Status Report:

Implementation of Enhancements to Human Research Protections at the University of Minnesota

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At the request of Dr. Brian Herman, Vice President for Research at the University of Minnesota, I offer the following observations and recommendations on the University’s response to the February 2015 External Review of its human subjects protections program. This report draws upon discussions with members of the university community during my visit in late March; telephone and in-person meetings with faculty and staff prior to and subsequent to the visit; and review of available draft and final reports and documents related to the University’s efforts to fulfill its commitment to human subjects protections.

In response to the recommendations of the External Review, the University has set a course to re-establish and re-invigorate its human research protections program. The call for change has been fully embraced by the University and the effort reflects extraordinary resolve, effective leadership, and teamwork at many levels. Progress to date has been impressive, but the success of Advancing Human Research Protections will be measured over years and will require ongoing commitment and refinement of newly implemented structures, policies and practices.

**Background**

In July 2014, University’s Faculty Senate commissioned an external review to address continuing criticism of the human subjects protections program at the University of Minnesota, including concerns raised by its own faculty and staff. In response, University leadership contracted with the American Association of Accreditation of Human Research Protections Program to hire a team of external reviewers to examine the current state of policies, procedures and practices related to human subjects protections, with special attention to research participants with impaired decision-making capacity.

In February 2015, the external review team provided a report of its findings and recommendations (hereafter, the “the External Review,” or “The Report”). The Report was widely critical of University practices, and identified both fundamental shortcomings and missed opportunities requiring attention if the University was to satisfy its critics and achieve its stated goal of establishing a clinical research enterprise that met or surpassed best practices.

In response, in April 2015, the University convened an Implementation Team whose June 2015 work plan “Recommendations of the External Review of the University of Minnesota Human Research” outlined a university-wide effort and an 18-month timeline to remake its human subjects protection program and establish its commitment to high ethical standards in clinical research. To support and guide the
effort under the umbrella term, “Advancing Human Research Protections,” the Office of the Vice President for Research established a standing Research Compliance Advisory Committee (RCAC). The university designed and launched this effort and component processes (e.g. “IRB Renew”) with broad input and representation.

In keeping with its commitment to transparency, all plans, work products and meeting summaries were made available to the public. Descriptions of progress toward fulfilling each of the objectives of the Work Plan are well catalogued in easily accessible documents on web pages dedicated to this now 14-month long effort.

The recommendations of the External Review were numerous, broad in scope, and emphasized six overlapping and interrelated problem areas. These categories form the structure of the report that follows:

I. The involvement by university, medical school, and hospital leadership in human research protections
II. The quality of IRB review
III. Education and training of investigators in research ethics and research subject protections
IV. Policies and practices related to informed consent and the inclusion of research subjects with impairment in consent capacity
V. Research within the Department of Psychiatry
VI. University culture and values
I. The Involvement by University, Medical School, Hospital and Departmental Leadership in Human Research Protection Program

A central conclusion of the External Review was that leadership at the University, the Academic Health Center, and at the department level was not sufficiently engaged in the activities and mission of human research protections. For example, the report noted, “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 [in order to] expand oversight responsibilities beyond the IRB.”

Observations:

University leadership has embraced the many recommendations of the External Review with extraordinary resolve and energy. The development, implementation, and success to date of the Advancing Research Protections initiative itself derive from a new and vitally important degree of involvement by leadership.

The creation of a central Research Compliance Office, the development of a Community Oversight Board, and the introduction of a Fairview University Research Oversight Committee (FUROC) represent three important new structures central to the effort.

The March 2016 “Hierarchy of Accountability” specifically defines the larger network of interrelated committees, programs, and reporting relationships focused on human research protections. The “Fairview Research Administration (FRA) Chain of Command” (Appendix) illustrates the integration and coordination of institutional research oversight responsibilities.

The External Review called for the involvement of Fairview staff in “gatekeeping” functions to ensure that clinical interests remain priorities in research in the hospital setting. The FUROC is co-chaired by Fairview’s Interim Chief Medical Officer and the VP for Health Sciences, and includes the University’s VP for research and the Chief Nursing Executive of M Health, among others. According to a summary of its charge, FUROC will:

...serve as a place for researchers, staff, and the public to share concerns and to achieve a response or resolution to those concerns. The committee is to monitor the entire spectrum of clinical research across the Fairview Health System to insure...both research and clinical regulatory obligations are met...research protocols are appropriate and
feasible within the concurrent demands of patient care [and] that Fairview staff members have a voice in the conduct of research.”

