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MEMORANDUM

DATE: February 10, 2016

TO: The Honorable Dean Johnson, Chair
The Honorable David McMillan, Vice Chair
The Honorable Thomas Anderson
The Honorable Richard Beeson
The Honorable Laura Brod
The Honorable Linda Cohen
The Honorable Thomas Devine
The Honorable Michael Hsu
The Honorable Peggy Lucas
The Honorable Abdul Omari
The Honorable Darrin Rosha
The Honorable Patricia Simmons

FROM: Brooks Jackson, Dean of the Medical School and Vice President for the Health Sciences Brooks Jackson

RE: Update on the Department of Psychiatry

The Implementation Team report regarding human research participant protections, endorsed by the Board of Regents in June 2015, included a recommendation that the Clinical Translation Science Institute (CTSI) assume management of interventional drug and device trials in the Department of Psychiatry. CTSI contracted with a consultant to develop a management plan in response to that charge.

The consultant issued a report of her findings to CTSI which has been requested through DPA by the media and others. That report, along with CTSI's management plan* and our reponse, is enclosed for your review. In addition, Vice President Herman and I will be available at the February 11, 2016 Audit Committee meeting in order to discuss this report and answer your questions.

CC: President Eric Kaler
Brian Herman, Vice President for Research
Gail Klatt, Associate Vice President, Office of Internal Audit

* The attached management plan has been updated from the earlier draft received by the Board of Regents.

February 10, 2016

Report on Psychiatric Trials
Delivered to CTSI

The University's Board of Regents approved a plan to enhance our commitment to the ethical and appropriate engagement of volunteers who participate in clinical research in June 2015. This comprehensive plan is currently being implemented with the goal of reaching full implementation by December 2016.

An important focus of this plan was to address concerns and criticisms about clinical research activities that take place in the Department of Psychiatry. One recommendation to ensure the integrity of clinical research in the Medical School's Department of Psychiatry was accelerating the process for the Clinical Translational Research Institute (CTSI), to assume management of interventional drug and device trials in the Department of Psychiatry.

To understand the current situation with respect to clinical research activities in the Department of Psychiatry and to determine how best the CTSI could manage this activity, CTSI hired Jan Dugas, with Clinical Research and Compliance Consulting, to help with the development of a management plan. She was asked to review the current clinical research studies in the department to assess study status, feasibility, issues and concerns with quality or completeness of study documents and regulatory files. She was also asked to make recommendations to leadership on studies to keep open and enrolling, studies to close, and staff to retain.

After conducting interviews with faculty and staff in the Department of Psychiatry, and evaluating a number of ongoing clinical trials, Ms. Dugas issued an extensive report of her findings. This review was conducted in early fall 2015 shortly after the implementation plan was approved by the Board of Regents. It reinforces many of the issues about research practices in the department and a culture of mistrust among faculty and staff that had already been identified by the external review and implementation team. These are the very issues the implementation plan, and CTSI's management plan, are in the process of addressing.

The Department of Psychiatry has reviewed and endorsed a draft of the management plan. It will be implemented in the coming months. In addition to the University already having suspended drug studies in the Department of Psychiatry and outsourcing those studies for independent review by Quorum (these reviews are now complete and Quorum remains the IRB of record), some of the key elements of this plan include:

- Hiring a CTSI Clinical Research Manager to supervise psychiatric research staff, facilitate management of the research portfolio, ensure proper training of all research staff, and to uphold ethical research principles through all clinical trials.

- Hiring a CTSI Regulatory Specialist to manage all regulatory activities around human research in psychiatry.
- Requiring all faculty members/investigators to participate in a competency-based training program through CTSI
- Developing a quality assurance program to ensure research studies are conducted in a manner that safeguards research participants and that results in verifiable data.

In addition, we will contract for additional monitors to ensure research quality and compliance while the CTSI plan is being implemented.

Beyond the research protocol issues, Ms. Dugas' report raises a number of concerns about the culture within the Department of Psychiatry and potentially serious violations related to clinical trials. The University is aggressively investigating these claims to verify them and determine appropriate corrective action.

Finally, there are comments or general observations in the report that have been investigated and found to be without merit. These include:

- Allegations that Principal Investigators were depositing federal grant money into their personal accounts. This is simply not true, and is not even possible because federal grant money is not provided proactively. Investigators with federal grants need to submit expenses to NIH for reimbursement.
- All nine of the studies listed on pages 11 and 12 of the report submitted data and safety monitoring plans to the IRB.
- The critical finding regarding consent of children without their parents' involvement is untrue.
- Records do show that adverse events are being reported, although there is an issue regarding PIs keeping up to date logs of these reports.

University of Minnesota internal monitors and PIs (in the last quarter of 2015), had also identified many of the documentation deficiencies and oversights that Ms. Dugas reported during that same time frame. Corrections for many of these issues are already underway and future issues will be avoided through implementation of the management plan.

The University is committed to correcting all issues identified by the many reviews that have occurred over the past year to ensure the safety of all human research participants, and to be sure that all research is conducted in the most thorough and ethical manner. We are providing monthly updates about the progress we're making on our implementation plan (http://research.umn.edu/advancehrp/index.html).

We are confident that we will be successful in meeting our goal of establishing a clinical research program that can be seen by others as the model to emulate.

The University issues monthly reports to the legislature on the status of the human research protection plan implementation. The following table is from the February report, and it shows the progress that has been made on the plan over the past six months.

The CTSI Psychiatry Report interviews and reviews took place from September to October 2015. This was only two months after the approval of the implementation plan by the Board of Regents. As the chart shows, there are a number of areas that are part of the implementation plan that are directly aimed at addressing the issues that were raised in the CTSI report. These include:

- Changes to IRB membership
- The development of a research oversight committee in partnership with Fairview
- Establishment of a Research Compliance Office
- Hiring new study monitors
- The transition of psychiatric trials to CTSI management
- Education and training of investigators around human research protection
- Implementing an updated Conflict of Interest policy

In addition to these steps, the psychiatry faculty have developed additional guidelines for their own research that go beyond the implementation plan. This includes a provision that prevents a doctor from serving as both a patient's primary physician and as the principle investigator in a trial for that patient.

While there are no quick fixes, we are moving forward as quickly as possible with all of the recommended changes in an effort to be sure we are protecting human research participants while conducting vital clinical research.

Advance HRP Implementation

FEBRUARY 2016 Progress Report

Work plan Section	Status	Lead	Scope
IRB Membership	√	Billings, Biros	Recruit membership
			Form new committees; restructure biomedical; target membership to accurately reflect protocol submission
			Set compensation structure and policy for medical and nonmedical IRBs
FUROC	√	Herman	U establish committee jointly with Fairview
For Cause Investigations	√	Webb	Establish Research Compliance Office (RCO)
		Waldemar	Transition For Cause Investigations to RCO; establish more robust procedures specific to complainant and SAE reporting
Community Oversight Board	√	Herman	Establish board structure and guidelines
			Finalize membership; appoint chair
			Invite members
External Advisor	√	Herman	Hire external advisor (external review panel member); 2015 AAHRPP Accreditation; Compass Point compliance review

Scientific Review of Studies	√	Billings, Biros	Eliminate department reviews
			Define a new IRB process and policy in consultation with other required reviews e.g. CTSI
Cultivating a Culture of Ethics	O	Aronson, Zentner, Wolf	Create language explaining the University's commitment to research participant protection
			Clear statements on HRPP, IRB, OVPR and AHC websites
			Host a campus conversation or other forum on human research participant protection
			Regular benchmark our program against our peers
IRB Protocol Review Process	O	Dykhuis	Implement new eIRB technology – IRB Renew
			Implement Huron Toolkit IRB forms and procedures
			Add new FTEs
			Complete benchmarking visits
Monitoring of Studies	O	Dykhuis	New FTEs
			Reengineer PAR function; Includes work with Compass Point to further refine methodology
Human Research Participants Who Have Impaired or Fluctuating Capacity to Consent	O	Miles	Implement tool to assess capacity
	O		Train and communicate change to researchers
	O	Dykuis	Implement LAR policy changes
	√		Implement 72-hour hold policy
Department of Psychiatry	O	Paller	Transition to CTSI management of trials
			Engage consultant for climate assessment, plan
Engaging Research Participants	O	Eder	Create a research participant satisfaction survey and a plan to collect and analyze data
			Revise IRB forms to include a section expressing appreciation and a plan for sharing research results
			Create and publicize mechanisms for participants and families to provide confidential feedback and report concerns, develop a small handout
			Create and publicize procedures for handling concerns and for notifying reporter when they have been handled
			Create position of Community Liaison officer
			Create link to Community Oversight Board
Education and Training of Investigators	O	Ingbar, Schacker	Integrate and coordinate HRPP training
			Curriculum development
			Training delivery
Accountability Metrics	O	Waldemar	Track and report accountability metrics
Conflict of Interest	O	Durfee	Implement updated COI policy

√= Completed

O= In Progress

= Not Started

For more details see about the work scope and alignment with the external review panel recommendations, see Advance HRP
Website: http://research.umn.edu/advancehrp/index.html

CTSI Recommendations for Integration of Clinical Research Studies in the Department of Psychiatry into the University of Minnesota Clinical and Translational Science Institute (CTSI)

Version 1.0

February 11, 2016

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Executive Summary

Background:

On June 11, 2015, President Kaler and the Board of Regents approved the "Implementing the Recommendations of the External Review of the University of Minnesota Human Research Protection Program Work Plan." This work plan specified that the University of Minnesota Clinical and Translational Science Institute (CTSI) assume responsibility for the conduct of clinical interventional research conducted in the Department of Psychiatry.

In late June, 2015 Dr. Schacker, Director of the Clinical Translational Research Services (CTRS) Group at CTSI, authorized hiring a consultant to assess the portfolio of clinical trials being conducted in the Department of Psychiatry and the standard operating procedures used to conduct this research. The goal was to have this assessment complete within six months to inform recommendations on how best to transition these trials to the full management of and oversight by the CTSI by the targeted implementation date of June 30, 2016, and ensure that all trials in the Department of Psychiatry: 1) meet the highest ethical standard possible, 2) are conducted using the GCP guidelines developed by the International Conference on Harmonisation, and 3) conform with federal and University of Minnesota policies and regulations for conduct of clinical research.

The assessment included a review of studies conducted in the Department of Psychiatry. A list of open research studies and clinical trials was obtained from the University of Minnesota Institutional Review Board (IRB). During the interval this assessment was conducted there were 124 open research studies/clinical trials in the Department of Psychiatry, and, of those, 116 were reviewed to assess current status (e.g. active, open only for data analysis, inactive, closed), interventional and non-interventional, study type (medical or social), and funding. Monitoring was completed on nine randomly chosen studies to provide an understanding for what the regulatory needs of Psychiatry studies will be going forward. In addition, Department of Psychiatry faculty and staff were interviewed to gain a more complete knowledge of how clinical research was conducted in the Department, what problems and obstacles to success could be identified, and to gain understanding about training needs going forward. The individuals interviewed were based on a list generated by the independent consultant after discussion with Department of Psychiatry leadership and with the Office of Human Resources. Each potential interviewee was sent an email invitation and 58% of those invited agreed to meet. All interviewees were asked similar questions.

The data generated from these reviews and interviews formed the basis for the recommendations made below.

Management Plan:

The management plan presented was informed by 54 interviews and the review of 124 open research studies or clinical trials being conducted within the Department of Psychiatry. Medical and social and behavioral studies were represented, as were clinical trials – including investigational drug and device studies. All are referred to as "research studies" in the management plan.

The main conclusion of this review process is that there is variable understanding of best practices for clinical research among the faculty and staff which should be addressed. The Department of Psychiatry in collaboration with the University of Minnesota CTSI should modify the infrastructure for clinical research in the Department to ensure that all faculty and staff

engaged in research have the resources available to them to conduct clinical research that meets the highest research standards possible. A well-developed infrastructure will provide support to investigators by ensuring that staff receive the proper training to best support the research and will help to develop a culture where staff, faculty, and graduate students collaborate with others throughout the Department of Psychiatry, Medical School, Office of the Vice President for Research (OVPR), and the Human Subjects Research Protection Program (IRB). Finally, this infrastructure should support a structure for investigators and staff to comply with the evolving regulatory requirements for conduct of human research.

Summary of Recommendations:

1. **Hire a Clinical Research Manager.** This 1.0 FTE will be an individual dedicated to and with the necessary training and skills for facilitating clinical research studies in the Department of Psychiatry. This individual will be hired by CTSI and will report up through the Clinical Research Implementation Services (CRIS) arm of CTRS. Faculty in the Department of Psychiatry with significant research responsibilities will participate in the hiring process. The responsibilities of this 1.0 FTE include supervising research staff, facilitating the management of the research portfolio by conducting/monitoring feasibility assessments for studies (both initial review and ongoing monitoring utilizing the assessment process being implemented for all studies managed by CTSI), ensuring all staff receive adequate training and remain current with training requirements, managing the Ambulatory Research Center (ARC), and other responsibilities for protecting research participants, investigators, and sponsors. This individual will partner with the Psychiatry investigators to uphold ethical research principles, to ensure that human subjects' rights, welfare, and protection are protected, and to ensure staff are adequately trained to conduct the assigned function.

