role of treating psychiatrist/investigator was addressed. In one protocol, the IRB deferred an approval decision due to its inability to assess the adequacy of the evaluation for consent capacity. In that case, a "nonaffiliated party" was required to observe the consent process if the investigator was also the treating physician. In a recent IRB investigation that addressed a complaint related to a subject who was recruited for a study and in fact provided consent to research while under a temporary involuntary hold, the potential impact of that status (i.e., being held involuntarily) on the subject's ability to provide consent was not referenced.^{F8}

^{F8} The report states that the subject was admitted from the emergency room and held for a three day involuntary evaluation, and was recruited for the study during that time. In its review of the consent process, the report found that the complainant was "oriented and reasonably insightful" and "answered questions about study requirements and risks correctly at the time of research consent." In assessing whether the subject might have been pressure to consent, the report references that the "subject was unemployed and without insurance coverage" and medication and hospitalization were covered by the sponsor. Thus there was no observation of the potential impact of the individual's involuntary status. [Report of Investigation 1]

3.4.2.3. Conclusions

While recent policy changes -- and their application -- lay important groundwork for improvements in research involving subjects who may be vulnerable to undue influence or coercion, they do not mitigate the need for an explicit policy requiring the IRB to assess and impose the need for safeguards in studies where individuals subject to the threat of involuntary confinement are considered or approached for enrollment. The University should directly and thoughtfully address the specific issues related to the context in which acutely ill psychiatric patients are identified, recruited, and asked to consent to research. Policies are needed that reflect the imperative to refrain from seeking consent when there is situational impairment as a result of an acute physical or psychological event.

3.4.2.4. Recommendations

In light of these observations the external review team has the following recommendations:

1. Develop standards that protect against real or perceived coercion in psychiatric treatment settings in which individuals may fear involuntary court proceedings;
2. Encourage and support the use of independent consent monitors, particularly in those cases where the treating physician is also the investigator, so as to minimize the possibility for undue influence or coercion.

3.4.3. Longitudinal Assessment of Capacity

3.4.3.1. Observations

The new policy on Adults Lacking Capacity to Consent (Policy 506) includes consideration of the potential for fluctuating capacity. Among other elements, it includes the question...“Does the consent process include plans to avoid, if feasible, periods during which subjects are likely to experience greater than normal impairment?” and, “Should provisions be included to anticipate fluctuations in capacity?”¹² However, the policy does not guide the investigator as to when such considerations should be raised and/or applied. The absence of guidance on this complicated and high profile topic is evidenced by the lack of substantive responses to these questions in the 24 protocols the team reviewed that were submitted since the new policy became effective. There was also inconsistent evidence as to whether the IRB was appropriately identifying the requirement that capacity be reassessed in protocols when the potential for fluctuating capacity was clear.

Appendix I (the newly revised attachment, referenced in subsection 3.4.1) requires that protocols include a plan to reassess a subject's ability to consent if capacity fluctuates.¹³ Some of the protocols reviewed by the IRB from September through December of 2014 were submitted on the updated forms and several stated with clarity what would happen if subjects lost capacity – or if they appeared to have increased levels of impairment – but only one of the 24 provided any proactive plan to monitor for such changes in persons who are at risk based upon their clinical condition. Although options for IRB requirements include, “re-evaluating subjects’ capacity over the course of the study,” re-evaluation plans were seen in only a few of these protocols, none of which involved psychiatric research. To the extent that these best practices *are* occurring at the University, they were initiated by research teams themselves. The IRB’s role in encouraging or requiring such procedures was nowhere in evidence. In addition, re-consent when a person regains capacity, an essential component of assuring subject autonomy, is rarely referenced in IRB review documents.^{14, 15}

3.4.3.2. Conclusions

The team found a lack of robust guidance and consistent application of policy in situations in which fluctuations in capacity can be reasonably anticipated as a component of a subject's condition. An individual may regain capacity, requiring direct consent, or, may lose capacity and thereby lose the ability to protect his or her own interests regarding continuation in the study.

3.4.3.3. Recommendations

In light of these observations, the external review team has the following recommendations:

1. IRB policies should more clearly require that protocols involving adults with potentially limited decision-making capacity include a plan for monitoring subjects who are likely to have fluctuating capacity, including the steps to be taken if capacity diminishes over the course of study participation;
2. IRB policies should more clearly require that protocols involving adults with potentially limited decision-making capacity specify the plan for re-consent when a subject regains capacity.

3.4.4. Legally Authorized Representatives (LAR) and Applicable Law in Minnesota

3.4.4.1. Observations

Federal regulations state that “no investigator may involve a human being as a subject in research... unless the investigator has obtained the legally effective informed consent of the subject or the subject's legally authorized representative” (45 CFR 46.116).¹⁶ A Legally Authorized Representative (LAR) is defined as “an individual or judicial or other body authorized under applicable law to consent on behalf of a prospective subject to the subject's participation in the procedure(s) involved in the research.” 45 CFR 46.102(c)¹⁷

IRB Policy 403-C, Minnesota Laws That Affects Research, summarizes provisions that relate to the identification of LARs. It identifies the fact that there is *no state law* on point with regard to consent to research, although there are several statutes that explicitly limit consent.¹⁸ For example, the guardian of an incompetent adult may not consent to research without a court order, and a person under a stay of commitment order cannot consent without a court order.¹⁹

The University policy also states that, “Based on legal advice and established practice, the research community follows the rules that apply to surrogate consent to treatment. Legally authorized representatives of incompetent or incapacitated adults are determined in the following order of priority: 1) healthcare agent previously appointed by the individual through a healthcare power of attorney; 2) spouse; 3) parents; 4) adult children; and finally, 5) adult siblings.”²⁰ It cites the state’s health care agent authority and two state laws that establish the hierarchy of persons who can access the medical records or health data of a deceased person.²¹