A new practice, under the direction of FUROC, now requires the involvement of leadership and line clinical staff in the process of research protocol development, implementation, and ongoing monitoring. The Clinical Research Study -Fairview Behavioral Service Checklist (Appendix) outlines this requirement and documents its fulfillment. “Climate” assessments are planned and will help leadership gauge the impact of these new oversight efforts.

The Community Oversight Board, with whom I had the opportunity to meet, includes a diversity of expertise, interests and constituencies from within and outside the University. The group demonstrated enormous enthusiasm and recognized its potential to serve both consultative and oversight functions with regard to human research protections and research ethics more broadly. There is evidence of bidirectional communication; the IRB has presented to the COB, and the COB has offered input on the Research Subject Bill of Rights. However, the stated desire by members of the COB to understand their role was the topic of much of the discussion during my meeting with the group. Many members seemed uncertain of their responsibilities, their access to information about research practices, and whether they were to be “responsive or proactive.”

The University has taken a valuable step, also referenced in the External Review, to draw upon the strengths of its highly regarded academic programs. Linkages between University compliance functions, the Consortium on Law and Values, and the Center for Bioethics have already enriched activities such as educational programming and the development of a statement of core commitments.

The External Review called for the involvement of department level leadership in research oversight functions. The Departments of Psychiatry and Neurology have been working with the IRB to develop educational programming; the IRB anticipates more widespread participation by the departments in this work. However, the Medical School has yet to specify a role for department chairs in supporting routine compliance activities (or where they sit within the Hierarchy of Accountability).

At the time of my visit in March, some roles and responsibilities within the nascent oversight hierarchy remained only partially defined, as did the relationships and boundaries between others. One member of the RPAC was critical of the purpose and
uncertain of the responsibilities of this steering committee. Elsewhere, concerns were expressed with regard to the relative roles and responsibilities of the Research Compliance Office, the CTSI, and the IRB.

What is not evident from document review and web-browsing, however, but became immediately apparent during my visit to the University, was the degree of involvement by senior leadership of the University and Health Sciences Center, the vast number of faculty and staff of all disciplines engaged in the work of implementation, and the commitment and enthusiasm they brought to the work. The IRB leadership, with whom I had the opportunity to spend several hours, expressed pride in the evolving changes in their operation and optimism about what they hoped to achieve with the additional support and resources made available to them by the University.

**Discussion:**

Under the direction of University leadership, the University has conceived and crafted an impressive infrastructure with the potential to drive and sustain meaningful progress in human research protection. It is substantially responsive to the External Review.

Rapid change of the sort required of the Work Plan will almost certainly be associated with missteps and require some reanalysis. The need for course corrections and iterative refinements should be anticipated, encouraged, and carefully guided by leadership as it prepares to transition from implementation to maintenance and assessment phase.

The Community Oversight Board can mature to assume multiple roles on behalf of the HRPP, and its membership should work with leadership to define how its relationships within and outside the University can best support and shape the University’s vision of ethical research, patient/subject and family engagement, and research advocacy. As a semi-independent body, the COB can provide a non-institutional perspective on policy matters of importance to the University. In its oversight function, it can promote accountability to subject and community interests and influence practice.

The Fairview University Research Oversight Committee bridges a wide gap that existed between clinical care and research functions at Fairview. It supports a vital interaction that can promote joint responsibility between hospital-based clinical functions and University research. While I did not meet with representatives of Fairview, summaries
of FUROC meetings describe a plan to become actively engaged in the review of policies, monitoring findings and event reports. FUROC will periodically assess the effectiveness of Fairview’s efforts to promote “gatekeeping” functions by its clinical teams.

The External Review emphasized the value of Departmental accountability for compliance activities, and with some exceptions, this does not appear to be central to the implementation plan. Department heads involved in matters such as setting compensation, evaluating effort, supporting faculty for academic promotion, and otherwise assessing the state of departmental activity, are uniquely positioned to support the University’s educational and compliance agenda, and do so in manner that is tailored to the nature of the work of the department and the investigator. Department chairs should be aware of compliance problems within their service area or among their faculty. They can play a valuable role in enforcing IRB rules and identifying “local” solutions to the non-compliant investigator. The external review noted, “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.”
II. The Quality of IRB Review

The External Review identified problems with the quality of IRB review and with the value of a department-based scientific review process. The examination of IRB membership rosters and meeting attendance raised concerns about reviewer expertise and workload, and IRB documentation suggested that IRB deliberations lacked necessary substance. The extent of involvement of IRB leadership in investigations of non-compliance was seen as an unnecessary additional burden on the operation.