2. **Research staff in the Department of Psychiatry will become CTSI employees and will report to the Clinical Research Manager and participate in all CTSI functions.** The staff positions affected by this change would include but not be limited to: Clinical Study Coordinators, Community Program Specialist/Associates, Coordinator, Research Coordinator, Project Coordinators or research personnel with similar responsibilities, students/trainees, including post-doctoral associates. This process will begin after the Clinical Research Manager is hired and specific plans for the transfer of personnel to CTSI are formulated. Student involvement may take the form of an internship, part-time coordinator, or study assistant. **However, anyone involved in any aspect of a research study or clinical trial conducted within the Department of Psychiatry should be either a University employee or registered student. Volunteers can be involved using temporary/casual appointments without pay provided they comply with all the University rules, policies, and procedures regarding volunteers**. This policy will make training of staff easier to accomplish and monitor.

3. **Hire a CTSI Regulatory Specialist to manage all regulatory activities of conducting human research in the Department of Psychiatry**. The Regulatory Specialist for the Department of Psychiatry will require 1.0 FTE effort in the first year and then will be reduced to a 0.5 FTE, if there is consensus between the Department of Psychiatry leadership and CTRS leadership that this will be adequate effort otherwise the position will remain a 1.0 FTE. This will be a new hire of someone with expertise in behavioral/psychiatric research and also experience in IND/IDE/IRB and monitoring requirements for the conduct of these types of studies. This individual will be part of the regulatory group of CTSI (housed at CTSI) but will be dedicated to supporting Psychiatric faculty research and will give priority to Psychiatry faculty in the regulatory affairs of their studies.

4. **Participate in a competency-based training program for research staff in the UMN CTSI**. Faculty members/investigators will be required to complete this training when it has been fully implemented in accordance with the recommendations from the Education and Training Investigators work group of the Implementation Plan.

5. **All research studies/clinical trials using investigational drugs should use Fairview's Investigational Drug Services (IDS**). This applies to the receiving, storing, and dispensing of the investigational product.

6. **CTSI's Financial Services Hub should be used to develop budgets for all clinical studies and for the subsequent financial management of all grants.**

7. **All research studies conducted in the Department of Psychiatry should utilize University systems set up to support research. Specifically the OnCore clinical trials management system (CTMS) and REDCap should be used**.

8. **Develop a quality assurance (QA) program** to ensure that research studies are conducted in a manner that safeguards research subjects and results in verifiable data.

9. **CTSI will manage the Ambulatory Research Center (ARC).** Day to day operation of the ARC will become the responsibility of CTSI.

Timeline for implementation: This report will be delivered in a draft form to Psychiatry Department leadership in the middle of January 2016 for review and comment. This will likely include discussion and feedback from Department of Psychiatry faculty. Following this review and discussion it is suggested that Department of Psychiatry Leadership and CTRS Leadership meet and discuss what, if any, modifications to the recommendations might be made in the last two weeks of January. The report of recommendations will be finalized in early February and submitted to Dr. Brooks Jackson, Vice President of the Academic Health Center, and Dr. Brian Herman, Vice President for Research, for final approval. Full implementation will be guided by final approval from AHC Leadership and identification and allocation of resources required to implement these recommendations. Once approved CTSI will work with the Department of Psychiatry, AHC, OVPR, and OGC to implement the plan.

I. Department of Psychiatry Clinical Research Manager

The Department of Psychiatry needs an experienced professional to serve as point person to help coordinate all Department research activities, including educational programs.

Recommendation: Hire a Clinical Research Manager through CTSI, dedicated to Psychiatry, to coordinate all clinical research for the Department. This model has been successful for other Departments and provided a point person to help coordinate all research activities, including educational programs. The Clinical Research Manager should have clinical research experience, both academic and industry, including medical device, pharmaceuticals and behavioral research. It is recommended that the position be a 1.0 full-time equivalent and report to the Brenda Prich, R.N., Director of CRIS, with a dotted line to the Department of Psychiatry Chair (or their designated representative). Department of Psychiatry Senior faculty will participate in developing the job description and the hiring process.

The Clinical Research Manager is expected to partner with the Department of Psychiatry administration, faculty, and PIs to ensure that research requirements are being met and departmental research needs are addressed (i.e., facilitating a research support staffing plan that aligns competent staff with research areas in which they have experience/expertise). This individual will be expected to partner with other Clinical Research Managers in the Medical School to build cross-collaborative relationships and will also serve as a liaison between CTSI, Faculty/PIs, Fairview hospital, Sponsors, and research participants. This individual will help PIs and their staff navigate all study start up procedures (regulatory, budget, etc.) so that the process occurs rapidly and efficiently. This individual will also monitor all study related activities throughout the life of the studies.

II. Department of Psychiatry Research Staff

During the conducted interviews, research staff expressed concern regarding conflicting work direction, lack of research knowledge and training, and conducting study testing/treatments beyond their capabilities, training and expertise. A common theme of the interviews and monitoring was that the study team needed better training in the clinical research requirements for conducting studies.

Recommendation: To ensure consistency of work research practices throughout the Department of Psychiatry, **Research staff will become CTSI employees and will report to the Clinical Research Manager.** This means the responsibility for HR and personnel issues (including promotion, education, and adherence to regulatory affairs) will be with the Clinical Research Manager. Day-to-day activities for study personnel will be coordinated by the Principal Investigator. The positions affected include (but are not limited to): Clinical Study Coordinators, Community Program Specialist/Associates, Coordinator, Research Coordinator, Project Coordinators or research personnel with similar responsibilities, students/trainees, including post-doctoral associates. Student involvement may take the form of an internship, part-time coordinator or study assistant and could be paid or volunteer. **However, anyone involved in any aspect of a research study or clinical trial conducted within the Department of Psychiatry should be either a University employee or student. Volunteers can be involved using temporary/casual appointments without pay provided they comply with all of the University rules, policies, and procedures regarding volunteers.** This will provide a process to ensure that everyone involved in the conduct of a study can be monitored for up-to-

date training and will have accountability to the institution for their activities related to a study. The Clinical Research Manager will ensure personnel working on research studies are qualified, adequately trained, and credentialed for the assigned responsibilities.

III. Regulatory Specialist

It is the policy and expectation of the University of Minnesota that all regulatory policies and procedures related to the conduct of human research will be carried out and maintained in a current status.

Recommendation: Hire a CTSI Regulatory Specialist to manage all regulatory activities for the conduct of human research in the Department of Psychiatry. The Regulatory Specialist for the Department of Psychiatry will require 1.0 FTE effort in the first year and then will be reduced to a 0.5 FTE if there is consensus between the Department of Psychiatry leadership and CTRS leadership that this will be adequate effort. This will be a new hire of someone with expertise in behavioral/psychiatric research and also experience in IND/IDE/IRB and monitoring requirements for the conduct of these types of studies. This individual will be part of the regulatory group of CTSI (housed at CTSI) but will be 100% dedicated to supporting Psychiatric faculty research.

The Regulatory Specialist will manage regulatory activities and documentation to ensure accuracy and completeness for Psychiatry studies including, but not limited to:

- Handling IRB submissions and correspondence
- Preparing consent forms in accordance with protocol
- Reviewing existing IRB research documentation for accuracy
- Maintaining all regulatory documents
- Communicating with the faculty, IRB, and study sponsor, as applicable
- Coordinating all IND activities with the CTSI and IRB IND specialist
- Ensuring a DSMB is convened when required and that all required documentation and follow-up is completed by the study staff
- Coordination of all required monitoring activities, assisting the PI with any Post Approval Review processes (PRA), and assuring that issues identified during routine or PAR monitoring are promptly corrected. If issues are identified that directly impact risk to human health the Regulatory Specialist will ensure that IRB is promptly notified. The Regulatory Specialist will work with the PI to correct all issues identified during the course of any monitoring activity. If these issues are not addressed and/or corrected within after four weeks of delivery of the report the Regulatory Specialist will notify the Head of the Department of Psychiatry, the Office of the Vice President for the AHC, and the Office for the Vice President of Research for further action.

IV. Training and Education

A career in clinical research increasingly requires high levels of preparation, training, and commitment. The interviews conducted and records reviewed demonstrated that faculty and staff conducting research studies/clinical trials were unaware of key fundamental research requirements and were not following requirements within the protocols or study plans. This includes but is not limited to: Good Clinical Practices, reporting of adverse events and protocol deviations, source documentation, documentation of informed consent, inclusion/exclusion

criteria assessment prior to consenting, and safety monitoring. Failure to follow these established standard procedures places the institution and investigator at risk of noncompliance of federal and local regulations.

Recommendation: Participate in a competency-based training program for research staff in the UMN CTSI. Faculty members/investigators will be required to complete this training when it has been fully implemented in accordance with the recommendations from the Education and Training Investigators work group.

V. Fairview Investigational Drug Services (IDS)

Investigational Drug Service (IDS) is the pharmacy service responsible for managing and dispensing investigational drugs for Fairview Health Services and the Academic Health Center (AHC). It is important that all federal and industry guidelines for the management of investigational drugs be followed to the highest standard.

Recommendation: All research studies/clinical trials using investigation drugs should use Fairview's Investigational Drug Services (IDS) for all receiving, storing, and dispensing of the investigational product.

VI. Study Budgets and Grants

The University has made a significant investment in infrastructure to assist in planning financial management of clinical studies and continue to work with Fairview Research to streamline and expedite the process. Leveraging the expertise of this dedicated clinical trials financial management team for preparation of study budgets, contracting and ongoing financial reporting and oversight will ensure better cost recovery, trials management, and avoidance of study deficits.

Recommendation: CTSI's Financial Services Hub should be used to assist Psychiatry investigators with grants, budgeting and contracts. Prior to implementation, additional details about what activities the CNC administrative staff will continue to perform and which responsibilities the CTSI staff will perform will need to be worked out.

VII. Data Management, PHI

Protection of clinical trial participant data information, especially protected health information should be at the center of all activities and decisions around conduct of clinical trials. Investigators must establish secure safeguards around the confidentiality of subject research data.

The confidentiality of records that could identify subjects must be protected, respecting the privacy and confidentiality rules in accordance with the applicable requirements. The Department of Psychiatry has had no consistent process for managing study documentation including IRB renewals and regulatory annual reports. Systems are now in place through the CTSI to assist investigators with management of regulatory documentation and management of PHI that others have found of great benefit.

Recommendation: All research studies conducted in the Department of Psychiatry should utilize University systems set up to support research. Specifically the OnCore clinical trial management system (CTMS) and REDCap should be used. A CTMS is a software system used in clinical research to manage planning, performing and reporting functions, along with participant contact information, tracking deadlines and milestones. It is the policy of the AHC that all studies involving human research be registered within the University of Minnesota CTMS to provide minimum information about the study. However we recommend that all Psychiatry studies utilize the full functionality of the system. The tool can be used for electronic case report forms, scheduling patient visits, monitoring endpoints, etc. Those who obtain private information from patients and subjects will be required to protect the information, and any records that contain such information, from deliberate or accidental disclosure. The combination of clinical research training and the use of CTMS should allow all clinical research staff to manage clinical trials consistently and within requirements. Exemptions may be permitted on a case-by-case basis for clinical trials that are using a different CTMS or are already using a secure data management system (e.g. a multisite clinical trial).

VIII. Quality Assurance (QA)

A quality assurance program is a proactive process that encompasses all aspects of clinical research by identifying non-compliant trends before a serious problem occurs with a system in place to prevent future re-occurrences. The program should systematically review all components of the work to assess and determine if the required standards and requirements are being met. Currently within the Department of Psychiatry the clinical quality initiatives are self-regulating and no one faculty member or principal investigator has oversight to ensure the clinical quality objectives are met throughout the research initiatives.

Recommendation: Develop a quality assurance (QA) program to ensure that research studies are conducted in a manner that safeguards research subjects and results in verifiable data. A quality assurance program will minimize risk factors for misconduct, safeguard patient safety, prevent protocol non-adherence, ensure quality data, ensure ethical conduct of research studies and clinical trials, and ensure regulatory compliance. In areas of needed improvements, a correction action and preventative action plan will be documented and effectiveness of the plan(s) be monitored. The specific areas the QA program could address are:

1. Adherence to protocol and adequacy of source documentation.
2. Documentation of the informed consent and process used to obtain it.
3. Proper recording and reporting of adverse events.
4. Adherence to proper procedures for maintaining the CRFs.
5. Use of DSMB when mandated by federal or state regulations.
6. Use of the NIMH Guidance on Risk-Based Monitoring that requires enhanced monitoring for NIMH-supported human subject research that is minimal risk or more than minimal risk.
7. All protocol deviations are properly recorded and reported.
8. Appropriate study monitoring occurs at required intervals and then reports are generated and delivered to the appropriate regulatory groups in a timely manner.