The external review team requested further information on the legal basis for surrogate consent to *treatment*, and was informed that, “Minnesota Statutes, Chapter 145C, establishes the authority of a health care agent to make health care decisions for an adult who lacks decision-making capacity.” Minnesota Statute 13.384, subdivision 3(e), establishes the authority of surviving heirs of the nearest degree of kinship to obtain medical records of decedents from government entities. By analogy, we have applied these statutes to determine the hierarchy for establishing a legally authorized representative for purposes of research consent.”²²

OHRP has offered guidance and disseminated opinion letters on what constitutes “applicable law” under 45 CFR 46.102 (c): “The issue as to who can be an LAR is determined by the laws of the jurisdiction in which the research is conducted (e.g., local or state law). Some states have statutes, regulations, or common law that specifically address consent by someone other than the subject for participation in research. Most states have no law specifically addressing the issue of consent in the research context. In

these states, law that addresses who is authorized to give consent on behalf of another person to specific medical procedures or generally to medical treatment may be relevant if the research involves those medical procedures or medical treatment.”²³ As the team understands OHRP’s interpretation of federal regulation and related compliance actions with regard to the enrollment of subjects who lack decision-making capacity, there is no “applicable law” in Minnesota that supports its current approach to surrogate consent to research. Further, its reliance on “established practice” also does not seem to comport with OHRP interpretation; inappropriate reliance on standard practice has previously been the subject of OHRP noncompliance determination letters for other institutions.²⁴

3.4.4.2. Conclusions

The University’s interpretation of the regulatory term “applicable law,” and therefore its policies defining who may serve as a legally authorized representative in federally funded research, do not appear to adequately conform to federal regulations and related guidance.

3.4.4.3. Recommendations

In light of these observations, the external review team has the following recommendations:

1. Policies and procedures related to the use of LARs must be comprehensively re-assessed in accordance with the foregoing observations and conclusions;
2. The OVPR and HRPP leadership should consider consultation with OHRP or DHHS on this topic.

3.4.5. Use of Surrogate Consent

3.4.5.1. Observations

University policy and IRB protocols reflect inconsistencies and, in some cases, appear to be at odds with Minnesota law. For example, the policy on Surrogate Consent (Policy 703) contradicts the cross-referenced legal explanation (Policy 403C) and appears to reflect a misunderstanding of terminology by suggesting that a LAR and a next-of-kin decision-maker are different, although both are acceptable for purposes of surrogate consent; in fact, if the next-of-kin was eligible to provide surrogate consent, the individual would *be* a LAR²⁵ Also, the prohibition against research consent by a legal guardian *without a specific court order* does not appear to be applied consistently, as guardians are sometimes referenced in research protocols as fulfilling the LAR’s function without mention of any authorization by the court. None of the IRB minutes reviewed by the team reflect discussion about who may serve as a LAR.

The review team also observed inconsistencies with regard to the planned inclusion of subjects who lack the capacity to consent. Often, within the same protocol, it would state that only subjects with the capacity to consent would be included, and then might later state that LARs would be used when potential subjects lacked capacity. Many of these conflicting messages were contained in applications from the Department of Psychiatry, despite the fact that members of that Department told the external review panel that they do not use LARs for any studies.^{F9} The IRB minutes reviewed by the team did not address these discrepancies.

Although there was little indication of instruction or education for LARs on their responsibilities, the team did review some protocols that impressively described LARs receiving education or at least instructions related to their roles. The new IRB Review Guide for Appendix I includes a question as to whether there should be procedures required for selecting LARs or informing them of their responsibilities (as occurs at some institutions), but it is routinely checked “no,” except in one instance in which a reviewer stated, “already done as part of program.”^{26, 27}

Further, policies fail to promote the importance of maximizing subject participation in the consent process when a LAR is providing the legally authorized consent, or of ensuring direct subject consent when capacity returns. The IRB does not appear to consider the issue of “dissent,” or evidence -- verbal or non-verbal -- that a subject who is not able to consent for herself or himself is nonetheless able to demonstrate an *unwillingness* to participate in research or a research procedure.

Finally, some of the new policies address the issue of obtaining assent from decisionally impaired prospective subjects, but the implementation appears to be irregular, not surprising with any newly-promulgated policies. As a result, protocols submitted during the fall of 2014 and reviewed by the team thereafter continued to showed inconsistent attention to the assent process.^{F10}

^{F9} This statement by the Department was directly contradicted by a protocol submitted in September that was explicit about the intended use of LARs when subjects lacked decision-making capacity

^{F10} In October, 2014, one failure to include assent information was identified and referred to the Executive Committee, while the month before a response to an “Appendix I” question in a cancer study stated, “no plan for assent,” but was not questioned. A protocol deferred in September required the addition of “an assent form” but was approved with only the addition of an *assent* acknowledgement and signature.

3.4.5.2. Conclusions

The policies and practices adopted by the IRB do not yet provide adequate guidance for investigators on the best means of identifying and educating those individuals who are permitted to function as a LAR in a given situation. Protocols and other information reviewed by the team indicate wide disparities and failures in understanding the definition and appropriate selection of LARs. Only a few sets of the IRB minutes that were assessed by the external review team commented on these discrepancies, and none addressed the question of legal authority. This evidenced a lack of appreciation for the gravity of replacing an individual's autonomous consent with that of a surrogate in the research context. It should be well understood by all those involved in research with prospective subjects with limited decision-making capacity that the use of a surrogate for research consent calls for heightened levels of scrutiny.

3.4.5.3. Recommendations

In light of these observations, the external review team has the following recommendations:

1. The HRPP should develop effective strategies to educate research personnel on the legal use of surrogate decision-makers when considering the involvement of research subjects with limited decision-making capacity;
2. The IRB's review of protocols proposing the use of surrogate decision-makers be rigorous and in keeping with applicable laws and best practices, as well as with University policies;
3. IRB policies should require:
 - a. A process for informing prospective LARs about their responsibilities;
 - b. Maximization of assent, with consideration of the use of an assent form in appropriate circumstances;
 - c. A verification of the lack of dissent when assent is not possible;
 - d. A plan for re-consent if a subject regains capacity; and
 - e. A plan for monitoring subjects who are likely to have fluctuating capacity, including the steps to be taken if capacity diminishes.