Observations:

In response to the External Review, the University developed an ambitious plan to reform its IRB operations and IRB review processes. The University engaged internal and external consultants, examined other nationally recognized University programs, and committed significant new funding to support system-wide change.

The IRB leadership team, with whom I had the opportunity to spend considerable time, is a talented and highly professional group with great pride in its work and commitment to excellence in human research protections.

An analysis of the scope and content of the University’s human subjects research portfolio was used to estimate demand for review and categories of required reviewer expertise in order to plan for a restructured IRB committee process. Implementation of the plan was slowed, however, by difficulty in recruiting new IRB members; feedback indicated that the planned meeting schedule would place excessive demands on faculty time. With the input of external consultants, the University made a prudent mid-course correction in the design and timeline for the new IRB committee structure. At the 12-month mark, new IRB members have been identified, oriented, and trained. Four of 8 planned panels commenced or will soon commence review.

In the interim, the IRB review process has undergone considerable refinement. Important changes include the addition of meetings so that there is now a single Continuing Review and a single Biomedical IRB meeting each week, a capping of the number of items that can be addressed at any meeting, and a review format that demands a more structured and systematic evaluation of each research proposal.
The University has contracted with Huron consulting, and has begun to make use of the Huron Toolkit that provides forms, templates, and checklists to facilitate review, and supports training of both IRB staff and reviewers on standard operating procedures. For example, a checklist prompts IRB administrators to assess and document whether the required number of reviewers is present and whether reviewers with appropriate expertise are present at the IRB meeting. With this, and with enhanced staffing, IRB professionals plan to conduct a more robust administrative and regulatory pre-review of research, thereby facilitating a more focused committee review.

The University has outsourced IRB Review of industry-sponsored research in the Department of Psychiatry to a highly regarded independent (commercial) review board, Quorum Review.

The University has allocated funds to pay IRB members, augment members’ salaries, or offset departmental contributions to salary. Other methods of providing incentives or requirements are currently being examined.

Responsibility for for-cause monitoring has shifted to the RCO. At the time of my last meeting with IRB, the respective roles for the CTSI, the RCO, and the IRB required clarification.

The External Review was critical of the existing department-based scientific review of human subject research protocols: there was little evidence that the process was substantive, and in some departments, it was likely to be influenced by bias or conflicting interests. Also, scientific review was not considered by the IRB in its deliberations. As part of the Work Plan, department-based scientific review has been eliminated and replaced by an online process of review by scientifically qualified IRB members. The process requires two reviewers to make a determination based on two broad questions:

1. Is the scientific question reasonable?
2. Will the methods described in the protocol answer that question?

Several “sub-criteria,” such as “the research has the potential to provide new and useful knowledge,” and “the principal investigator is qualified to conduct the research,” are intended to assist in the categorical decision to “Accept” the protocol for IRB review or “Do Not Accept.” Both reviewers must “Accept” for the protocol to be forwarded for IRB
submission. No other information about the reviewer’s assessment is provided to the IRB. A “Do Not Accept” decision requires the reviewer to solicit additional information from the researcher.

Plans are underway to introduce a new electronic IRB submission tool by Spring 2017.

Discussion:

The University has made a substantial material and intellectual investment in the structure and function of the IRB. Interim measures to increase the number of meetings, limit reviewer workload, and to better structure deliberations, address key concerns raised by the External Review and represent important accomplishments. New approaches to member training, the addition of members and panels, and the introduction of a toolkit to promote a more effective review process all represent a significant re-making of IRB review.

Ongoing attention to the outcome and effectiveness of these operational improvements is essential; regular measurement of IRB adherence to quality is planned. While the University’s effort to remake its IRB process is well underway, success will require ongoing refinement of policies and procedures in response to performance measures. The University plans an annual assessment of IRB operations.

It is not surprising that the recruitment of new IRB members has been slow and difficult. Increased willingness to serve on the IRB may occur as the new cohort of reviewers report back on their experience within an enhanced IRB operation. The University and Academic Health Center should continue to identify financial and academic incentives for IRB participation, and gauge satisfaction among new member in terms of training, workload, and efficiency. Finally, a requirement for research departments to have representation on the IRB in proportion to the size of their research portfolio is not unreasonable.