Studies that require monitoring by the CTSI Regulatory specialist will be identified and assigned to the monitoring group of CTRS. Monitors review study materials (documents, records, drug/device accountability, Case Report Forms, etc.) to assure that the study is conducted, recorded, and reported in compliance with FDA Good Clinical Practice. Monitors will also ensure that the study is conducted in accordance with the protocol and inclusion/exclusion criteria as approved by the IRB. CTSI monitoring services are provided at no cost to University of Minnesota investigators. Our goal is to promote and facilitate compliance with Good Clinical Practice through: regular monitoring visits, data query resolution, review of study regulatory files, adverse event/serious adverse event (AE/SAE) reviews, and compliance consultation services. Typical review of subject specific documents includes but is not limited to: signed informed consent/HIPAA documents, case report forms (CRFs), medical records (for AE/SAE), regulatory binders, communications with FDA/IRB, and investigational product (IP) distribution logs.

IX. Ambulatory Research Clinic (ARC)

The Ambulatory Research Clinic (ARC) is a Department of Psychiatry outpatient research facility located in the west wing of Fairview Riverside hospital. It includes a centralized nursing station, one exam room, four consultation rooms, two small computer rooms, and a lab processing room. The four consultation rooms are used for research staff to conduct informed consent, psychotherapy sessions or other research related activities. The two computer rooms are used for research participants to complete electronic questionnaires. The exam room has one bed, which could accommodate research procedures. The ARC also has an area for medication storage and a lab processing room with one refrigerator, and one centrifuge.

Recommendation: CTSI should manage the ARC. CTSI will assume day-to-day operation of the ARC. Study coordinators will only conduct diagnostic testing and treatment only if they are trained and credentialed to perform such. Activities that require a licensure/credential/certification will be provided by a CTSI representative such as phlebotomy, vital signs, specimen collection, processing, and shipping, ECG/EKG, glucose tolerance testing, and spit testing will be provided by a properly credentialed CTSI representative.

Upon adoption of this management plan CTRS staff will immediately begin working with faculty and administrative staff in Psychiatry to plan for this transition. This will include developing plans for improving operational efficiencies and compliance and to ensure that this will be appropriately resourced. This transition will occur within six months of identification of the Clinical Research Manager

X. Summary

These recommendations are made based on the assessment of the current clinical trials research portfolio and activities in the Department of Psychiatry and our understanding of what have been the issues and challenges with conduct of human interventional research in the Department. These recommendations also guide the kinds of resources that will be required for CTSI to assume responsibility of the studies and our understanding of what the issues and challenges are to the conduct of human interventional research in the Department of Psychiatry. We believe this transition can be made in an efficient way that will not only enhance the conduct of research in the Department of Psychiatry but that will also provide the infrastructure for the faculty to successfully engage in these activities to meet personal, Departmental, and institutional goals. After consideration of any new information that may become available and

necessitate changes in the listed approaches or priorities and upon final approval of the management plan, CTSI will begin to work with the Department of Psychiatry on implementation. Our goal will be to have the new personnel (Research Clinical Manager and Regulatory Specialist) in place by June 30, 2016 with a rapid transition to full implementation of this management plan. All existing regulatory issues identified in the CRCC report or via CTSI monitoring will be corrected on or before June 30, 2016.

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Department Name and Address:	University of Minnesota Department of Psychiatry 2450 Riverside Avenue South Minneapolis, Minnesota 55454
Assessor:	Jan Dugas, Pr. Consultant/Auditor/Assessor Clinical Research & Compliance Consulting
Date(s) of interviews:	July 23, 2015 – September 9, 2015
Date(s) of assessments:	September 10, 2015 – October 6, 2015
Date(s) of management plan:	October 6, 2015 – December 31, 2015

Jan Dugas

Jan Dugas, Author/Independent Consultant/Assessor

December 31, 2015

Date

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1. Introduction

On June 11, 2015, Dr. Kaler and the Board of Regents approved 'Implementing the Recommendations of the External Review of the University of Minnesota Human Research Protection Program' Work Plan. Within the Work Plan, the Board of Regents recommended the University of Minnesota Clinical and Translational Science Institute (CTSI) accelerate the process of assuming management responsibilities of interventional drug and device trials being conducted by the Department of Psychiatry.

In order to understand the best approach for "assuming management responsibilities", Board of Regents further recommend that an independent consultant be hired to assess the clinical and research climate concerning psychiatric studies conducted at Fairview to develop a plan that addresses shared concerns and creates a climate where clinical research with psychiatric research participants can occur that meets the highest ethical standards of research possible.

An independent consultant was hired by CTSI and began work on July 13, 2015. The objective was to work with the Director and Assistant Director of the Clinical Translational Research Services team to assess the Department of Psychiatry clinical research portfolio. Tasks were to include:

- Review the current clinical research studies to assess:
  - Study status,
  - Feasibility - financial, operational, and recruitment,
  - Issues/concerns found with the quality/completeness of the study documents, regulatory files, etc.
- Make recommendations to leadership on:
  - Studies to keep open and enrolling,
  - Studies to close,
  - Staff to retain.

In addition to reviewing the current clinical research studies, the consultant met with faculty and research staff members to obtain feedback regarding past and current research activities and to understand the current Department of Psychiatry environment.

A Department of Psychiatry Management plan was developed per CTSI management directive, oversight, and authorship of the executive summary, recommendations and summary of information.

This document is a summary of activities and observations in relation to the assigned tasks. It will reflect the activities conducted and information obtained from the 54 interviews and review of 124 open research studies or clinical trials that was being conducted by the Department of Psychiatry.

2. Objective

The objective was to "assess the clinical and research climate concerning psychiatric studies

conducted at Fairview to develop a plan that addresses shared concerns and creates a climate where clinical research with psychiatric research participants can occur that meets the highest ethical standards of research possible".

Note: Faculty and Research staff refers to M Health - University of Minnesota Medical Center and University of Minnesota Masonic Children's Hospital as either "Fairview Riverside Hospital" or "Fairview Hospital".

3. Faculty and Research Staff Interviews

The purpose of the interviews was to acquire a general understanding of the current Department of Psychiatry environment. Each faculty and research staff member was invited to meet with the interviewer to discuss past and current research experiences.

In order to conduct the interviews, a comprehensive list of personnel working in the department needed to be developed as the Department of Psychiatry was unable to provide a list of staff members. A search was conducted using the U of M directory and Google searches. The U of M Department of Human Resources provided a limited study coordinator list but a full list of all personnel working in the department was not available. During this process, significant gaps were identified. The U of M Department of Psychiatry directory was not current. There is no mechanism in place to search for students or volunteers working in the Department as student volunteers on research studies.

Additional employees, students and volunteers were identified as the interviews progressed. One study coordinator, hired in September 2015, told me that her hiring manager, a Department of Psychiatry faculty member, ask that she not let anyone know she was hired and working on studies.

This same faculty member also utilizes volunteers to assume study research responsibilities. Two volunteers were identified. Neither of the volunteers had previous research experience nor had they completed required University research training. CTSI and the Department of Human Resources (HR) were immediately notified. HR had no record of either of these people however, each had University of Minnesota email addresses.

During the time period of July 22, 2015 to September 10, 2015, 92 invitations were sent, several on multiple occasions, and 54 interviews were conducted with University of Minnesota Department of Psychiatry faculty, research study staff, graduate students and volunteers. All those interviewed had responsibilities to at least one research study or clinical trial. Of those that responded, faculty and staff members were cooperative and willing to share information regarding their research practices although some were notably displeased or distrusting with this activity. During the interview process, I felt intimated and was verbally abused on two separate occasions by faculty members. One faculty member who was clearly upset by this activity, walked up very close to me and shook a finger in my face and said, "If CTSI thinks they are going to come in and dictate anything done in my department or my staff, they will have a war on their hands". The other faculty member paced in his office. He was clearly upset by the assessment activity and wanted to know why he was not informed about the study

assessment before Dr. Paller sent the email message. He accused me of seeking and reporting information to Carl Elliot. Both occurrences were reported to CTSI management immediately.

The interviews typically lasted about one hour. However there was some variation in the length of time. To eliminate bias, predefined questions were asked of each person, which included what they thought was going well in the department, opportunities for improvement, training, responsibilities, recruitment, overall concerns, and past experiences with CTSI.

Going well

Interviewees identified what is going well in the Department of Psychiatry. Responses included: Everything is going well (10); we have a great team, collaboration and learning (18); the vice chairs and committee structure have improved involvement of staff (5).

Opportunities for improvement

Significant concerns regarding overall leadership and management of the department were expressed. The lack of strategic planning, inclusion of staff, transparency and the existence of "silos" (37) were noted.

Current Department leadership was criticized for the management of [redacted] document forgery. Interviewees stated that leadership lacked direction, guidance or communication with the Department faculty and staff (18). Several faculty members believed [redacted]. In addition, faculty members expressed frustration with the burden of too many research requirements and delays in document approvals (18).

Interviewees state that the recruitment and well-being of human subjects is compromised by conflict of interest (8). Specific comments include being "very worried about recruitment and conflict of interest," "enrolling subjects for personal gain," and "enrolling subjects to satisfy research participation."

Ineffective and inefficient allocation of resources was identified as a barrier to accomplishing the work. This includes consistency of work load, space, computer access, and standard operating procedures (30). The Ambulatory Research Center (ARC) is an effective research setting. However, it is underutilized and ARC leadership is unavailable to resolve issues.

Training

As noted above, two volunteers, nonstudents, were found to be working full-time on research studies without formal training including CITI, CPR, and HIPAA. These two individuals were not in the HR U of M system.

Responses varied widely when interviewees were asked about the adequacy of training

provided for conducting research procedures. Current required training includes CITI, CPR and HIPAA. This was believed to be sufficient (8). Requests for more formalized training (7) included topics of Good Clinical Practice (GCP) (3) and research requirements.

Others commented there is no formal training provided (9), that training is on the job (7) and that training provided allows the staff member to conduct assessments. Lack of formalized training means that clinical trial staff is self-taught and must use a trial and error method when conducting research (5).

Interviewee comments continued with significant concerns from faculty and staff members who reported research staff are working and taking responsibilities beyond their role (10).

Responsibilities

Interviewees provided details in the response to questions about responsibilities. Staff members and volunteers report that their responsibilities include coordination of all of the research activities, write grants, annual reports, and working on protocols. This includes application to the IRB, management of IRB correspondence, completion of adverse event (AE) and mandated reporting. Staff members design the studies, define subject questionnaires, recruit subjects, run appointments, meet with subjects, complete data entry, conduct data analysis, and write publications. They also conduct IQ testing, assessments, MRI scans, and lab tests. The staff members manage grants and resources. In many instances, the faculty member has minimal involvement in the study activities.

Recruitment

Human subject recruitment includes a variety of methods such as social media, flyers, advertisements on Pandora, and on Craigslist. Settings utilized to recruit human subjects include outpatient clinical treatment settings, inpatient recruitment (with study activities initiated at discharge) and the delivery of flyers to residents in a treatment setting.

Overall concerns

When asked about overall concerns, several topics were identified. These include general concern about the direction of the department with a new Dean (3), faculty retention, funding, standing in the community and added scrutiny to research studies (6).

One interviewee said, "Staff members go behind the scenes to fix study documents and processes." Two other interviewees stated it took 6-8 weeks to fix documents in preparation for an IRB review. A separate example identified by an interviewee "we discovered a PI hadn't signed consents, we fixed the problem." Additional comments included, "What people don't know won't hurt them" and "We have to teach people to shut up and don't say anything to anyone."

"We have spoken to many people including the IRB and nothing gets implemented" (3). "It will take a strong leader to come into the Department and turn things around, stand up to those who have their own agenda" (6).

Past experiences with CTSI

When interviewees were asked about CTSI involvement in studies, there was variation in their perception of the helpfulness of CTSI. Several have utilized CTSI services in the past and found them helpful (5). They appreciated the opportunities to utilize the mentorship program and training curriculum for grant writing, IRB application writing and general research (13).

Several respondents have a history with CTSI. This created hesitation and concern about the potential for more involvement with CTSI. CTSI does not have expertise with psychiatry, interviewees said. Do not have world or industry experience (8). Some interviewees expressed concerns regarding the loss of autonomy over research projects and staff supervision (9). An interviewee said that he or she had requested CTSI resources on three separate occasions but that he or she had never received a response. Other interviewees said that CTSI has made promises and did not deliver on deadlines (5), and that CTSI never submitted the FDA annual progress report which resulted in an FDA audit (1).