References for Section 3.4

¹ Letter from President Eric Kaler to Vice President for Research Brian Herman re: Human Subject Research Review, Dated Jan 24, 2014 [See Appendix 1 for full copy]

² University of Minnesota IRB Policy 501: Vulnerable Populations Dated 05/16/14; University of Minnesota IRB Policy 506: Adults Lacking the Capacity and/or Adults with Diminished Capacity to Consent Dated 08/21/2014; University of Minnesota IRB Policy 703: Research Involving Human Participants Unable to Consent- Surrogate Consent Dated 05/16/14; University of Minnesota Form-APP-020_Appendix I, , Section 1. Targeting or Including Adults Lacking Capacity To Consent and/or Adults with Diminished Capacity To Consent Updated Sept 2014 [See Appendix 13 for full copies]

³ University of Minnesota IRB Policy 506: Adults Lacking the Capacity and/or Adults with Diminished Capacity to Consent Dated 08/21/2014 [See Appendix 13 for full copy]

⁴ US Department of Health and Human Services, Office of Human Subjects, Protections Frequently Asked Questions “What is informed consent and when, why, and how must it be obtained?” accessed at <http://www.hhs.gov/ohrp/policy/faq/informed-consent/what-is-informed-consent.html> [See Appendix 14]

⁵ US Department of Health and Human Services, Secretary’s Advisory Committee on Human Research Protections (SACHRP) Recommendations from the Subcommittee for the Inclusion of Individuals with Impaired Decision Making in Research (SIIDR) March, 2008 [See Appendix 15]

⁶ University of Minnesota Form-APP-020_Appendix I, , Populations with Additional Considerations, Section 1. Targeting or Including Adults Lacking Capacity To Consent and/or Adults with Diminished Capacity To Consent, Updated Sept 2014 [Appendix 13]

⁷ Silverman ,H. Protecting Vulnerable Research Subjects in Critical Care Trials: Enhancing the Informed Consent Process and Recommendations for Safeguards, Ann Intensive Care, 2011, 1:8, accessed at <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3224458/>

⁸ University of Minnesota Form-APP-020_Appendix I, , Populations with Additional Considerations, Section 1. Targeting or Including Adults Lacking Capacity To Consent and/or Adults with Diminished Capacity To Consent, Updated Sept 2014 [Appendix 13]

⁹ University of Kentucky Impaired Consent Capacity Policy, Research studies involving adult participants with impaired consent capacity [Appendix 16]

¹⁰ 45 CFR 46.116 General requirements for informed consent; 45 CFR 46.111(b) Criteria for IRB approval of research

¹¹ See, Final Report of Investigation 1: Accepted by the IRB in October 2014.

¹² University of Minnesota IRB Policy 506: Adults Lacking the Capacity and/or Adults with Diminished Capacity to Consent Dated 08/21/2014 [Appendix 13]

¹³ University of Minnesota Form-APP-020_Appendix I, , Populations with Additional Considerations, Section 1. Targeting or Including Adults Lacking Capacity To Consent and/or Adults with Diminished Capacity To Consent, Updated Sept 2014 [Appendix 13]

¹⁴US Department of Health and Human Services, Office of Human Subjects, Protections Frequently Asked Questions, “When may a legally authorized representative provide consent on behalf of an adult with diminished decision-making capacity? ...Should the subject regain or develop the capacity to consent, then his or her consent must be obtained for any further research, as the consent of the legally authorized representative is no longer valid.” Accessed at <http://www.hhs.gov/ohrp/policy/faq/informed-consent/legally-authorized-representative-provide-consent-adult-diminished-decision-making-capacity.html> [Appendix 14]

¹⁵See, e.g., Smart, A., Thompson, B.T., Needham, D.M., Hopkins, R.O., Williams, A., Burnham, E.L., Moss, M. Surrogate Consent for Genetic Testing, the Reconsent Process, and Consent for Long-Term Outcomes in Acute Respiratory Distress Syndrome Trials; *Am J Respir Care Med.* 2013 Dec 1;188(11):1370-1373.

¹⁶45 CFR 46.116 General requirements for informed consent

¹⁷ 45 CFR 46.102(c) Criteria for IRB approval of research

¹⁸University of Minnesota IRB Policy 403C: MN Laws that Affect Research Dated 3/21/14

¹⁹Minnesota Statute 524.5-313 Powers and Duties of Guardian; Minnesota Statute 253B.095 Release Before Commitment [Appendix 17]

²⁰University of Minnesota IRB Policy 403C: MN Laws that Affect Research Dated 3/21/14

²¹Minnesota Statute 13.384, Medical Data (which establishes the hierarchy of persons who can access the medical data of a deceased patient as “the surviving spouse, parents, children, siblings, and health care agent of a deceased patient or client or, if there are no surviving spouse, parents, children, siblings, or health care agent to the surviving heirs of the nearest degree of kindred”), Minnesota Statute 144.291, Minnesota Health Records Act, which establishes a patient’s right to health records and defines a patient as including “the surviving spouse and parents of a deceased patient, or a person the patient appoints in writing as a representative, including a health care agent;” Minnesota Statute 145C.02 Health Care Directive [Appendix 17]

²²See Appendix 7 for Documents Requested by the External Review Team.