The University has eliminated department-based scientific review, but it is not clear if this new approach offers advantages over scientific review that is conducted by the IRB itself. It is also not clear, in the new approach, if the IRB is expected to conduct its own assessment of study merit. Approval criteria require an IRB to determine whether “risks to subjects are reasonable in relation to anticipated benefits to subjects, if any, and the importance of the knowledge that may reasonably be expected to result.” The categorical determination of merit (Accept vs Do Not Accept) under the current practice will provide the IRB with no meaningful information
about the reviewer’s assessment of study benefit. For example, the current method may not
serve to address concerns about an industry-sponsored study of a “me too drug” which is
scientifically sound, but adds little “new knowledge” and therefore may not justify risks to
subjects. Also, absent benchmarks or anchors for decision-making, how will a categorical
Accept/Do Not Accept” choice be made? A default mode for all but the most concerning
research may well be “Accept.” To promote a more substantive review, the University should
consider requiring reviewers to comment and rate each criterion and to “Accept with
comments.” If unchanged, the process should be tracked and its value and validity assessed.
Expectations for review of merit by the IRB should be defined in policy.

The implementation of the NIH policy on the use of single IRBs in multicenter research in 2017,
like the anticipated publication of a revised Common Rule later this year, will introduce new
requirements and place new demands on the development of institutional and IRB policies and
procedures. The completion of the implementation timeline and transition to a “maintenance”
phase, and the introduction of the electronic IRB submission system at the University will also
occur in at the same time; these may well place strain on both the IRB and researcher
communities. Advanced planning is warranted.
III. Education and Training of Investigators and Staff

The External Review stated, “The broader educational policies and practices at the University fulfill minimal standards but represent a missed opportunity for a richer and more sophisticated institute-wide approach to investigator training.”

Online “ethics training” under the auspices of the Collaborative Institutional Training Initiative (CITI) has become a standard human subjects protection and good clinical practice educational requirement for universities and other clinical research enterprises nationwide. The extent to which CITI provides effective training, however, is not known. Given the nature of the problems identified, the External Review suggested that the University would benefit from advanced and specific educational opportunities and requirements, particularly in relation to matters involving informed consent and the inclusion of vulnerable populations in research.

Observations:

The University engaged an external educational consultant to evaluate its human subjects training activities and evaluate these against standards and national norms. Based on this assessment and its priority recommendations, the Education and Training Work Group (Appendix) concluded:

... that the University of Minnesota strengthen the current knowledge-based human research protection training and work to develop, assess and implement skill and attitude-based training over the next three years. The resulting training program should be comprised of a hybrid of online, discussion, peer learning, case and simulation, problem-solving practice, learning assessment, and demonstration of competence. The training needs to insure the appropriate levels of training for the specific research being performed and that human subjects are appropriately protected. Simultaneously the training must be high quality and the potential burdens for investigators and staff to understand, obtain and remain compliant with the required training should be minimized. Advanced training should be strongly encouraged, supported and rewarded.

The planned introduction of a range of learning formats--“skill and attitude-based” training, “learner assessment,” as well as ongoing program evaluation”--reflects a significant commitment to meaningful education in human research protections and will doubtless place the University in the forefront of such efforts.
Plans to develop and pilot advanced training for researchers working with vulnerable individuals and those with diminished capacity, and to pilot consent training programs in the Department of Psychiatry, represent a joint effort by the CTSI, IRB and the Center for Bioethics.

Other enhancements involve: the hiring of an IRB education and outreach specialist; monthly IRB newsletters and HRPP Education and Outreach reports for the research community; course offerings from the Center for Bioethics; day-long conferences on ethics and research protections; video-training opportunities; and new educational toolkits for study coordinators.

Discussion:

CITI training has become the national standard because it is inexpensive, scalable, and trackable. However, most agree it offers little more than “lip-service” to the notion of ethics training, at least there is no data to suggest otherwise. How best to educate and sensitize researchers is ultimately an empirical question. Given the many groups contributing to training initiatives at the University, a central infrastructure or “clearinghouse” for education could offer a promising model for the coordination and study of education and training. The extent to which individual research departments and centers can be assisted in developing their own educational programming should be explored, as should “train-the-trainer” efforts.

Tailoring educational programming to the learning needs of researchers in different disciplines and assessing competencies and skills will represent a leap forward for the University and for the field. However, substantial effort and funding will be required to develop and fully implement the education and training program envisioned in the Work Plan. The University is prudent to focus implementation on priority areas (enhancing the consent process, assessing capacity in vulnerable populations, identifying and minimizing risks in research) with active and iterative modification before larger scale roll-out. This may shift the implementation timeline, but will ultimate prove more effective.