Some said that it would be beneficial to have more discussion about what has gone well, what has not gone well, and how they could help faculty in research projects (4).

The most frequently expressed comment was, "Why are we being punished for one error in judgement that happened 10 years ago?"

Critical violation identified during an interview

One faculty member, who had been unresponsive, agreed to meet on October 26, 2015. During the discussion, she talked about how she recruits in-patient pediatric/adolescent patients and her informed consent practices. She approaches in-patient children, without parental consent, to see if they would be interested in participating in her study. If the child agrees to participate, she will then contact the family.

If the parent is not available in person, she will obtain approval via telephone contact or email. "I will send them an email, if they respond "yes", we are good to go." "It doesn't matter when the parent signs the form. If they respond 'yes', I start the child in the study. If we wait, they may not be interested." "It is not a concern when the parent signs the form as long as they say yes, we can start enrolling."

She was adamant that no one will tell her or her staff how to conduct research. Training is not welcomed, she said, "It would complicate my good research."

CTSI management was immediately notified of this critical violation to regulations and

IRB requirements. In response, was told that Dr. Schacker will discuss with Dr. Paller. In a follow-up meeting CTSI leadership did not believe this was a serious violation and said, "this is not really a problem".

Unbeknownst to the assessor, while interviews were being conducted, six clinical research coordinators within the Department of Psychiatry staff were notified that their position was being eliminated and five decided to leave the department due to current research practices and job realignment.

Refer to Appendix C for a condensed list of interview responses. A full list of de-identified interview responses will be provided upon request.

4. Department of Psychiatry: Research Studies & Clinical Trials

4.1 Identifying Current Research Studies & Clinical Trial

Approximately four weeks after the initial request, a list of 124 open research studies and clinical trials was obtained from the University of Minnesota (U of M) Institutional Review Board (IRB).

The studies were reviewed with the principal investigator to assess current status (active, open only for data analysis, inactive, closed); interventional or non-interventional; study type (medical or social); funding source; and current practices. The assessor's work was then prioritized and scheduled based on the type of study and faculty/investigator availability.

During the review process it became apparent the list of open research studies and clinical trials provided by the U of M IRB was outdated. Upon further investigation, it was determined that the provided information was based on open studies being conducted by the Department of Psychiatry as of January 1, 2015. A request to IRB was submitted to obtain a list of current studies, but this list was not provided.

Discrepancies in the studies included inaccurate or outdated information. For example, one principal investigator (PI), listed as currently conducting a study, had died in 2011 (information of his death was obtained through a google search and confirmed with the administrative assistant). Additionally, four PI's listed on the report had left the University one to seven years earlier but were still listed as active principal investigators. Several listed PIs were incorrect and one PI denied conducting the study for which he was listed. However, he had provided IRB renewal documentation to the IRB only one month earlier.

A complete list of noted deficiencies was developed (refer to Appendix B). This report does not include information on research studies/clinical trials that may have started since January 1, 2015.

The Department of Psychiatry conducts a variety of research including but not limited

to; research studies, clinical trials, medical social, investigational drug and investigational device. For the purposes of this report, all research studies and clinical trials will be referred to as studies.

4.2 Research Studies & Clinical Trial Status

Of the 124 open studies within the Department of Psychiatry, 116 were reviewed for current status. Of those 116 studies, the level of review was based on observations, CTSI directive, and the audit activities scheduled through the Office of the Vice President for Research (OVPR).

It is unknown at this time if the outsourced audits, being conducted through OVPR, included studies being conducted in the Department of Psychiatry. Although requested, this information was not provided.

Studies and personnel within the U of MN Tobacco Research Programs, under the guidance of Dorothy Hatsukami, Ph.D., were not included in the interviews nor were the studies reviewed. Per CTSI management, this department currently has clinical research management in place but not under the leadership of CTSI.

Initially, studies were reviewed with each PI to assess current status (active, open only for data analysis, inactive, closed), interventional and non-interventional, study type (medical or social), funding source and current practices.

All 124 studies (refer to Appendix B), were considered open and active per the IRB report. Of the studies reviewed, the study status of 57 were inappropriately assigned and eight are unknown. This is primarily due to the fact the PI (faculty) had not submitted the appropriate information to IRB for status change. Nor had the IRB inquired about current study status. Some studies had been open and inactive for several years.

- 59 open and active studies
- 38 open and active studies. These studies remain open only for data analysis. These should be moved to "inactive" status.
- 19 open and active studies in which all study activity have been completed. The status should be moved to "completed."
- Eight remaining open and active studies. Further investigation is needed.
    - Five are being conducted at the VA
    - In three studies the PI was unresponsive

The Assessor's request for updated study information was sent to IRB. Debbie Dykhuis, Director - Human Research Protection Program. She responded, "The IRB does not release documents or information to persons other than the PI or the PI's study team members listed on the IRB application, except when requested by University-wide oversight/compliance groups or requests that come in under the Data Practices Act".

4.3 Study Assessments

The purpose of the assessment was to gain a better understanding of the current research practices being conducted in the Department of Psychiatry and assess the conduct of the studies for compliance with research requirements, regulations and standards.

The assessment was conducted to evaluate conformity to research requirements, to confirm the integrity and accuracy of study data, and ensure that the safety, rights and welfare of study subjects are protected. This assessment included but was not limited to adherence with;

- Protocol requirements,
- External regulations and requirements as applicable;
  - 21 CRF 50, 54, 56, 312, 314, 812, 814, and 820, as applicable,
  - FDA guidance documents, as applicable,
  - National Institute of Health (NIH) Clinical Research Policies, as applicable,
  - National Institute of Mental Health (NIMH Clinical Research Policies, as applicable,
  - University of Minnesota Institutional Review Board (IRB) policies, as applicable,
  - University of Minnesota Office of the Vice President of Research (OVPR) policies, as applicable,
  - Fairview Health Services policies, as applicable,
  - International Conference on Harmonization Good Clinical Practices (ICH-GCP E6).

The assessment plan (Appendix A), was developed to ensure all studies were being reviewed in a consistent manner. The assessment plan was reviewed by the CTSI management prior to implementation.

On August 20, 2015, Dr. Mark Paller, Senior Associate Dean of the University of Minnesota (U of M) Medical School and Interim Head for the Department of Psychiatry sent an email to faculty members conducting a study, as a notification of the upcoming assessments.

> *I would like to extend my gratitude to those who took the time to talk with Jan Dugas so she could better understand the department's research activities. As we continue to develop the plan for clinical research management as mandated by the University's Advancing Human Research Protections plan, Jan will be assessing individual clinical trials and research studies (medical/social) in the department.*
>
> *Jan is a certified clinical auditor and has extensive experience conducting these types of assessments. All studies being conducted in the department will be*

considered for review. Jan will work with each PI and coordinator or staff member to obtain the study documentation. This could include, but is not limited to protocols, IRB and informed consent submissions and approvals, clinic or medical records, adverse events, protocol deviations, etc. Please be assured that the confidentiality of all records will be strictly maintained.

Jan will be notifying you when she will be reviewing your studies. You and your staff will need to provide all documentation and be available periodically throughout the day to answer questions while the assessment is being conducted and at the end of her review to discuss any observations.

Thank you for your cooperation.
Mark S. Paller, M.D., MS

Senior Associate Dean
Interim Head, Department of Psychiatry

Initially, each study was reviewed to determine current study status (refer to section 4.2: Research Studies & Clinical Trial Status).

The study assessments were then prioritized in the following order: investigational, interventional, medical, and social.

The study assessment review activities commenced on September 14, 2015. On October 6, 2015, study assessments were discontinued per email received from Lisa Johnson. One section of the message received, "As we have talked previously, the reviews of the studies you are doing is helpful to provide an overview of the issues that need to be addressed in the management plan, however, at this point, the inability to truly understand each study in depth (given that we were asked to not do a complete audit of each) tells me that it isn't productive to continue to review of the current findings in detail. While this information will be helpful to support aspects of the management/training plan, I don't think anything you are identifying is either actionable immediately (and if it is it needs to be reported to the IRB) or new information (we can understand how these items are happening in this setting)."

Inquiries were made to CTSI management about writing a report including observations noted during the study assessment. Each time the assessor was told not to write a report. On November 19, 2015 CTSI leadership gave the directive to write the study assessment report and told the assessor she would be the only one to see and review the report.

During the three and a half weeks of study assessments, 42 critical or major observations were noted. It seems questionable that such information was not actionable or new to CTSI.

From August 10, 2015 to October 28, 2015, the independent consultant/assessor met with Dr. Paller, Sr. Associate Dean of the U of M Medical School and Interim Head for the Department of Psychiatry on four separate occasions to communicate serious concerns including but not limited to; University liabilities related to study research activities, conflict of interest, and noncompliance. The concerns were immediately minimized and discounted the issues of noncompliance and conflicts of interest. He said, "This is nothing new, it happens all over the university".

Weekly meetings were conducted with Lisa Johnson of CTSI to provide weekly summary of activities, noncompliance observations, and concerns. Dr. Schacker was notified on some occasions of noncompliance.

The following information is based on the study assessments and discussions with faculty members conducted from July 22, 2015 until October 6, 2015.

4.4 Study assessment activities

Prior to the study assessment discontinuation, the following information is based on the study assessments conducted from September 14, 2015 to October 6, 2015.

4.4.1 Studies Reviewed

Study Name	Principal Investigator
A multi-center, randomized, double-randomized, 12-weeks, parallel group, placebo-controlled proof of concept study to investigate the efficacy and safety of R05285119 in individuals with Autism Spectrum Disorder.	Suma Jacob, M.D., Ph.D.
IOTN - Industry Sponsored	Suma Jacob, M.D., Ph.D.
Integrated Cognitive Affective Therapy for Binge Eating Disorder: A Randomized Controlled Trial	Carol Peterson, Ph.D.
An Adaptive Treatment Strategy for Adolescent Depression	Meredith Gunlicks-Stoessel, Ph.D.
Effects of Sertraline on Brain Connectivity in Adolescents with OCD	Gail Bernstein, M.D.

High Field Brain Imaging in Adolescents	Kathryn Cullen, M.D.
Open Label IV Subanesthetic Ketamine	Kathryn Cullen, M.D.
Collaborative Initiative on Fetal Alcohol Spectrum Disorder: Mapping the Brain, Face, and Neurocognitive Function in FASD.	Jeff Wozniak, Ph.D.
A Long-term Follow-Up Study for the Evaluation of Patients who have a Deep Brain Stimulation System for the Adjunctive Treatment of Major Depressive Disorder	Barry Rittberg, M.D.

4.4.2 Assessment Observations

Observations are classified as Critical, Major, or Minor. (See Appendix A: Assessment Plan) There were a total of 42 observations made during the assessment; 35 observations were considered Critical, 5 were considered Major. Only Critical and Major Observations are summarized in this Executive Summary. Details for all three classifications of observations can be found in the Audit Narrative.

Although this report is focused on deficiencies and areas of concern or improvement opportunities, within the department two faculty members were conducting research studies and clinical trials according to the regulations and requirements; [redacted] No observations were written for these two studies.

Although observations were written, one faculty member – [redacted] – was eager to learn how to conduct and apply research requirements within her studies.

4.4.3 Critical Observations

Section 6.1	Non-adherence to study protocol requirements.
Section 6.2	Principal Investigators Responsibilities in Clinical Studies
Section 6.3	Subject Informed Consent & PHI
Section 6.4	Data and Safety Monitoring Plans and Board
Section 6.5	Adverse Events and Protocol Deviations/Violations
Section 6.6	Study Records, Data Management
Section 6.10	Training and Education

4.4.4 Major Observations

Section 6.7	Monitoring Activities
Section 6.8	Ambulatory Research Clinic (ARC)
Section 6.9	Study Finance Management

4.5 Audit Narratives

4.5.1 Research Studies and Clinical Trial Protocol/Study Plan

Description	**Classification: Critical**

The following were recognized as non-adherence to the following; protocol requirements, FDA 312 & 812, ICH-GCP E6, NIH, NIMH and U of M IRB policies and procedures:

- **Observation 1**: The study plans and protocol did not contain all the essential elements.
- **Observation 2**: Protocol requirements not being followed:
  - Per the PI, source document requirement was added to the protocol as part of an IRB requirement. Standard language was provided by a faculty member and incorporated in the protocol for a "quicker review and IRB approval". Neither the PI nor the study coordinator understood what "source documentation" meant nor were they complying with the requirements of the protocol.
- **Observation 3**: Adverse events not documented as specified in the protocol.
  - Protocol stated, "Information on all adverse events will be recorded immediately in the source document, and also in the appropriate adverse event module of the case report form (CRF)." This study did not have an adverse event CRF nor were adverse events being recorded in source documentation.
- **Observation 4**: Protocol changes not documented or submitted for IRB review.
  - "New" study rules were implemented but not documented in a protocol revision or submitted for IRB review;
    - Subjects are not considered enrolled into the study until four to eight weeks after consent was signed because of the high drop-out rate after randomization.
- **Observation 5**: Assessor was told not to review the first eight subjects enrolled in the study because "They were our practice patients" and "They don't count in the study." These subjects had signed informed consent forms and were following the protocol requirements.
- **Observation 6**: Incomplete CRFs during follow-up visits. Justification for the missing

data included statements such as "We really don't need data at those visits".