²³US Department of Health and Human Services, Office of Human Subjects, Protections Frequently Asked Questions, “Who can be a legally authorized representative (LAR) for the purpose of providing consent on behalf of a prospective subject?” <http://www.hhs.gov/ohrp/policy/faq/informed-consent/legally-authorized-representative-for-providing-consent.html>

²⁴Compliance Letter, Office of Human Subject Protections, RE: Human Research Subject Protections Under Multiple Project Assurance (MPA) M-1363, June 26, 2002 [See Appendix 14]; See also, Saks, E.R.; Dunn, L.B.; Wimer, J; Gonzales, M., and Kim, S. (2008) "Proxy Consent to Research: The Legal Landscape," *Yale Journal of Health Policy, Law, and Ethics*: Vol. 8: Iss. 1, Article 2. Accessed at: <http://digitalcommons.law.yale.edu/yjhple/vol8/iss1/2>

²⁵University of Minnesota IRB Policy 403C: MN Laws that Affect Research Dated 3/21/14 includes: Investigators’ Responsibilities:.. If an adult participant is identified and is incompetent or lacks decision-making capacity for healthcare decisions and consent, the treating physician, and/or consulting physician(s) must document in the medical record: ... The identity of the legally authorized representative and if none, the next-of-kin.” [Appendix 13]

²⁶ University of Minnesota Form-APP-020_Appendix I, , Populations with Additional Considerations, Section 1. Targeting or Including Adults Lacking Capacity To Consent and/or Adults with Diminished Capacity To Consent, Updated Sept 2014 [Appendix 13]

²⁷For discussion of LAR education and a sample educational brochure, See, e.g. brochure, University of Kentucky, Advice to Legally Authorized Representatives of Adult Participants [Appendix 18] and Research Involving Individuals with Questionable Capacity to Consent: Points to Consider, National Institutes for Health, accessed at <http://grants1.nih.gov/grants/policy/questionablecapacity.htm> [Appendix 19]

3.5. Research Protections and the Department of Psychiatry

3.5.1. Introduction

The University's charge to the external review team required specific examination of research involving disorders or conditions characterized by the potential for impaired decision-making capacity.

Information was gathered and reviewed and/or interviews were conducted in relation to the range of relevant human research activities in psychiatry, neurology, intensive care, and emergency medicine. Nonetheless, it quickly became clear that many of the persisting concerns related to human subjects protections at the University point to a relatively small clinical research portfolio within the Department of Psychiatry ("Department"), and research from the Department became the natural focal point of the team's review.

The review team observed that the University has undertaken efforts over the past decade in attempt to understand and remedy this problem. In 2006 and 2009 the University conducted surveys of the Department's staff to identify problems within the Department; in 2009 there was an internal audit of the Department designed to identify deficiencies and potential areas for improvement.¹ In parallel to this review, in 2014, there were at least two ongoing internal investigations into complaints related to research within the Department.² Observations and recommendations are offered elsewhere in this report that directly or indirectly address research within the Department.

Without question, some individuals with psychiatric disorders are not fully able to protect their own interests through the process of informed consent. Some are also uniquely susceptible to harm associated with some research interventions. While the federal research regulations call for "additional safeguards" when research includes individuals "vulnerable to coercion or undue influence," they offer little direction, leaving it to investigators, IRBs, and institutions to craft appropriate protections.³

The review team's observations and recommendations with regard to the Department of Psychiatry focus on the evaluation of the risks and benefits by the IRB, informed consent practices, the relationship of research to clinical care at the Fairview Health System ("Fairview") with specific reference to Psychiatry, and Departmental leadership.

3.5.2. Observations

3.5.2.1. Evaluation of risks and benefits

The federal research regulations permit an IRB, in the course of its protocol review process, to exercise broad discretion in determining when research risks are reasonable in relation to benefits and when research risks are minimized. As stated elsewhere, the review team found little evidence that the University's IRB engaged in a meaningful process of evaluating research risk. While this issue was not unique to the Department, it has particular implications for research within the department for individuals with limited decision-making capacity. For example, in research on treatments involving subjects uniquely susceptible to harms associated with a relapse or worsening of illness (for example, aggressive behavior, self-injury, job loss), an IRB requirement for the operationalization of dropout criteria for subject worsening could create an objective benchmark for dropping that individual from the study. Such a pre-established procedure would help ensure that patients exposed to a treatment that is new to them (experimental or otherwise) will not be maintained in a research study when it is clearly not in their best interests to do so.

Given the nature of impairment in certain psychiatric disorders, some patients are not likely to request removal from the study even when they are doing poorly. Anticipating those situations, an IRB could, for example, establish criteria that would require the study team to re-evaluate or withdraw such subjects from the research. Similarly, depending on the study, an IRB may minimize risk by excluding subjects from enrollment in treatment studies when they are benefitting from and tolerating their current treatment or, when it is viewed as inappropriate to enroll a patient who has never had access to standard care. Lastly, and perhaps most importantly, an IRB can impose a range of requirements on a given study, including, but not limited to, specifying: 1) the frequency of a subject's follow-up assessment during study participation, 2) the qualifications of staff involved these assessments, and 3) the documentation required. Such interventions can adapt the otherwise standardized procedures commonly found in industry and investigator written proposals by helping to tailor protections to specific populations (e.g., a patient with a new onset psychosis) and recruitment settings (e.g., an emergency department). Such modifications by an IRB must be carefully tailored to the research and subject populations in order to enhance protections without adding unnecessary burden or compromising the science. Effective review of this sort requires a collaborative give-and-take between

IRB and investigator prior to and in the course of the review. The review team did not observe such efforts on the part of the IRB or Department researchers in the review of psychiatric research.