Regardless of quality, educational opportunities such as the March 2016 lecture on consent for study coordinators (also available online) or the 15-week lecture series “Standards for Research with Human Subjects” are not likely to attract the desired
audience and may serve only to “preach to the converted.” The University should mandate training beyond CITI for IRB members and all those involved in human subjects research.
IV. Policies and practices related to informed consent to research and the inclusion of research subjects with impairment in consent capacity

The External Review offered an extensive analysis and a series of recommendations related to the process of informed consent, the assessment of capacity, and safeguards related to the enrollment of research subjects with impaired decision-making.

Observations:

With regard to the inclusion of subjects with impaired consent capacity or those who lack the capacity to consent, the University introduced two important additions to the Policy and procedure manual, both dated March 2016. Entitled Adults Lacking Capacity and/or Adults with Diminished Capacity to Consent and Vulnerable Populations these additions established new standards for IRB review and, therefore, for research protocol design. In August, these policies were superseded by new policies, and associated IRB reviewer Checklists and investigator Standard Operating Procedures (SOPs) were added.

The SOP entitled “Informed Consent Process for Research” provides step-by-step “instructions” on consent for the investigator. While rudimentary, the SOP does establish certain guidelines to foster informed decision-making. For example, 1.1 to 1.3 (below) prompt the investigator to invite the subject’s questions and to allow the subject time to consider consent or confer with others before making a decision. Item 1.4 establishes an expectation that subject understanding should be assessed in all circumstances by the researcher.

1.1 Invite and answer the subject/representative’s questions.
1.2 Give the subject/representative time to discuss taking part in the research study with family members, friends and other care providers as appropriate.
1.3 Invite and encourage the subject/representative to take the written information home to consider the information and discuss the decision with family members and others before making a decision.
1.4 Ask the subject/representative questions to determine whether all of the following are true, and if not, either continue the explanation or determine that the subject/representative is incapable of consent:
   1.4.1 The subject/representative understands the information provided.
1.4.2 The subject/representative does not feel pressured by time or other factors to make a decision.

1.4.3 The subject/representative understands that there is a voluntary choice to make.

1.4.4 The subject/representative is capable of making and communicating an informed choice.

The IRB reviewer checklist entitled “Vulnerable Populations” prompts an IRB reviewer to consider a limited range of “additional safeguards” such as “Exclusion of the population if not required to achieve study objectives” and “Researcher should not have any role in decisions impacting subjects’ status (e.g. institutionalization).”

The policy entitled “Research Involving Adults With Absent, Diminished, or Fluctuating Capacity to Consent to Participate in Research” defines consent capacity and some general categories of disorders in which it may occur. This policy establishes the new requirement to use a standard instrument in the assessment of capacity:

The IRB recommends that the following validated tools be used to evaluate capacity to consent in research studies that involve adults with absent, diminished, or fluctuating capacity to consent:

- For greater than minimal risk research, the MacArthur Competence Assessment Tool for Clinical Research (MacCAT-CR) appropriate to the context of the research.
- For minimal risk research, a version of the UCSD Brief Assessment of Capacity to Consent (UBACC) appropriate to the context of the research.

This policy references the checklist entitled “Cognitively Impaired Adults” which specifies the IRB’s approval criteria for research that involves adults with absent, diminished, or fluctuating capacity to consent. It also references the SOPs entitled “Legally Authorized Representatives, Children, and Guardians,” “Informed Consent Process for Research,” and “Written Documentation of Consent” for detailed information regarding who can serve as an LAR and the process for obtaining and documenting informed consent from an LAR for subjects unable to consent.
The same policy establishes a requirement regarding subjects with fluctuating capacity to consent:

“The IRB expects that investigators include procedures to address fluctuating capacity, where applicable. Where fluctuating capacity to consent is anticipated in a subject population, the protocol must include plans for monitoring capacity for the duration of the study. “

The policy references the Checklist “Cognitively Impaired Adults” for the IRB’s approval criteria for research that involves adults with fluctuating capacity to consent and the SOP “Informed Consent Process for Research” for the process for obtaining informed consent from subjects with fluctuating capacity to consent.