- **Observation 7:** An open label drug study did not provide the revised protocol to the infusion team at Fairview Riverside Hospital, which is administering the drug to adolescents. In addition, training was not conducted on the protocol changes.

4.5.2 Principal Investigators Responsibilities in Clinical Studies

Description	**Classification: Critical**

The following were recognized non-adherence to following; 21 CFR 312, 21 CFR 812, FDA Guidance Dated October 2009: Investigator Responsibilities – Protecting the Rights, Safety, and Welfare of Study Subjects, NIH Delegation of Authority for Interventional and Observational Studies, ICH-GCP E6, ICH-GCP E6 (R2), U of M IRB: Policies 800, 800F, 800G, 801.

The principal investigator (PI) is responsible for all activities associated with the conduct of the research project, including compliance with federal, state and local laws, institutional policies and ethical principles.

To ensure human subjects protection, the PI remains ultimately responsible, even when some aspects of the research are delegated to other members of the study team.

PI's must personally perform or delegate to qualified research staff all the necessary tasks to carry out their study. For tasks that are delegated, the PI remains ultimately responsible for proper conduct of the study and fulfillment of all associated obligations.

According to standard requirements the PI must provide members of the research team with sufficient oversight, training, and information to facilitate appropriate study procedures and study adherence.

Observation 8: Lack of PI Oversight. Of the studies reviewed, the research staff/study coordinators are primarily responsible for the majority of study activities, with limited PI involvement. Beyond the expected study coordinator responsibilities, additional assigned tasks include:

- All recruitment, screening and enrollment
- Determining eligibility of study participants
- Conducting the informed consent process and assent process for children
- Conducting diagnostics testing including, MRI's on adolescents and laboratory testing
- Conducting psychotherapy sessions and assessments
- Conducting all study visits

- Conducting therapeutic and medical interventions including, Transcranial Magnetic Stimulation (TMS)
- Completing case report forms
- Clinical study files management
- Preparing documents for IRB submission

In addition, research staff, including study coordinators, told the assessor that the responsibilities of staff members and volunteers include coordination of all of the research activities, as well as writing grants, annual reports, and protocols. This includes applications to the IRB, management of IRB correspondence, and the completion of adverse event (AE) and mandated reporting. Staff members also design the studies, define subject questionnaires, recruitment, run appointments, meet with subjects, complete data entry, data analysis, and write publications. They also conduct IQ testing, patient psychotherapy assessments, MRI scans, and lab tests. The staff members manage grants and resources.

Observation 9: Documentation of PI delegated responsibilities was non-existent.

Observation 10: Inadequate training, licensing & credentialing. During the conducted interviews, many of the research staff expressed concern regarding conflicting work direction, lack of research knowledge and training, conducting study testing/treatments they may go beyond their capabilities, training and expertise. One individual who had completed the CITI training requirements expressed her lack of informed consent knowledge. She went on to say even though she doesn't understand the informed consent process she actively recruits and consents patients into a study.

Observation 11: Laboratory and Psychotherapy Testing. Research staff are performing protocol-initiated tasks and duties beyond the scope of their responsibilities. The required duties include but not limited to; psychotherapy assessments being conducted by nonmedical personnel with no secondary education, and no research training.

One department receptionist referred to herself as a "therapist" and routinely conducts psychotherapy study visits.

Additional activities include the following: nonqualified research staff are performing laboratory testing and are collecting human specimens without appropriate "blood borne pathogens" training for human specimen/fluid collection.

One research team of coordinators meets subjects at public coffee shops or fast food restaurants and collects urine samples. These urine specimens are generally stored in their purses. If it is later in the day, study coordinators will take the urine specimen home and bring it to the lab for testing the following day.

Observation 12: MRIs. PIs are delegating non-medical non-licensed and non-credentialed study coordinators to conduct MRI's on study participants, both adolescents and adults.

Per the Minnesota MRI Technician Licensing Certification: Minnesota does not have a

state-administrated MRI exam; instead, individuals must pass the American Registry of Radiologic Technologist exam. Fairview Riverside Hospitals also require MRI Technicians, at a minimum, to graduate from an accredited school of radiology, to have ARRT certification and to have MRI experience. Study coordinators performing these duties do not have the required credentials or licensure.

Observation 13: Transcranial Magnetic Stimulation (TMS). PIs are delegating non-medical non-licensed and non-credentialed study coordinators on conducting transcranial magnetic stimulation (TMS) on study participants, adolescents and adults

NIMH considers transcranial stimulation a greater than a minimal risk procedure/intervention. NIMH requires ongoing monitoring by the PI and the IRB, and may also require monitoring by an Independent Safety Monitor or an Independent Safety Monitoring Board.

Per NIMH, "Greater than minimal risk to subjects means the probability and magnitude of harm or discomfort anticipated in the research risks are more than minimal risk, but not significantly greater. Studies that fall under this category will range in their probability of a moderate-severity event occurring as a result of study participation (and the level of safety monitoring will depend on that probability) and there are adequate and surveillance protections in place to identify promptly and to minimize harm.

The assessor has been unable to obtain the Minnesota requirements for those conducting transcranial stimulation. However at other major universities across the country, (e.g., Johns Hopkins), minimal requirements include credentialing of TMS physicians by the hospital. The treatment itself is usually administered by the TMS physician or by an experienced TMS technician under the supervision of the TMS physician.

The U of M IRB Director was notified of these current practices. Several weeks after this meeting, the assessor was notified that the Center for Magnetic Resonance Research (CMRR) is no longer overseen by the IRB. Therefore, any questions or concerns need to be directed to the new administration of that area.

Observation 14: Delegation of protocol-initiated duties. Delegation of protocol duties should only occur if the individual have obtained the appropriate state licensure and certifications. The individual must also complete the appropriate education and training documented procedures for certifying personnel to conduct these protocol-initiated tasks. The individual must complete ongoing training as required and make sure that licensure/certifications are kept current.

Research staff without the appropriate training, education, and licensure/certification have been conducting diagnostic, interventional or therapeutic procedures including but not limited to; conducting MRIs, dispensing medication, administering transcranial direct current stimulation, or other procedures that are considered to involve greater than minimal risk.

Observation 15: Outstanding issues identified in repeated monitoring reports. Issues included: backdating of documents; failure to comply with Good Documentation Practices (correction on forms, drug distribution records/drug start date not recorded,

randomization documentation); double scoring done by same coordinator; protocol deviation logs not created or maintained; incomplete Delegation of Authority; lack of study training and documentation; backdating on inclusion/exclusion logs; numerous unreported protocol deviations; several attempts to get site up to date on queries and open action items; repeated violations that continue to occur. PI and study coordinator continue to collect urine specimens despite the fact they are not approved to do so.

4.5.3 Subject Informed Consent & PHI

Description	Classification: Critical

The following were recognized as non-adherence to the following; protocol requirements, FDA 21 CFR 312.60, 21 CFR 812.100, 21 CFR Part 50, 21 CFR Part 50.25(c), 21 CFR 55.55, 45 CFR 46, Subpart B & D, 45 CFR 46.111, 21 CFR 56.111, NIH NOT-0D-16-010: Inclusion of Children as Participants in Research Involving Human Subjects, ICH-GCP E6, U of M IRB: Policies 413, 414, 501, 501D, 704.

The consent process begins with subject recruitment, and it includes the advertising used to recruit subjects into the clinical trial. The consent form serves several purposes. It ensures that the subject receives the required information. It provides a "take home" reminder of the elements of the research study/clinical trial. It provides contact information in case additional questions or concerns arise. Finally, it documents the subject's voluntary agreement to participate.

Per NIH requirements, if some or all participants in a study are likely to be vulnerable to coercion or undue influence, (e.g., children, mentally disabled individuals, or economically or educationally disadvantaged people), a recruitment/informed consent plan should be developed that will provide safeguards, as appropriate, to protect their rights and welfare.

Observation 16: Informed consent plans have not been written for any of the studies reviewed that were enrolling children. None of the PIs had heard of this requirement.

FDA's guidance entitled "E6 Good Clinical Practice: Consolidated Guidance" (ICH E6) (Ref. 13) recommends that a child "should be informed about the trial to the extent compatible with the [child]'s understanding and, if capable, the [child] should assent, sign and personally date the written informed consent" (§ 4.8.12, ICH E6, Ref. 13). In addition, the "language used in the oral and written information about the trial should be understandable" to the child or the child's parent or guardian (§ 4.8.6, ICH E6, Ref. 13). If a child is deemed capable of assent, and the assent requirement is not waived under§ 50.55(c) or (d), the language used should be understandable to the child in order for the child's assent to be meaningful (§ 2.6.3, ICH E 11, Ref. 1).

Observation 17: Studies enrolling adolescents were written at levels beyond the adolescent's comprehension. For example, child assent forms were written at a 10th

grade level, while the studies were enrolling 12 year olds or 6th grade level. The clinical study coordinator confirmed that children generally do not ask questions concerning the information contained in the informed consent or what they may not understand.

Observation 18: During an interview, the PI stated that she approaches children hospitalized at the Fairview Riverside Hospital to see if there would be interested in participating in a study before talking with the parents. If the child agrees to participate, she will then contact the family. If the parent is not available at the hospital, she will obtain consent by telephone or email. "It is not a concern when the parent signs the form as long as they say yes, we start enrolling. If we wait, they may not be interested." This is a major violation of CFR Part 50: Protection of Human Subjects.

Per requirements; informed consent must be documented for each prospective research subject (or legally authorized representative) before the subject begins to participate in the research. It is the PI's responsibility for ensuring that each potential subject understands the nature of the research and participation in the project and give informed consent to participate.

Observation 19: Informed consent process documentation was non-existent in all studies reviewed.

The confidentiality of records that could identify subjects should be protected, respecting the privacy and confidentiality rules in accordance with the applicable requirements. "Every precaution should be taken to respect the privacy of the subject, the confidentiality of the patient's information and to minimize the impact of the study on subject's physical and mental integrity on a personality of the subject." (Declaration of Helsinki)

Observation 20: In one study that was reviewed, frontal facial pictures had been taken of subjects and placed in the subject's records along with copies of the subject's driver's licenses. Study team members had taken pictures of study subjects and made copies of the subject's driver's licenses so they could recognize the subjects when they came to clinic. Additionally, the subject's full names were written on file folders as a means of identifying subject records in the study related files. Research staff and PIs were unaware of the Protection of Privacy requirements.

4.5.4 Data and Safety Monitoring Plans and Board

Description:	**Classification: Critical**
The following were recognized non-adherence to the following; protocol requirements, 21 CFR 312.60, 21 CFR 812.100, FDA Guidance Document: Establishment and Operation of Clinical Trial Data Monitoring Committee, NIH Policy for Data and Safety Monitoring Boards, NIH Policy for Data and Safety Monitoring Plan Writing Guidance, NIMH Policy Governing the Monitoring of Clinical Trials, HHS: Data and Safety Monitoring Boards in NIH Clinical Trials, ICH-GCP E6, U of M IRB: Policy 800.	

The data and safety monitoring board is a process designed to protect the safety of individual participants in research studies and to ensure the validity of research results and scientific integrity of a study. Food and Drug Administration (FDA), National Institute of Health (NIH) and National Institute of Mental Health (NIMH) require an independent Data Safety Monitoring Board (DSMB) to ensure that patient safety and adequate provisions are in place for monitoring the data.

The DSMBs play a critical role in ensuring the safety of human subjects and the merit of clinical trials. DSMB members are required to have multidisciplinary representation of at least three people who have not had any involvement in the design and/or conduct of the study; as well as no significant conflict of interest either financially, intellectually or professionally.

It is essential to ensure members have access to unmasked data, maintaining a pool of qualified and independent individuals to serve on the DSMB. They initially review the research protocol/plan, evaluate the progress of the study including periodic assessments of data quality and timeliness, participant recruitment, accrual and retention, participant risk versus benefit, performance of the PI or faculty member conducting the research, and other factors that could affect study outcomes.

The following was noted: Non-adherence to data safety and monitoring plan, data safety monitoring membership, data safety monitoring meeting & documentation not conducted as required per protocol, FDA regulations, and NIH/NIMH requirements.