3.5.2.2. Informed consent

In the aftermath of a series of national scandals in the 1990s related to psychiatric research, and in the context of an emerging conceptual and empirical literature on the ethics of research involving persons with mental illness during that same period, an expanding repertoire of additional methods to safeguard the participation of patients with impairing psychiatric and neuropsychiatric disorders in research was developed.⁴ In the ensuing years, while no gold standard has emerged, many such methods have found their way into the mainstream of research practice. These include, but are not limited to, empirically validated interviews or other methods to assess and document subject capacity to consent and the use of an independent assessor of capacity.^{5,6}

The external review team requested and received information related to the mechanisms through which capacity to consent is established for research subjects enrolled in studies conducted through the Department. The team noted that, as a matter of routine, the Department's clinical trials employed a six item "evaluation to sign consent" form (See Appendix 20) that must be completed and signed by a member of the research team who certifies that "the above subject is alert, able to communicate, and able to give acceptable answers to the items above." While this approach has the advantage of requiring some discussion between the investigator and the potential subject, in the review team's judgment, it is insufficient. A more complete process would, for example, rely on one of the published semi-structured interviews or scales noted above and would thereby come closer to a "best practice." With these commonly accepted assessment methods, domains most relevant to decision-making, and reflecting commonly applied standards for capacity, are probed, evaluated, and documented.

It is the external review team's opinion, that, in the context of the many concerns raised about recruitment and enrollment in Departmental research, the University, IRB and investigator should have introduced an *independent assessment of capacity* for relevant research. For example, some institutions require (for defined categories of research) that an assessment of capacity be made by a trained individual who is not a member of the research team and who does not report to the principal investigator. In this manner, neither the investigator nor his/her paid staff are responsible for

determining whether the prospective subject meets a reasonable standard for capacity to consent; such a separation of responsibilities between the investigator and prospective subject helps ensure that real and perceived conflicts of interest are mitigated or even eliminated.

An IRB should also consider the training and qualifications of the staff member(s) designated to document consent and assess subject capacity. The decision that a prospective research subject can or cannot make a consent decision for herself or himself is one that requires considerable training or expertise. Boilerplate language inserted in many of the IRB protocols reviewed by the team state, “All study personnel have completed University of Minnesota HIPAA and CITI training. Study personnel will be trained and certified by the sponsor to administer rating scales. Research coordinators may conduct the preliminary consent discussion, but consent will be obtained by the Principal Investigator or Co-Investigator.” This is inadequate, though, since neither HIPAA, CITI, nor sponsor training (i.e., those sponsors with which the team is familiar) address the relevant details of consent and capacity to consent. The question as to whether an investigator (and his or her coordinator) is appropriately trained and able to devote the time required to the consent process is one that the IRB should consider in its review and monitoring efforts.

As mentioned previously, “live” consent monitoring or other methods should be used to evaluate the investigator’s approach to the consent discussion. In some IRB materials provided to the team, for example, the protocol indicates that the investigator or study coordinator will read the consent form to the prospective subject. If, in fact, an investigator or staff member were to read aloud a twelve to sixteen page consent form verbatim, this would represent a uninformed and unacceptable approach to informing subjects about a proposed study.

We found no indication that investigators from the Department included supplemental methods to support comprehension and decision-making for research. We also found no evidence of real-time consent monitoring. Given the intense scrutiny to which the University, and this Department in particular, have been subjected, practices that have been adopted in other academic settings to support consent could have easily been introduced.^{7, 8, 9, 10}

Finally, the external review team examined three protocols from the Department, all of which were submitted subsequent to the implementation of new policies and forms in September 2014. The IRB

appropriately deferred the approval of all three protocols, citing the inadequacy of information describing the ways in which the capacity evaluation and the risk/benefit profile would be assessed. While these deferrals included evidence of a more substantive discussion by the IRB related to the specific protections needed for research subjects with mental illness, not all Departmental protocols submitted after the noted policy changes received the same level of increased scrutiny. In a protocol involving a psychiatric drug washout, for example, the IRB asked for further information about the risk/benefit profile, but no augmented strategies were required in order to bolster the boilerplate assessment of capacity.

3.5.2.3. Integrating research and clinical care – Research within Fairview Health System

The external review team first became aware of the historically distinct mission of Fairview from that of University-based operations in an interview conducted with Fairview leadership late in the course of the review. In addition, we learned that, until recently, there has apparently been an absence of administrative structures to integrate properly Fairview's community oriented healthcare system with the research/academic activities of the University.

To this day, and despite rebranding, a new joint operating agreement, and a newly defined mission, Fairview has little involvement in priority setting for research activities conducted at the facilities it owns and operates. More specifically, the Fairview leadership and staff reportedly have no input in the approval process for human subjects research, and no program for monitoring or quality assurance of ongoing research. According to the Fairview leadership, one specific consequence of this inability to participate in the vetting of protocols by their staff is that studies are often approved for which the subject population required is simply not among the patient populations *available* for recruitment, or are not available in the numbers required.

Fairview has introduced a number of initiatives in an attempt to address what has been described as a "historic divide" between its clinical mission and the academic/research missions of the University. For example, to assess and change the culture, Fairview has conducted staff interviews, focus groups, educational meetings, and has created teams comprised of researchers and administrators to discuss current research activities. However, we were told that such efforts are seen as having little impact on research from the Department. Staff interviewed attributed this to a "pervasive lack of trust" specific to

“behavioral” research at Fairview. Others reported a perception of the Department’s “overly aggressive” approach to subject recruitment, which is seen as being at odds with patient-centered clinical priorities. A review of records of complaints and concerns submitted via the Fairview Research Helpline by Fairview staff has provided additional support for these perceptions.^{F1}

What has *not* been considered to date is the opportunity to engage the clinical psychiatry staff at Fairview in the research mission and as *gatekeepers*. Requiring that non-researcher/clinicians serve as gatekeepers can provide additional safeguards in recruitment procedures, consent, and ongoing monitoring during study participation. The hospital can limit the extent to which research staff approach and recruit patients directly in clinical setting, requiring instead that a member of the clinical team determine whether it is appropriate to do so; psychiatrists, psychologists, and social workers who are employed as members of the clinical staff can be trained and then called-upon to conduct independent assessments of capacity; nursing staff can also play a role in the ongoing clinical assessment of research subject capacity and other measures of the subject’s clinical status.