The checklist “Cognitively Impaired Adults” establishes approval criteria for research with subjects who “are cognitively impaired,” and although not explicitly defined, appears to mean cognitively impaired subjects “who have been judged to lack the capacity to consent.” Approval of greater than minimal risk research is only allowable when there is anticipated direct benefit to the subject, and includes additional safeguards, such as “Subjects will be withdrawn if they appear to be unduly distressed.”

The Policy Research Involving Adults under Court Jurisdiction specifies:

“researchers may not recruit or enroll the following persons in any clinical drug trial under Minnesota law (effective August 1, 2016) and/or existing IRB Policy: 1) individuals subject to a commitment petition; and/or 2) individuals temporarily confined involuntarily under: a) 72-hour emergency admission holds; b) “intent to leave” periods; or c) peace officer/health officer authority (formerly “transport hold”) or a court apprehend and hold order.

Further,

“an individual who has had a commitment hearing, and is released by the court before a commitment order is issued, is prohibited from participating in a psychiatric clinical drug trial during the period of a stay of commitment, unless the court specifically authorizes the participation. Investigators wishing to recruit such individuals must provide justification for doing do and a process compliant with the terms of the statute.
In addition, no member of a study team may participate in a decision to rescind or discontinue a patient’s involuntary status (as described above) before its expiration, provisionally discharge a committed patient, or rescind a provisional discharge, when the patient is a prospective research subject for a study conducted by the study team.

The SOP “Legally Authorized Representatives, Children, and Guardians” establishes a hierarchy of LARs who may provide consent for an adult determined to lack capacity and other restrictions:

1.5 Unless the IRB has waived the requirement to obtain consent, when research involves adults unable to consent, permission must be obtained from a legally authorized representative. Minnesota law does not specifically address the issue of research participation by incapacitated adults.

1.5.1 Based on legal advice, the IRB follows the Minnesota laws on surrogate consent in health care to determine surrogate consent for research participation, including specifically the law on surrogate consent for treatment of incapacitated patients undergoing in-patient mental health treatment. When research is conducted in Minnesota the following individuals meet this definition in order of priority:

- 1.5.1.1 Healthcare agent previously appointed by the individual through a health care power of attorney;
- 1.5.1.2 Spouse;
- 1.5.1.3 Parents;
- 1.5.1.4 Adult children; and
- 1.5.1.5 Adult siblings.

1.5.2 The legally authorized representative may not be a member of the clinical or research staff or an employee or beneficiary of the sponsor of the research project.

1.5.3 Under Minnesota law, an incapacitated adult who has a court appointed guardian or conservator may not receive experimental treatment of any kind unless: 1) a court first approves the treatment through a court order; or 2) the court’s guardianship order specifically authorizes the guardian to consent to research participation in addition to medical treatment generally.

1.5.4 For research outside Minnesota, a determination of who is a legally authorized representative is to be made with consultation from legal counsel.
Discussion:

The introduction of these policies on consent and approval criteria is a step forward. How effectively they will be disseminated and applied in the IRB and in the research clinic will depend to a large extent, however, on the quality of new training initiatives. The University should remain active in evaluating the value of such tools and checklists and in assessing the education and training efforts that are underway.

The IRB could develop rules and standards to better guide reviewer decisions. For example, as currently written, it appears to be solely at the reviewer’s discretion to require the presence of a witness during consent, or to require the live monitoring of a consent process. The active use of consent observation as a monitoring and educational tool should be encouraged and policy driven.

While the Department of Psychiatry has established a rule preventing clinician researchers from being “involved in the research consent process” when the prospective subject is in their care, it is not clear if this same rule extends to recruitment. In the interest of preserving voluntariness of consent, clinicians should not approach their patients to solicit interest in their studies. The IRB should also consider whether this rule should extend beyond Psychiatry.
V. Research practices within the Department of Psychiatry

The External Review identified a number of system-wide deficiencies in oversight of research that had implications for Psychiatry, such as the *pro forma* departmental scientific review of IRB proposals. Other problems were specific to Psychiatry. Questions about the integrity of two clinical investigators, one of whom was the department head, were at the core of concerns by many faculty, staff members, and external critics. In the aftermath of the Markingson case, and in the context of ongoing criticism of industry sponsored clinical trials in the Psychiatry at the University of Minnesota, too little was done within the department to acknowledge the seriousness of the allegations or to address the department’s broader obligations to support human subject protection.

**Observations:**

Without question much has changed within Psychiatry as a result of the Advancing Human Research Protections initiative.