Observation 21: DSMB sections were included in the study protocols. However, in all studies reviewed, the DSMB protocol requirements were not being followed.

Observation 22: In all studies reviewed, DSMB plans had not been developed per the protocol requirements.

Observation 23: Most studies reviewed had no mechanism in place to collect or report adverse events.

Observation 24: Potential conflict of interest exists in all studies reviewed as the DSMB members were found to be professional peers within the department and not independent reviewers.

Observation 25: DSMB meeting have not been conducted per protocol and requirements.

Observation 26: DSMB meeting minutes were not appropriately documented. And there is no mechanism in place to collect or report adverse events. All of which are major violations of the requirements.

Observation 27: Faculty members said they were not aware of the NIMH Guidance on Risk-Based Monitoring that requires enhanced monitoring for NIMH-supported human subject research that is minimal risk or greater more than minimal risk.

4.5.5 Adverse Events and Protocol Deviations/Violations

Description:	Classification: Critical

The following were recognized non-adherence to following; protocol requirements, 21 CFR 312, 21 CFR 812, FDA Guidance for Clinical Investigators, Sponsors, and IRBs Dated January 2009: Adverse Event Reporting to IRBs — Improving Human Subject Protection, NIMH: Policy on Governing the Monitoring on Risk Based Trials, NIMH: Guidance on Risk Based Monitoring, NIMH: Inclusion of Children as Participants in Research Involving Human Subjects, NIMH:NIH Policies and IC Guidance for Data and Safety Monitoring of Clinical Trials, NIH Guidance: HIPAA Privacy Rule Information for Researchers, NIH Guidance: Research Involving Individuals with Questionable Capacity to Consent: Points to Consider, NIH: SOP16: Reporting Requirements for Unanticipated Problems, Adverse Events and Protocol Deviations, ICH-GCP E6, ICH-GCP E6 (R2), U of M IRB: Policies 409, 411, 412A, 412B, 800, 800F, 800G.

Adverse Events:
Reporting safety during a clinical trial is one of the most important tasks the investigator and clinical study team can perform. Per regulations, the PI is responsible for adhering to the regulations and protecting the rights, safety, and well-being of subjects in a trial.

Adverse events encompass both physical and psychological harms. They occur most commonly in the context of biomedical research, although on occasion, they can occur in the context of social and behavioral research and must be evaluated each time interactions are conducted with a study participant.

Observation 28: Collection of adverse events, safety, is the most important piece of data collected in a study. Collection and review of adverse events by the PI is required in every study. However, it was noted only the industry sponsored studies had a mechanism and case report forms to capture adverse events. All other studies, including a physician sponsored IDE study had not been capturing or recording adverse events in the study.

One PI did say that her team is working on developing a case report form and is planning to implement it in an ongoing study.

Observation 29: A physician sponsored IDE trial has been monitored by CTSI monitors and the lack of adverse event collection and reporting was not included on the monitoring report.

Protocol Deviation:
Protocols have been developed to safeguard the health and safety of the study participants as well as to provide sufficient statistical power within a study. Deviations from the approved procedures could therefore harm the subjects in the study and/ or compromise the analysis of the data collected.

A protocol deviation is any change, divergence, or departure from the study design or procedures of a research protocol that is under the investigator's control and that has not

been approved by the IRB. A deviation may be due to the research subject's non-adherence, or an unintentional change to or non-compliance with the research protocol such as:

- A rescheduled study visit
- Failure to complete a self-reported assessment
- Subject's refusal to complete scheduled research activities

Or a protocol deviation could increase risk or decrease benefit, affects the subject's rights, safety, or welfare, or the integrity of the data such as:

- Failure to obtain valid informed consent
- Not following inclusion/exclusion criteria

Whether unplanned or planned in an effort to protect study subjects, any deviation from the protocol must be recorded and its severity assessed. IRB functions and operations. In order to fulfill the requirements of 21 CFR §56.108, each IRB shall:

- Follow written procedures:
  - For ensuring prompt reporting to the IRB of changes in research activity (e.g., protocol deviations); ...
  - For ensuring that changes in approved research, during the period for which IRB approval has already been given, may not be initiated without IRB review and approval except where necessary to eliminate apparent

Deviations initiated by the clinical investigator must be reviewed and approved by the IRB prior to implementation, unless the change is necessary to eliminate apparent immediate hazards to the human subjects (21 CFR 312.66), or to protect the life or physical well-being of the subject (21 CFR 812.35(a) (2)). NIH also has established criteria for NIH studies being reviewed by NIH IRB and non-NIH IRBs.

Observation 30: No study reviewed had a mechanism in place to collect protocol deviations nor had the PI's or study staff heard of this requirement.

Observation 31: Protocol deviations have not been pre-approved by the IRB or reported to the IRB on an annual basis.

Observation 32: A physician sponsored IDE trial has been monitored by CTSI monitors and the lack of protocol deviations collection and reporting was not included on the monitoring report.

4.5.6 Study Records, Data Management

Description:	**Classification: Critical**
The following were recognized non-adherence to following; 21 CFR 312, 21 CFR 812, FDA Guidance for Clinical Investigators, Sponsors, and IRBs Dated January 2009: Adverse Event Reporting to IRBs — Improving Human Subject Protection, Good	

Documentation Practices, NIMH: Clinical Trials, NIH: Good Documentation Practices in Clinical Research, HIPAA Privacy Rule Information for Researchers, SOP16: Reporting Requirements for Unanticipated Problems, Adverse Events and Protocol Deviations, Essential Documents Policy and Guidance, ICH-GCP E6 & ICH-GCP E6 (R2), U of M IRB: Policies 412A, 412B, 422, 800, 800F, 800G.

Good documentation practices ensure the study results are built on the foundation of credible and valid data. It should enable an independent observer to reconfirm the data.

Source documentation is the medical record of the subject before, during and after the trial. In research studies and clinical trials, source documents are the original document, data, and records where the research is first written. This would include; data, records, hospital medical records, clinical notes, subject evaluations or assessments, checklists, etc. Retention of these documents are required.

Additionally, it includes all records, in any form including but not limited to; written, electronic, magnetic, scans, etc., that record the methods, conduct or results of a trial.

Management and retention of these documents demonstrate the compliance of the PI and research staff.

Observation 33: Required study documents are non-existent. There is no awareness of what a trial master file is or the required contents or good clinical practices.

Observation 34: While reviewing studies with the PIs, the following was noted: a general lack of good documentation practices; white-out use for corrections; incomplete CRFs; testing not completed; and justification of missing data was non-existent. Reasons given for these deficiencies included; lack of time and "We really don't need data at that visit."

Investigators must establish secure safeguards of the confidentiality of subject research data. Subjects should be told the limits, legal or other, to the investigators' ability to safeguard confidentiality and the possible consequences of breaches of confidentiality.

Observation 35: Study data is currently being collected and stored using a variety of software packages, most commonly Microsoft excel and a department shared drive. Study and subject information are not protected and fellow staff members have access to enter, edit or delete data and required study information.

4.5.7 Monitoring Activities

Description:	**Classification: Critical**
The following were recognized non-adherence to following; study protocol, U of M 412A, 21 CFR 312, , ICH-GCP E6 & ICH-GCP E6 (R2), CTRS SOP 212.	

Effective monitoring is critical to the protection of human subjects and the conduct of high-quality studies. Investigators conducting clinical trials involving drugs are required to provide oversight to ensure adequate protection of the rights, welfare, and safety of human subjects and, per regulations, are required to monitor the conduct and progress of their clinical investigations.

Monitoring was being conducted by CTSI.

Observation 36: In one open-label drug studies, adolescent subjects are receiving IV drug therapy in the infusion area of Fairview Riverside Hospital. However, the protocol had been revised, and monitors had not reviewed product allocation/distribution/storage/etc. records. The monitor had not reviewed records in the Fairview Riverside Hospital infusion area.

Observation 37: The study protocol in the infusion area was outdated. The revised study protocol had not been provided to the team infusing ketamine into adolescent subjects, nor had training to the revised study protocol been completed.

Observation 38: Monitors had not reported on lack of AE reporting, lack of protocol deviation collection/reporting, lack of monitoring log signatures and follow-up on outstanding issues from one year prior.

4.5.8 Ambulatory Research Clinic (ARC)

Description:	**Classification: Critical**

The Department of Psychiatry currently supports two clinical outpatient research facilities on campus at the University of Minnesota. Both facilities are available to investigators to conduct clinical research and are staffed with Psychiatry research staff.

For the purposes of this report, the focus will be on the Ambulatory Research Clinic (ARC) that is located on the University of Minnesota west bank in the Department of Psychiatry. The ARC is an outpatient facility where research is being conducted by the Department of Psychiatry on both the adult and pediatric population. The ARC is located within the Fairview Riverside Hospital on the 2nd floor of the west wing and includes a centralized nursing station, one exam room, four consultation rooms, two small computer rooms, and a lab processing room.

The four consultation rooms are used for research participants and staff to discuss informed consent, psychotherapy sessions or other research related activities. The two computer rooms are used for research participants to complete electronic questionnaires. The exam room has one bed, which could accommodate research procedures. The ARC

also has an area for medication storage and a lab processing room with one refrigerator, and one centrifuge. During the month of September only 45 subjects were seen in the ARC. The majority of the subjects were seen to either complete self-assessments or psychotherapy assessments administrated by the study coordinators and the ARC receptionist. The ARC is underutilized. **Observation 39:** As stated above, study coordinators are conducting diagnostic testing, laboratory specimen collection and conducting psychotherapy sessions without the appropriate documented training, and required licensure/credential/certification.

4.5.9 Study Finance Management

Description:	**Classification: Critical**
During the interviews, study coordinators consistently stated that the PIs deposit grant money, including federal grant money, in their personal bank accounts. If money is needed to compensate subjects per the protocol, the study coordinator notifies the PI and the PI will go withdraw the money from their account. Study coordinators also told the assessor, "Huge problem, if the coordinators don't like doing something or do not understand why they need to do something, they just don't do it. TASCS (Time and Study Collection System) is a perfect example, they don't like it so they don't do it. Subjects, testing and study activities are not billed appropriately or just not being billed." **Observation 40:** Study billing is not being completed per U of M or Fairview Riverside Hospital requirements. Because of the discontinuation of the study assessment, this information could not be further investigated. Additional information is needed on the laws and requirements for federal grant money being deposited, distributed from personal bank accounts and billing within the Fairview Riverside Hospital and U of M facilities.	

4.5.10 Training and Education

Description:	**Classification: Critical**
The following were recognized non-adherence to following; 21 CFR 312, 21 CFR 812, FDA Guidance Dated October 2009: Investigator Responsibilities – Protecting the Rights, Safety, and Welfare of Study Subjects, NIMH: Clinical Trials, NIH: Human Subjects Research Requirements for Training, NIH Training SOP: Responsible Conduct of Research, ICH-GCP E6 & ICH-GCP E6 (R2), U of M IRB: Policies 412A, 412B, 422, 800,	

800F, 800G, 801.

A career in clinical research increasingly requires high levels of preparation, training, and commitment.

Research training has proven to significantly affect the data being captured in a study as well as the safety and well-being of the study participants. The impact of research training can be difficult to quantify, but the absence of good training can result in significant costs related to corrective actions, data integrity complications and regulatory noncompliance. Failure to train staff members adequately can cause research studies and clinical trials to be jeopardized.

Observation 41: Faculty and research staff were not aware of the most fundamental regulatory and institutional requirements pertaining to the conduct of clinical research studies. Many were unaware of the protocol requirements and did not comprehend the terms and conditions written within the protocols. Faculty and staff members demonstrated a complete lack of initiative in understanding the requirements for conducting research.

Although they had completed the CITI required training, the vast majority of those interviewed said they had not heard of International Conference on Harmonization Good Clinical Practices (ICH-GCP), fundamental clinical research requirements, and most requirements from the FDA regulations, as well as NIH and NIMH guidelines.

Many stated they had trained to the SOPs required by the U of M IRB. However, they were unaware of the requirements within the SOPs and they were not in compliance with those requirements.

This noncompliance included but was not limited to: collection and reporting of adverse events and protocol deviations, recruitment and informed consent processes, documentation of informed consent, and documentation of inclusion/exclusion criteria assessment prior to consenting and safety monitoring.

Observation 42: Documentation of study staff training on specific protocols or training to the delegated responsibilities was non-existent. This documentation should have included student volunteers being the first point of contact during patient recruitment and phone screening activities.

Observation 43: One faculty member hires volunteers to work on research studies. These volunteers are not within the U of M system, nor are they students, nor have they completed any required training as required by the University for those working on research studies.