In order better to integrate clinical and research priorities, the IRB could require review and approval of research by Fairview administration prior to the submission of a protocol to the IRB. This would ensure that adequate resources, including prospective subjects, are available to the researcher(s). Perhaps more importantly, this would also ensure that the proposed research is compatible with the healthcare system’s mission and vision. Finally, the review team understands that the electronic medical records system at Fairview does not permit data entry by research staff. As a result, monitoring and quality review of research by Fairview’s clinical and administrative staff is currently not possible.

3.5.2.4. Leadership

In the course of our interviews, many concerns were voiced about the commitment to human subjects protection of _____ and _____. While anecdotal, the clear pattern that emerged was of two investigators whom faculty and staff do not trust and who fail to communicate a set of priorities that align their own research agenda with the best interests of patients and patient care.

^{F1} The External Review Team requested the record of complaints from the Fairview Research Helpline from the past three years. Among the calls were four from staff complaining about research practices. Two expressed concern (2012 and 2014) about “a UMN-employed research staffer potentially acting outside of scope of practice,” and two complained about “the lack of information provided to clinical staff” and either inadequate consent practices (2013) or “the high level of involvement of the sponsor in the conduct of the trial” (2014).

Similarly, administrative staff involved in IRB review voiced criticisms of the care taken by _____ in _____ protocol submissions and in _____ interactions with the IRB.^{F2} Documentation of IRB review provides some additional support for these statements and an example of resistance by _____ to IRB efforts to introduce the use of an independent consent monitor.^{F3}

In other ways, it appears that _____ does not take a sufficiently active role in efforts to promote higher ethical standards with the Department. For example, by emphasizing human subjects protections in the department's strategic plan, _____ could have communicated the priority of this work and make a compelling statement to the Department and beyond. For a department as embattled as the Department of Psychiatry with regard to the ethics of research, the omission of ethics from the strategic plan indicates an insensitivity to matters of paramount concern within the Department, the University, and the community.¹¹

3.5.3. Conclusions

In the aftermath of the death of Dan Markingson, persistent attention has cast doubt on the ethics of psychiatric research at the University. Numerous internal and external investigations have failed to resolve concerns or shed light on the basis for the ongoing negative attention. The external review team is aware that mental illness, psychiatry, and psychiatric research are poorly understood and remain the focus of considerable stigma. Certainly some of the unrelenting criticism of research in the Department from outside the University can be attributed to this. But the persistence of criticism and doubt about psychiatric research and the oversight of psychiatric research are not without merit. In our view, the current human subjects protection program as it involves psychiatric research does not reflect the best efforts of a University of this caliber.

^{F2} In 2012, the IRB warned. _____, "Please be advised that the committee noted this application was poorly completed, which made it difficult to appropriately assess risks and review. Please know that, in future, applications of this caliber may be returned for extensive revision before they can be reviewed." The IRB nonetheless approved that application. In 2014, the IRB then deferred approval of a protocol submitted by _____ "due to the inability to make an accurate risk determination" because further information "as to how the washout [of other medications] will occur and the dangers surrounding it are required."

^{F3} In September of 2014, _____ did not amend a study in response to an IRB stipulation requiring a "nonaffiliated party" to "meet with patient to assure that the consent process is voluntary" when the prospective subject was a patient of the investigator or co-investigator. This practice was in place at other sites involved in the study. After a meeting with IRB representatives in November, _____ agreed to the witnessing of consent.

Opportunities for more informed policy development, innovative practice, aggressive quality assurance, community engagement, and staff training and accountability are needed. The Department chair and senior faculty should take a leadership role in this effort. Recent progress associated with the introduction of new IRB forms and appendices in September 2014 is an important first step, but additional changes are required.

Finally, based on interviews and document review, there is a need on the part of the University, Fairview, and the Department to acknowledge, understand, and remedy the evident mistrust of the work of [redacted] With that the University can begin to develop a model program of research and research oversight that would better serve this vitally important area of inquiry.

3.5.4. Recommendations

The external review team recommends that:

1. IRB membership, expertise and training should more effectively address risk evaluation and management for psychiatric research;
2. Best practices regarding consent and capacity to consent should be introduced and made routine;
3. Fairview staff should be involved in protocol review, in gatekeeping functions, and in research monitoring;
4. [redacted] as the focus of ongoing concern and criticism, should receive supervision, coaching in leadership, and advanced training in human subjects protections.

References for Section 3.5

¹ 2006 and 2009 Department of Psychiatry Staff Surveys and 2009 Internal Audit of the Department of Psychiatry; See Appendix 7 for Documents Requested by the External Review Team

² Investigation 1 and Investigation 2; See Appendix 7 for Documents Requested by the External Review Team

³ See 45 CFR 46

⁴ For example, see a brief description of a multidisciplinary team of clinical research advocates at the NIMH who “provide several protective function for vulnerable subjects” at <http://www.nimh.nih.gov/labs-at-nimh/scientific-director/office-of-clinical-director/office-of-the-clinical-director-hspu-mcru.shtml>

⁵ [Dunn LB](#) et al. Assessing decisional capacity for clinical research or treatment: a review of instruments. [Am J Psychiatry](#). 2006 Aug;163(8):1323-34.

⁶ [Jeste DV](#) et al. A new brief instrument for assessing decisional capacity for clinical research. [Arch Gen Psychiatry](#). 2007 Aug;64(8):966-74.

⁷ Appelbaum P, Grisso T. The MacArthur Competence Assessment Tool for Clinical Research (MacCAT-CR). Sarasota, FL: Professional Resource Press, 2001

⁸ [Dunn LB](#)¹, [Jeste DV](#). Enhancing informed consent for research and treatment. [Neuropsychopharmacology](#). 2001 Jun;24(6):595-607.