Following the External Review, Dr. Charles Schulz stepped down as Head of Psychiatry. His departure was a necessary and more than simply symbolic event that was important to efforts to rebuild trust in Psychiatry.

Dr. Mark Paller, Senior Associate Vice President of the Academic Health Center was named Interim Head of Psychiatry and also charged with overseeing the implementation effort as it applied to the department. Under his stewardship, Psychiatry has been affirmatively engaged with the component functions of Advancing Human Research Protections initiative. While implementation is incomplete, the design of new programs, policies, requirements, and practices reflects the thoughtful and willing engagement by Psychiatry leadership, staff and faculty.

Following a nationwide search, Dr. Sophia Vinogradov, formerly Professor and Vice Chair at UCSF, was named Head of Psychiatry. Her own research examines cognitive training in schizophrenia and the neural underpinnings of the disabling cognitive deficits associated with serious mental illness. Dr. Vinogradov has announced plans for a department wide strategic planning initiative, and has signaled her commitment to human research protections, discussed further in the next section, with plans for the development of a consumer advisory board to provide “important viewpoints on
ethical, compassionate, and consumer-relevant approaches to all of the department’s activities.”

Dr. Stephen Olson is no longer actively involved in clinical trials. Should he seek permission to conduct research again, his request will be subject to review and his work will be subject to special educational, supervisory, and monitoring requirements outlined in the Work Plan.

As noted, as an interim measure, the University has outsourced the review of industry-sponsored research in Psychiatry to the Quorum IRB. The CTSI has assumed the management of the conduct of all clinical trials in Psychiatry.

An ambitious plan for competency-based training (Appendix, Department of Psychiatry Final Report) in informed consent has/or is soon to be piloted in Psychiatry. The goal of the Good Clinical Practices: the Informed Consent Process is to train staff to:

Confidently, ethically, and humanely carry out all tasks appropriate to their roles within the research team in the informed consent process for regular and special populations of participants according to the FDA 21CFR50.25 and 45CFR46.111, ICH GCP principles and Good Clinical Practice guidelines, Minnesota Law, and University of Minnesota guidelines.

To “mitigate issues of therapeutic misconception,” the Department of Psychiatry has developed and implemented the “Dual Role Consenting Policy,” (Appendix) which is also cross-referenced in IRB policy “Research Involving Adults With Absent, Diminished, or Fluctuating Capacity to Consent to Participate in Research.” The policy prohibits clinicians who are treating patients from “being involved in the consent process” when they are also the study’s investigator. The policy also requires patients to be given an opportunity to confer with another clinician about treatment options when choosing whether to take part in research. Beyond simply addressing patients’ tendency to overestimate the clinical benefit of research involvement (“the therapeutic misconception”), this policy addresses the clinician-investigator’s conflicting interests in serving the best interest of the patient and fulfilling the needs of the research. It also recognizes that patients may have difficulty declining research participation when it is offered/suggested by their caregiver.

The “Clinical Research Study Checklist Fairview Behavioral Health Services” seeks to promote the involvement of clinical staff in gatekeeping functions. The purpose of this
The checklist is to “provide a process so that leadership and clinical staff can provide input into how clinical research is developed and performed on the Fairview Behavioral Health Services.”

Discussion:

The Department of Psychiatry, in concert with other components of AHRP, has taken important steps to address a number of problems identified by the External Review. The introduction of new policies regarding consent and capacity, and especially the involvement of Fairview clinical staff in gatekeeping functions, represents genuine progress. The successful recruitment of a new Department Head offers opportunities for the credible engagement by leadership in setting new expectations and new standards for the ethical conduct of research. While some have expressed frustration with the pace of change, for the first time, the Department has completed the necessary groundwork in policy to foster improvement in research protections.

Much of the work of implementation is now beginning, and the key challenge will involve evaluating the effectiveness and sustainability of newly introduced requirements and making necessary refinements.

The External Review recognized the need for greater IRB expertise in the review of research with vulnerable populations. Psychiatry may choose to play a more central role in setting standards for the ethical conduct of research by insuring that Psychiatry is well-represented on the IRB and by working with the IRB to develop such standards, as it has done with the “Dual Role” policy.