5. Management Plan

Upon discontinuation of the research study assessment, CTSI assigned the assessor/independent consultant the task of working with CTSI management to develop a management plan. Per the University of Minnesota Work Plan dated June 11, 2015:

> "independent consultant be hired to assess the clinical and research climate concerning psychiatric studies conducted at Fairview to **develop a plan** that addresses shared concerns and creates a climate where clinical research with psychiatric research participants can occur that meets the highest ethical standards of research possible."

Prior to writing the plan, the assessor was given the directive to work with two CTSI managers for their input into the plan. It was evident that the CTSI recommendations for the management plan was determined prior to the assessor's hire date. Over several meetings, the assessor was told what information and recommendations to incorporate into the plan. A draft management was submitted for review in on November 9, 2015. Upon receipt, the contents of the management plan were rewritten by the CTSI leadership. The psychiatry management plan was does not accurately reflect the work or recommendations of the independent consultant and will not achieve the deliverable of meeting the highest ethical standards of research possible, as directed in the 'work plan'.

As of today, December 31, 2015, the report is still under revision by CTSI leadership and has not yet been finalized.

6. Conclusion

Conducting research studies/clinical trials involves a tremendous amount of work and responsibility. During the study assessments, the assessor provided guidance documents and copies of Good Clinical Practices to attempt to educate the study teams on responsibilities and requirements for conducting clinical research.

However, the standard research practices in the Department of Psychiatry demonstrate a profound lack of knowledge about how to conduct clinical research and an intentional lack of adherence to requirements set forth by the U of M IRB and state and federal regulatory agencies. It will be important to communicate to faculty members that conducting research is not a faculty right, but a privilege, and that requirements are established to protect all those involved.

Given the feedback received during these activities, there is concern that practices – similar to those observed within the Department of Psychiatry – are systemic across the University.

The assessor recommends a full comprehensive audit for each study being conducted by the Department of Psychiatry. This will ensure all issues have identified and appropriate corrective actions and preventative actions can be implemented.

In addition, the Department of Psychiatry would benefit from hiring a clinical research operations leader, someone from outside the University that has research, industry, and compliance experience. This person's responsibilities will be to ensure that research studies/clinical trials are being conducted to protect the study participants safety and welfare and reach the highest ethical standards possible. Such a resource would also serve as a medical liaison for the Fairview Riverside Hospital and CTSI. It is recommended that this person maintains independence from CTSI but work as a liaison with CTSI and report directly to the Chair of the Department of Psychiatry.

APPENDIX A: RESEARCH STUDIES/CLINICAL TRIALS ASSESSMENT PLAN

UNIVERSITY OF MINNESOTA

Department of Psychiatry

Research Studies/Clinical Trials Assessment Plan

Jan Dugas

9/8/2015

A collaborative Department of Psychiatry and CTSI plan for assessing departmental research studies/clinical trials. This is a living document that may be revised during the assessments as new information becomes available. This plan was prepared by Jan Dugas with input from CTSI management.

1. Objective

In 2014, Dr. Kaler endorsed the conduct of two independent reviews of human subject research. The reviews resulted in recommendations for improving the human research protection program at the U of M, including the university must make changes if it wishes to have a leading program in research participant protection. Dr. Kaler charged the Vice President of Research and Vice President of Health Services to develop an implementation plan based on those recommendations.

On June 11, 2015, Dr. Kaler and the Board of Regents approved the 'Implementing the Recommendations of the External Review of the University of Minnesota Human Research Protection Program' Work Plan. Within the Work Plan, a recommendation that the University of Minnesota Clinical and Translational Science Institute (CTSI) accelerate the process of assuming management responsibilities of interventional drug and device trials being conducted by the Department of Psychiatry.

In order to understand the best approach for "assuming management responsibilities", CTSI, in consultation with the Interim Department Head for the Department of Psychiatry, determined that conducting an independent assessment of the clinical research currently being conducted by the Department of Psychiatry was necessary. The assessment included meeting with faculty and staff members to obtain feedback regarding past and current research activities and recommendations on future research department activities, as well as, a review of the Research Studies and Clinical Trials being conducted in the Department of Psychiatry. This assessment plan incorporates the steps of the review of the Research Studies and Clinical Trials.

2. Purpose

Understand the Research Studies/ Clinical Trials currently being conducted in the Department of Psychiatry and assess the conduct of the studies compared to the highest ethical and regulatory standards, in order to inform the recommendations for the CTSI management plan.

3. Scope

Review the research studies/clinical trials to evaluate conformance to the requirements, confirm integrity and accuracy of study data, and ensure study subjects safety, rights and welfare are protected. This may include but not limited to adherence with;

- Protocol requirements,
- University of Minnesota (U of M) and Fairview Health Services policies,

- External regulations and requirements.

4. Responsibilities

- Interim Department Head, Department of Psychiatry:
  - Communication with faculty members
  - Provide support and guidance as needed

- Assessor:
  - Request faculty meeting to review listing of current active, approved IRB studies and current status of research studies/clinical trials,
    - Notify faculty and clinical study team of scheduled reviews, at least one week advanced notice
  - Contact faculty member or study team member for clarification or questions,
  - Review research study/clinical trial assessment results with each Principal Investigator (PI) and CTSI.

- Faculty members:
  - Availability to review research studies/clinical trials when PI responsibilities are listed,
  - Availability for questions, clarifications,
  - Review research study/clinical trial assessment.

- Staff members:
  - Availability to provide Assessor with requested documentation,
  - Availability for questions and clarifications during reviews.

5. Assessment Schedule

An IRB "List of Psychiatry Studies" was obtained from, U of M Office of Human Research Protection Program, in August 2015. Studies listed on the report will be review for correctness and assessed for review applicability. The clinical assessments shall be prioritized and scheduled on the basis of faculty/investigator availability and;

- IRB committee review (full, expedited, exempt, non-exempt),
- Interventional or Non-interventional,
- Study type, (medical or social),
- Current status (active, open only for data analysis, inactive, closed),
- Funding (e.g., NIH, Grant, Sponsor)
- Risk level of the research study/clinical trial,

- Feedback or other evidence of possible noncompliance with study or study process,
- Involvement of a particular investigator/faculity member.

With faculty approval and cooperation, the assessments will be conducted by November 1, 2015. Refer to Appendix B for a list of research studies/clinical trials being conducted by the Department of Psychiatry.

6. Protocol/Informed Consent Assessment

The assessment will include evaluating consistency within and between the protocols, informed consents and other study documents.

As a research study/clinical trial progresses, protocols may have undergone changes that would result in required formal amendment approval from either the U of M IRB or Quorum prior to implementation. A review shall be performed to assess consistency between versions of the protocol and informed consent with the exception of those with only administrative changes.

7. Monitoring

Monitoring activities will be assessed for compliance.

Ensure the monitoring plans for applicable studies/trials are in place and contain the appropriate monitoring requirements. Monitoring activity will be assessed to ensure monitoring have been completed according to the monitoring plan.

For those studies not requiring monitoring plans, special consideration will be made to ensure the appropriate data and study information have been reviewed by PI and reported according the applicable requirements.

8. Trial Master File Assessment

The assessment will include a review of the trial master file (TMF) documents against the applicable regulations and requirements.

This assessment shall include study, investigator and subject level TMF records.

9. Research Studies & Clinical Trials Assessments

The Research Studies/Clinical Investigator assessments shall be conducted in the Department of Psychiatry or the research study/clinical trials file locations. If faculty members and study/trial documentation are readily accessible, a standard 2-3 days will be spent on research studies.

Assessment conduction time for interventional trial assessments will be determined by trial start date, number of protocol amendments, type of study, number of subject enrolled and adverse events. These assessments may take up to 5+ days.

An attempt to contact faculty members, who have PI responsibilities, to review study(s)/trials(s) listings and documentation will be made prior to reviewing study/trial documentation. If after three attempts the Assessor has not received faculty response, Interim Department Head, Department of Psychiatry will be notified.

9.1. Pre-Assessment

The Assessor will provide an assessment confirmation date to each faculty member, including the documents which will need to be reviewed, prior to the assessment. These study documents may include but are not limited to the investigational plan/protocol/informed consent template, monitoring plan, monitoring visit reports, monitoring visit follow-up letters, study deviations, serious adverse events, device/drug accountability log enrollment/implant listing and select data listings.

The Assessor will confirm the faculty member and personnel's availability to assist with the assessment process, confirming the availability of study records, answering any questions about the process and during the assessment. Daily debriefs may be provided upon faculty and personnel's availability and request.

The following documents, as applicable to the study/trial, will be requested for review:

- Regulatory Binder including:
  - Clinical Investigational Plan/Protocol
  - Investigator Brochure/Report of Priors
  - Fully executed clinical study or investigator agreement, statement of investigator commitment and/or Form FDA 1572 (PIs and sub-Is)
  - Investigator Acknowledgement of CIP/ Protocol
  - Financial Disclosure for all investigators
  - CVs and medical licenses for all investigators
  - Delegation of Authority Forms
  - Site personnel training documentation
  - Product Accountability Log
  - Monitoring Log
  - IRB approval, initial and continuing review documents, informed consent, recruitment and advertising materials, materials given to subjects, etc.
  - Protocol deviations
  - SAE reports, if applicable

- IND/IDE safety reports, if applicable
- Reports to IRB (SAEs, protocol deviations, annual reports) including correspondence

- Subject CRF binders/eCRF data and Data Clarification Forms/Queries
- Copy of Institutional SOPs (if available)
- Copy of IRB policies and/or reporting requirements

9.2. Assessment Execution

9.2.1. Management Control
The Assessor will evaluate the Clinical Investigator's oversight of the clinical/research study. Also included in this assessment will be an evaluation of written procedures that control the research activities, previous regulatory agency inspection history, delegation of responsibility to personnel, and the monitoring.

9.2.2. Facility Control
The Assessor will review the facility and the equipment used to conduct of the clinical/research study to determine if it adequately meets the protocol requirements. This assessment will include but not be limited to an evaluation of:

- The security and confidentiality of the patient/subject information
- The security and confidentiality of the study records
- The security and confidentiality of the investigational product
- Equipment calibration and maintenance records

The Assessor will verify the acceptability of the equipment necessary for the successful conduct of the study.

9.2.3. Personnel Control
A review will be conducted to assess the qualifications and training of study/trial personnel, including training on the study protocol, clinical regulations and responsibilities of the study/trial.
Any personnel who are delegated responsibilities that could impact subject safety or data integrity should be listed as sub-investigators on the delegation log and on the sub-investigator agreement/Statement of Investigator Commitment Form or the Form FDA 1572.

9.2.4. Subject Safety/Eligibility Control
The Assessor will evaluate the source documentation of the eligibility of the subjects. An evaluation will also be conducted to assure adequate clinical investigator/faculty member oversight of subject safety and if the IRB also

provides adequate oversight.

9.2.4.1. Informed consent process

The Assessor will review the subjects' source records to determine the adequacy of the documentation of the consenting process, if the medical discussion of the consenting process is performed by qualified personnel and appropriately documented by that individual.

9.2.4.2. Subject eligibility

The Assessor will review the subject's source records to confirm documented evidence that subjects met all inclusion criteria and none of exclusion criteria.

9.2.5. Records Control

The Assessor will evaluate the overall records control for the regulatory documents, informed consent documents, and case histories for being attributable, legible, contemporaneous, original, and accurate.

The overall objective of this evaluation is to determine data integrity and the validity of study conduct. The Assessor will compare the Delegation of Authority Forms or assigned responsibilities to the handwriting samples seen in the source records. The Assessor will determine if the signature is dated by the same individual, if the signature is stamped or original, or if the documents are signed and dated by appropriate individual.

9.2.5.1. Regulatory documents

The Assessor will review regulatory documents listed in section 9.1 to confirm key dates and approval status for data verification purposes.

9.2.5.2. Informed consent documents

Informed consent documents (ICs) will be reviewed to determine compliance with regulatory requirements. For interventional trials, the priority of review will first be the informed consent documents of subjects exposed to the investigational product/therapy and then the screen-fail subjects.

The Assessor will determine the overall integrity of the informed consent documents by:

- Determine if correct version of informed consent was utilized.
- Determine if the consenting process was completed in a timely manner for subjects who were re-consented.
- Identify inconsistencies in handwriting on the ICs for the subjects and

site personnel.

- Examine the source records for the reviewed subjects and evaluate if the consenting procedure was performed prior to any study-related procedures (that were not considered standard of care) and that a copy was provided to the subject.
- Determine the presence of documentation of the consenting process including who conducted the medical discussion with the subject or subject's legally authorized representative, that is, explaining the medical risks, medical options, the known potential adverse events, and investigational product/therapy and procedures, if applicable, with the subject.
- Review source documents for translator/interpreter for non-English-speaking subject and ensure the IC used was in the appropriate language approved by the IRB.