⁹ [Jeste DV](#) et al. A new brief instrument for assessing decisional capacity for clinical research. [Arch Gen Psychiatry](#). 2007 Aug;64(8):966-74.

¹⁰ The Teach-Back method, developed initially to address problems with health literacy is now increasingly applied to research consent. See <http://healthliteracymn.org/sites/default/files/images/files/Teach-Back%20Program%20Guide.pdf>

¹¹ Department of Psychiatry Strategic Plan- See Appendix 7: Documents Requested by the External Review Team

3.6 Perceptions of Institutional Culture

3.6.1. Introduction

The external review team was favorably impressed by evidence of genuine commitment to human subjects priorities by many of those interviewed during its site visit; it was also clear that the University has a cadre of knowledgeable and dedicated individuals associated with its HRPP. The on-site interview process provided the external review team with the opportunity to learn first-hand of the perceptions of the University culture as it pertains to the ethical conduct of research. Review of University initiatives, policies, and its pattern of response to concerns about its human subjects research activities provided further information.

An institution's response to criticism reflects an important aspect of its culture. The University has experienced ongoing scrutiny of its human subjects protections program and components of its Department of Psychiatry research program, particularly research involving adults with the potential for impaired decision-making capacity. This University is not unique in the challenges it has faced. Research-related deaths and adverse events have occurred at other prominent institutions, including those with which some of the review team members are or have been affiliated. The internal and public responses of these institutions to events casting doubt on their research enterprise create a useful and public benchmark against which the University's actions can be considered. The response of Johns Hopkins University following the death of Ellen Roche in 2001 is one noteworthy example.¹ To quote a 2002 university publication, Edward Miller, the CEO of Johns Hopkins at the time "believed Hopkins had to do more than just tweak its review process. 'There has got to be a cultural change here,' Miller said. Miller challenged his colleagues to examine their fundamental approach to research on human volunteers. He exhorted them to go well beyond whatever the government required, to establish a new benchmark for human research subject protection. 'We're going to have to raise the bar higher,' Miller said. 'There can't be any slippage. None.'"²

Given the particular focus of this review, many of the problems referenced in the following section involve the human subject research activities of the Department of Psychiatry.

3.6.2. Observations

As described elsewhere in this report (See section 3.1), the University's "Risk Recalibration" initiatives³ led to changes in ethics education policy and practice. Whether or not the changes compromised the effectiveness of investigator education, or the initiative affected allocation of resources for the IRB, the perception among at least some staff was that it had. Of course, the messaging itself raised concerns among staff about the relative priority of research oversight and operational efficiency. It is interesting to contrast the recent federal initiatives, including the Advance Notice of Proposed Rulemaking entitled, "Human Subjects Research Protections: Enhancing Protections for Research Subjects and Reducing Burden, Delay, and Ambiguity for Investigators" which indicates that "Changes under consideration would *ensure the highest standards of protections for human subjects* involved in research, while enhancing effectiveness of oversight" [emphasis added].⁴ While appropriate measures to create efficiency and remove *unnecessary* administrative burdens should be welcomed, the institution must be cautious that such initiatives do not lead to real or perceived reduction in oversight capability.

There is a widespread and seemingly well-founded perception that the University has reacted to the death of Dan Markingson, and to the ongoing criticism in its aftermath, by assuming a *defensive* posture.⁵ In other words, in the context of nearly continuous negative attention, the University has not persuaded its critics (from within and outside the University)⁶ that it is interested in more than protecting its reputation and that it is instead open to feedback, able to acknowledge its errors, and will take responsibility for deficiencies and their consequences.

The University and its medical school do not appear to employ existing lines of reporting to define a hierarchy of accountability for human research ethics and thereby expand oversight responsibilities *beyond the IRB*, its monitoring function and University leadership. For example, the Dean of the medical school could craft policies requiring the departments to develop ethics education requirements and content, build relevant performance metrics into investigator evaluations, and most importantly, hold Chairs accountable for human subjects protections within their departments. Such initiatives effectively demonstrate the University's commitment and can signal a shift in culture.

In what follows, the review team discusses its observation that the University has missed some vital opportunities to promote an environment in which feedback is encouraged and helps drive change. We

also consider the use of public apology and other methods of communicating core values related to treatment of research subjects.

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. As noted in section 3.3.4.2, the University has developed several such communication channels.^{7,8,9} 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*.

With regard to “Institutional Culture,” it is of course difficult to collect information in a manner that is comprehensive or systematic, and many of our observations are not amenable to independent verification. Nevertheless, “*perceptions* of institutional culture” are simply that. Accurate or not, they appear to drive the many longstanding concerns the University is now addressing with the current independent review. For example, faculty and staff in Psychiatry repeatedly characterized the climate of work as a “culture of fear.” They provided stories of intimidation by researchers and fear of retaliation should staff voice opposition to practices that were of concern. While we do not endorse or refute these individual statements, we believe the “defensive posture” described earlier contributed to the impression that the University, Fairview, and the Department of Psychiatry were not interested and not effective in addressing serious and ongoing problems.

In this same context, concerns were also raised with regard to University policies on whistleblowing that include the language “no one will retaliate against individuals who acted in good faith in reporting.”¹⁰ The external review team was told a story by a longstanding University employee about another who was terminated after having expressed concern about a research study involving the elderly, and further, that the concerns were ignored. Again, the external review team cannot conclude that this indicates a problem with the institution’s response to “whistleblowers,” rather, that there is such a perception. True or not, the potential impact of such concerns is considerable.

Institutions are often criticized when they permit their response to error or subject injury to be driven by liability concerns, the generally defensive posture described above, or simple neglect resulting from a

diffusion of responsibility. Public and direct apologies to subjects demonstrate humanity sometimes missing in institutional responses. Several Universities have acknowledged research subject deaths with public expressions of condolence.^{11,12,13}

The University's motion to seek court costs from Mary Weiss, Dan Markingson's mother, for example, certainly did not create the impression of a humane response, and the team was told that the public perception is that she never received an expression of regret or apology in the aftermath of her son's death.^{14,15} In university and other settings, the way an institution responds to unwanted public or media attention often draws additional attention and can complicate an already difficult situation. Such appears to have been the case here.