New policies and guidelines can be developed to ensure that the rights and welfare of individual research participants are not treated as secondary to the interests of research and researchers. The commitment to protect psychiatric patients requires an understanding that some patients with serious mentally illnss are not able to protect their own interests through the process of consent, because of cognitive impairment, because research offers care not otherwise accessible, or because they have, or may perceive that they have, little or no freedom to exercise choice. This is not to say that psychiatric patients cannot choose, either on their own, or with input from others, to participate in research and assume certain risks in the pursuit of personal benefit or to benefit science. But protecting psychiatric subjects requires expert understanding of subjects’ susceptibility to risks associated with experimental therapies, transitions to
and from experimental therapy, and drug free states, among others. Finally, protecting research subjects who are “vulnerable to coercion or undue influence,” under-educated, and have limited access to healthcare, also means researchers must recognize that there may be a tension between what is best for the patient and what best serves research. Importantly, this conflict exists even when the investigator is not the treating clinician.

Even when prospective subjects are judged to have “capacity” to consent, they may be unable to fully protect their interests by making a careful and informed choice about study enrollment. An institution may provide additional protections by setting ethical standards in policy or in practice. For example, an IRB may determine in policy that patients who are stable and tolerating their current medication regimen should not be enrolled in research that entails discontinuing that medication, absent compelling justification. An IRB may request that an investigator exclude prospective subjects from participation in an experimental drug trial if they have never received standard and available treatment for the disorder, again absent compelling justification. Such “paternalism” recognizes the limits of informed consent.

Another related but distinct concern is the fact that current consent policy appears to be silent on the credentials required of staff responsible for discussing and documenting consent or making a capacity determination. Further, will (or how will) the department seek to validate the capacity determinations that result from the use of the McCAT-CR? What standards of care and monitoring should apply to transitions to and from protocol-based treatment? How will the department leadership respond to non-compliance?

The Department head and ultimately the IRB will need to make a determination about whether Dr. Olson, or for that matter any investigator, may serve as an investigator on a human subjects research protocol. Perhaps more important than this decision is whether the program for human subjects protections, as it operates within the Department, is setting necessary standards for the ethical conduct of research.
VI. University Culture and Values

The External Review faulted the University of Minnesota for its past failure to cultivate a culture that promoted the ethical conduct of research, and advised it 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.” As referenced in earlier sections, the creation of the Community Oversight Board and the Research Compliance Office, like the development of the Hierarchy of Accountability and Statement of Core Commitments, demonstrate an affirmative effort by the University to create structures and define values that serve its commitment to human research protections.

The ambitious campaign to communicate these values to University constituents and stakeholders similarly provides meaningful evidence of progress. The “Communicators Toolkit” for example, includes the Statement of Core Commitments in posters and flyers and digital formats, and a “Speak Up, It Matters” poster encourages feedback from research subjects. The use of a research participant contact card is intended to encourage research subjects to ask questions or lodge complaints; it also represents an innovative practice that underscores the importance of subject engagement. It is not surprising that Research Ethics now occupies prominent place on the home page of the Office of the Vice President for Research. But the emphasis on research ethics in the Medical School blog describing the recently appointed head of Psychiatry reflects the new messaging strategy:

Dr. Vinogradov is the right leader to move reforms forward; to implement the highest standards of ethical research; and to build a new culture of trust and cooperation as the department works to develop innovative state-of-the-art programs of care for patients, and to conduct important scientific investigations that will lead to better outcomes for those with mental illness.

“One of my first steps as the new Department Head will be to build on the work of the implementation team by creating a ‘consumer advisory group’ consisting of people with lived experiences of mental illness and other key stakeholders from the community, such as family members, advocates, and community providers,” said Dr. Vinogradov. “I will count on this advisory group to provide me important viewpoints on ethical, compassionate, and consumer-relevant approaches to all of the department’s activities.
The proposal to gather data to assess and track “culture” by employing an empirically validated instrument, the Survey of Organization Research Climate, represents a unique and potentially valuable method of measuring attitudinal change in response to interventions and to benchmark these findings against other institutions.

Certainly, the External Review became part of a national dialogue in the human research protections community. Dr. Herman’s willingness to participate in a panel discussion at PRIM&R’s annual meeting in 2015 demonstrated the University’s willingness to discuss the challenges it has faced and offer guidance to others.

**Discussion:**

The University has responded to the letter and spirit of the recommendations of the External Review and has undertaken a broad-based effort to affirm and communicate its commitment to human research protections, to accountability, and to community engagement.

While the benefits of Advancing Human Research will accrue over time with experience and as the new processes and functions evolve, there is impressive forward movement at present.

The considerable accomplishments of the many participants in AHRP, their drive, dedication and creativity, should be a source of pride throughout the University.