9.2.5.3. Case histories

The Assessor will:

- Review subjects records and subjects with serious adverse events and those that exited from the study prior to study completion. This will include case reports forms, source documentation (both electronic and paper), lab tests, protocol deviations and adverse events. Subjects shall be selected from the beginning, middle, and end of enrollment.
- Cross-reference the subject records and verify key endpoint and safety data with sampled subjects until a trend of compliance or noncompliance is established.
- Examine compliance or noncompliance to reporting general adverse events for each subject within the CRFs.
- Determine if the data is supported by source.
- Determine the Clinical Investigator/faculty member's overall involvement in the evaluation of eligibility and safety.
- Determine if there is documented evidence of the Clinical Investigator/faculty member's involvement. Determine if the data is attributable to qualified site personnel who were delegated the responsibility by the Clinical Investigator/faculty member and if they were appropriately qualified and trained.

The Assessor will evaluate if the inclusion and exclusion criteria are supported by documentation in the source records. The Assessor will cross-check against the applicable inclusion/exclusion criteria under which the

subject was enrolled.

The Assessor will determine if a medically qualified investigator/faculty member is evaluating the subjects' adverse events in a contemporaneous manner. The Assessor will determine if evaluation is supported by documented evidence of the qualified investigator/faculty member or a medically-qualified-and-appropriately-delegated sub- investigator's signature and date.

9.2.6. Investigational Product Control

The Assessor will evaluate the qualified investigator/faculty member control of the investigational product, if applicable, including but not limited to receipt, storage, dispensing, accounting, return, and/or destruction.

If applicable, the Assessor will review the process to ensure the chain of custody of the investigational product from time of receipt to return/destruction of used/unused investigational product can be fully reconstructed by documentation on site. The Assessor will:

- Review receipt of the investigational product. The personnel should acknowledge the receipt in a timely manner as well as note the condition of the investigational product, whether the stability or integrity of the investigational product has been assured during the shipment (drug).
- Evaluate the storage condition of the unused investigational product, that it is stored with authorized access only.
- Evaluate if product is adequately tracked at all points of transition from one site storage location to another.
- If applicable, determine if only non-expired investigational product is dispensed to subjects and that expired and unused investigational product is appropriately quarantined (separate from the other unused investigational product) and returned/destroyed per protocol requirements.
- Determine if only eligible subjects are exposed to the investigational product.
- Review the investigational product accountability records to evaluate accuracy of the information.
- Review the investigational product return/destruction documentation to evaluate accuracy of the information.

If applicable, determine if any miss-randomization or unblinding has occurred. If the investigational product is transported to a different location to be

dispensed/implanted, the Assessor will determine whether transportation was approved by the sponsor prior to the transport, that there is a written procedure for the transportation and that there is appropriate documentation to confirm the investigational product is not out of the control of authorized site personnel delegated the responsibility of transporting the investigational product.

9.3. Identified Noncompliance

Critical data integrity or subject safety issues shall be reported to CTSI leadership and Interim Head of the Department of Psychiatry.

9.4. Review Assessment Meeting

The Assessor will review any non-compliances and observations with the Clinical Investigator/faculty member and other site personnel during the assessment and on the last day of the review.

The key objective is to ensure the Clinical Investigator/faculty member and site personnel understand the significance of identified nonconformities so that they can initiate and implement corrective actions to study/trial compliance. The Assessor may offer recommendations for corrective actions; however, the Clinical Investigator/faculty member is responsible for taking corrective action.

Should the Clinical Investigator/faculty member not be available to due to unforeseen circumstances, the Assessor will offer the opportunity to discuss the review noncompliance's within 5 working days of assessment completion.

10. Report Assessment

Following completion of the assessment activities of each study/trial, a report shall be completed identifying assessment observations. A draft report shall be completed and submitted to CTSI management for review and comment. Upon finalization, the report will be submitted to CTSI management for storage in a secure location, separate from the research study/clinical trial records.

11. Definitions

11.1. Noncompliance Rating System

Rating	Definition
Critical	A noncompliance which will likely affect subject safety and/or data integrity and will likely result in inability to use part or all of the clinical data if not immediately corrected.
Major	A noncompliance which may affect subject safety and/or data integrity and may result in the inability to use part of or all the clinical data if allowed to continue and impact the study/process for a long duration.
Minor	A noncompliance which can be corrected immediately and will not affect subject safety and/or data integrity and will not result in the inability to use part of or all of the clinical data.

11.2. Appendix

Appendix	Description
A	Listing of Psychiatry Studies

12. Document Change History

Version	Version Date	Description of and Rationale for Change
1.0	08 Sep 2015	Initial Release

APPENDIX B: DEPARTMENT OF PSYCHIATRY REVIEWED RESEARCH STUDIES & CLINICAL TRIAL

<Due to email size restrictions, this document is attached.>

APPENDIX C: CONDENSED LIST OF INTERVIEW RESPONSES

Faculty Comments - Concerns:

- "We go behind the scenes and fix things up. What people don't know won't hurt them. "
- "Like the time we discovered a PI hadn't signed consents, we fixed the problem."
- "We have to teach people to keep their mouth shut and don't say anything to anyone."
- "Safety Monitoring – None of the trials have a safety board. They have talked about it and tell others they are doing it but don't know how to set one up or don't have the funds. They come to me all the time asking for help but have never actually set one up. "
- "You being here is a threat like in the mid 90's efficiency experts came in and decided who gets fired."
  I could talk for 2 hours but I won't know any more so this is frankly a waste of my time.
- "I hope you can make good changes."
- CTSI – We have not had good experiences: Tried to use them twice for study recruitment. Both times they were enthusiastic and wanted to work with us but dropped the ball both times. We ended up doing it all ourselves.
- "Working with the U of M IRB is very frustrating. They don't seem qualified or know what they are doing. Never can talk with anyone over there that knows or are giving accurate information. "
- "My biggest concern i[redacted]
- This department needs someone who can bring back the quality and excellent research it once had[redacted]
- "It will be very sad and incredibly discouraging[redacted]We need someone from the outside that has integrity, promotes transparency and can stand up to those who have their own agenda."

Faculty and Research Staff Comments - Need for Improvement:

[redacted]supports 4 coordinators that are paid with department funds. 3 of the 4 have nothing to do, there has been no work for them."

- "Concerned about studies are being conducted within the Psychiatry department, outpatient, in-patient."
- "They are all corrupt and self-serving. I am very worried about recruitment and conflict of interest."
- "Don't understand the resistance to being transparent and responding to the State's questions and concerns."
- "Coordinators are expected to write papers and submit manuscripts."
- "Faculty needs to be more mindful of study participants."
- "Department does not allowed to enter a patient's study participation or clinical notes into the EMR system."

- "Need to stress boundaries. There are certain ethical issues."
- "Problems are at multiple levels, we need to implement guidelines and processes."
- "It is very difficult to conduct research here, to many requirements to follow."
- "It is not broke don't fix it."
- "I intentionally moved within 2 miles of here so I can go to patient's homes, meet them in the ER or pick them up off of bridges."
- "Currently, I am ghost writing articles and papers for faculty in the department." When asked for who, [redacted] did not respond.
[redacted] advises people to do things that are against the law. [redacted] are basically the same people." When asked her to provide additional information, [redacted] refused.
- Department needs to put patient safety before recruitment. That is not always being done
- Department is not good at appropriate subject selection
- If IRB would have come in for a surprise audit we would have failed miserably. It took us 6 - 8 weeks to clean things up and prepare.
[redacted] about 80% [redacted]s time, his only responsibility is getting the actually grant money. Otherwise [redacted] was completely hands off.
[redacted] is responsible for overseeing the ARC bu[redacted]y checks in about twice a year and that is when something is going wrong."
- "We worked for 6 - 8 weeks preparing for the IRB audit. If we would have had a surprise audit we would have failed miserably."
- "Before recently we would go into people's home and sometimes that was very scary and unsafe. I would often be afraid."
- "I am very angry abou[redacted] on Wednesday afternoon and was not informed this email would be sent. "
- "It is a difficult department to work in. I have been here for [redacted] and I have been very worried about conflict of interest and enrolling subjects for personal gain for a long time. "
[redacted] completely hands of[redacted]y both assign inexperienced and unqualified people to conduct the majority of the trials."
- "This is a problem across faculty members, enrolling subjects to satisfy research participation and I am concerned it continues. Initially it was because of the pressure we have been getting[redacted]

Faculty and Research Staff Comments - Training:

- "I started and was trained in the mid-80's by others in department exactly how it is done today. No need to improve, we have it right."
- Serious lack of training. Self-taught and nowhere to go and learn.
- CITI, HIPAA, CPR. All the other training is informal. I believe I know everything about research, I don't need further training. (Didn't know what GCPs meant)
- "CITI, HIPAA, CPR. All the other training is informal and not enough. New people come in and they never receive appropriate training but are allowed to oversee clinical studies and trials. Many working way beyond their role, experience and education level. Some PI's never see the patients – the coordinators do everything and they are not qualified."

- "Experienced coordinators train new coordinators – tribal knowledge."
- "Have never been informed of research requirements."
- Inexperienced coordinators are just thrown into projects with no training.
- "Huge problem, if the coordinators don't like doing something or do not understand why they need to do something, they just don't do it. TASCS is a perfect example, they don't like it so they don't do it and things are not billed appropriately."
- "What do you mean by regulations? We don't do those, I work with very vulnerable people, and we can't do that."

Research Staff Comments – Responsibilities:

- [redacted] I do everything a coordinator does; consent subjects, conduct patient assessments, data entry, scheduling and conduct visits, data entry, etc."
- "I do it all. I write protocols, conduct all the research, do MRI scans, diagnostics, data analysis and write manuscripts and publications." – Study Coordinator
- "I am responsible for IRB paperwork, recruitment, phone screening, scheduling, consenting, IQ testing, MRI scans, lap-top games, Spit and UA collection, blood draws, oversee under grads, write annual reports and AE reporting." – Study Coordinator
- "All activities are done by staff members, we manage the grants, resources, design the studies, write all submissions, implement the programs, design all the assessment tools, provide training, manage resources, write the publications/manuscripts, managing all AE and mandated reporting. " – Study Coordinator

Faculty and Research Staff Comments – Recruitment:

- "We never recruit in-patient. We use our out-patient facilities and work with the neurologists who may share flyers with patients."
- "Primarily we recruit while in-patient and start study after discharge."
- "Every morning I go to the In-patient rehab faculty upstairs and approach all new admission to consider enrolling in our study. I place a document, talking about our study, under their door (they all have private rooms)."
- "We have permission from the IRB to look at hospital medical records. If something matches the criteria, we contact the parents."
- "Flyers, Pandora, go upstairs to in-patient department and talk with nurses and parents."
- "We use a mix or both in-patient and out-patient for recruiting subjects and referrals."

Faculty and Research Staff Comments – CTSI:

- "Have used CTSI in the past but they don't have the expertise I need. They seem to be home grown with U of M experience but minimal world or industry experience."
- "CTSI – have hired in the past. People were helpful but not engaged or committed to the project. Very frustrating to a PI."
- "Want you to know that I have used and continue to use CTSI more and more for study support. I have been very happy with their services."
- "Heard a rumor 2 days ago that CTSI will be taking all our support staff. That would be bad. I hope this is only a rumor."

- "I have tried to work with CTSI on a proposal but that was not successful. I would not use CTSI going forward because they don't have the expertise that I need and they are too expensive."
- "Don't want my staff reporting into CTSI."
- "If CTSI thinks they are going to come in and dictate anything done in my department or my staff, they will have a war on their hands."
- "Positives: CTSI has a good mentorship program.
  I could use them for accounting and business needs, staff training and grants management.
  Concern: We have a long legacy of CTSI problems.
  Where I have use them in the past, CTSI doesn't have the expertise needed. When we want help and for what we pay for the services, we expect a high functioning team."
- "I was working with the CTSI team on [redacted] patient recruitment. I was so excited but the project has gone nowhere. Didn't have a plan to recruit minorities. They made great promises and did not deliver, such a disappointment."
- "ClinicTrials.gov – CTSI missed the timelines and forgot to forward me the emails they have received. That is a reflection on me."
- "Services are too expensive."
- "Very relieved after the research meeting today. So good to hear we will continue to have full control over staff. We will continue to hire, determine salaries and provide full work direction."
- "CTSI is an intrusion"
- "Working with CTSI on a very complex trial was excellent."
- "We don't need CTSI. The only reason we are being forced to work with them is because they want to receive an award".
- "They cannot demonstrate they have any knowledge of psychiatry and we don't trust them."
- "From others trying to use their services, CTSI has shown us they are not equipped to handle our type of studies."
- "CTSI does not have the experience and knowledge needed."
- "Things need to change at CTSI if they want this to be a successful. We need people that are more qualified."
- "I think the monitoring and regulatory groups could provide value, if they had more experienced personnel."