3.6.3 Conclusion

Criticism of the ethics of an institution's clinical research requires a strategic but humane response. The response may require the re-examination of institutional operations and processes, and may call for a public reaffirmation of the institutional commitment to the rights and welfare of human research subjects. The broader public has been sensitized to the darker aspects of the history of human subjects research¹⁶ and is thus understandably vigilant regarding evidence of failures in an institution's approach to the *ethics* of research. Rebuilding community confidence in the institution's core values related to human subjects research is essential for any institution that serves the public interest, and as we have seen, failure to do so can have profound and protracted consequences.

The review team acknowledges that the University's decision to commission this independent review and make public its findings reflects the determination of leadership to achieve excellence in human subjects protections and take a bold first step in that direction.

3.6.4. Recommendations

The external review recommends that the University leadership:

1. Define a hierarchy of accountability for human research ethics and thereby expand oversight responsibilities beyond the IRB. Department chairs should be expected to review and approve the submission of IRB protocols, be engaged in follow-up compliance activities, develop department-specific educational programs, and share ultimate responsibility for human subjects protections within their departments.

2. Rework institutional messaging in policies and procedure to include unequivocal statements on the administration's intention to create and nurture a culture of ethics, and adopt communication strategies to bring these core values to life by investing in their visibility and adoption at all levels of the University community and beyond;
3. Establish both formal and informal means of stimulating a university-wide conversation about the manner in which this newly endorsed culture of ethics can be most effectively realized.

References for Section 3.6

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- ² Keiger D and DePasquale S. Special Report: Trials and Tribulation. Johns Hopkins Magazine, Vol 54, No. 1. Feb. 2002 Accessed at: <http://pages.jh.edu/~jhumag/0202web/trials.html>
- ³ Risk Recalibration. University of Minnesota, Office of the Vice President for Research website. Accessed at: <http://www.research.umn.edu/about/risk.html>
- ⁴ <http://www.hhs.gov/ohrp/humansubjects/anprm2011page.html>
- ⁵ Hammerschmidt, Dale. Important questions remain unanswered in U of M Markingson case. MinnPost. April 24, 2014. Accessed at: <http://www.minnpost.com/community-voices/2014/04/important-questions-remain-unanswered-u-m-markingson-case>
- ⁶ Lemmons, Trudo et al. Letter to President Eric Kaler and Professor Eva von Dassow dated October 21, 2013. Accessed at: http://www1.umn.edu/usenate/fsenate/docs/131205toronto_letter.pdf
- ⁷ Reporting Research Complaints and Concerns.” Accessed at: <http://www.irb.umn.edu/report.html#.VOlvdnF-gY>.
- ⁸ University of Minnesota UReport. Accessed at: <https://secure.ethicspoint.com/domain/media/en/gui/9167/index.html>.
- ⁹ Fairview Research Administration Helpline. Accessed at: <http://www.fairview.org/Research/ResourcesandInformation/FairviewResearchResources/ResearchAdministration/index.html>
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- ¹¹ Miller, ED. Our legacy to Ellen Roche. Hopkins Medical News. Fall, 2001. Accessed at: <http://www.hopkinsmedicine.org/hmn/f01/postop.html>
- ¹² Statement on the Death of Jesse Gelsinger by the University of Pennsylvania Health System Institute for Human Gene Therapy. Accessed at: <http://web.archive.org/web/20010629210725/www.med.upenn.edu/~ihgt/jesse.html>
- ¹³ Student dies at Rochester in MIT-based study. Accessed at: <http://newsoffice.mit.edu/1996/wandeath-0410>
- ¹⁴ Weiss vs. Board of Regents for University of Minnesota, Defendant Board of Regents of the University of Minnesota and Institutional Review Board’s Notice of Taxation of Costs and Bill of Costs and Disbursements, State of Minnesota, County of Hennepin, Fourth Judicial District, Wrongful Death court file number 27 CV-07-1679, April 29, 2008.
- ¹⁵ The technical title in Minnesota for suing for court costs if the suit against a defendant is being dismissed is "Taxation of Costs and Bill of Costs and Disbursements," and that is the motion the University filed. The total claim filed was for \$57,535.96.
- ¹⁶ The Ethics of Clinical Research, Stanford Encyclopedia of Philosophy, Section 3, “Abuses and Guidelines,” September 20, 2012 <http://plato.stanford.edu/entries/clinical-research/>

4. Conclusions

At the request of the University of Minnesota, an independent team of experts conducted an extensive review of the activities of the human subject research program. The University commissioned this review in support of its stated goal of developing a program of clinical research that meets or exceeds standards and best practices for the ethical conduct research. In the wake of nearly ten years of criticism of clinical trials within the Department of Psychiatry, the University specified that the review place special emphasis on its examination of research protections related to the involvement of individuals with impaired capacity for decision-making for research.

Given the charge from the University, the external review team applied standards and expectations that go beyond *de minimis* regulatory and accreditation thresholds. The following summarizes the report's conclusions:

- There are significant problems with core functions of the human research protections program, including IRB review, investigator education, practices related to consent to research, and the effective coordination of administrative oversight, clinical care, and research;
- Given the history of concern and scrutiny of its programs, the University leadership should have taken more informed and affirmative steps to identify and address deficiencies, particularly within the Department of Psychiatry;
- 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;
- The review team did observe much strength in the University's human subjects program and the value of newly implemented enhancements in policy and practice. The vast majority of faculty and staff demonstrated pride in their work, obvious dedication to the ethical conduct of research, and a desire to improve performance.

The review team believes the University is well positioned to make changes necessary to reach its goals.