March 9, 2016

TO:       Brian Herman, Vice President for Research

FROM:     Debra Dykhuis, Executive Director
           Human Research Protection Program (HRPP)

SUBJECT:  Compass Point Research Report and Review

As a result of the external evaluation of human research protections at the University of Minnesota, a March 2015 resolution passed by the University Board of Regents included a plan to sample additional interventional clinical studies to determine whether ongoing activities are appropriate and consistent with approved protocols.

The University engaged Compass Point Research (CPR), a full-service clinical and translational research management and consulting firm, to conduct a review of 100 active studies with at least one subject currently enrolled. In addition, CPR also was asked to identify and recommend relevant metrics and methodologies in support of UMN’s Post-Approval Review (PAR) program for the ongoing surveillance of investigator compliance.

I have reviewed several drafts of this report to correct grammatical and factual errors. I also discussed the report with CPR to gain more clarity and understanding about their findings. Enclosed is the most recent version of the report from CPR. I believe the report provides valuable information both with respect to their findings and the methodology applied. In addition to the report, I am also providing a list of intended IRB actions based on the report findings.

As always the IRB will move forward with the appropriate actions and we trust that you as the Institutional Official will share the report with the appropriate parties. I believe this report adequately addresses the March 2015 Board resolution and CPR is available to answer any questions you, University Leadership or others may have about the report contents.

Enclosure
Proposed PI Requirement: Require PI to complete a Report Form and Appendix I.

- Critical Finding 1: Appendix I must clearly indicate how capacity to consent is being determined and documented for all potential subjects.
- Critical Finding 2: Require PI to 1) explain the discrepancy between the date the consent was signed by the participant versus the caregiver and individual obtaining consent, 2) provide the date and describe the content of the consent discussion(s) with the subject, and 3) detail a corrective action plan to prevent similar occurrences.
- Critical Finding 3: Require PI to indicate which signature lines were completed. If only the caregiver signature line was completed, the PI should also detail a corrective action plan for obtaining valid consent of the subject in question (i.e. documentation that the caregiver is a LAR) and preventing similar occurrences.
- Critical Finding 4: Require PI to 1) clarify whether the caregiver was notified of the changes, and 2) detail a corrective action plan to prevent similar occurrences.
- Critical Finding 5: None; no institutional requirement.
- Critical Finding 6: Finding is not clearly described and is therefore not actionable.

Proposed IRB Action:

- Recommendations 1-4: The IRB will forward the PI’s completed Report Form and Appendix I to Quorum IRB. The HRPP will take appropriate action based on administrative review of the PI’s response and any determination and recommendations made by Quorum IRB.

Proposed PI Requirement:

- Major Findings 1-4: Request PI complete Report Form detailing: 1) specific circumstances under which prospective consent is being obtained versus in-operative identification of the need for emergent use; 2) what information is being provided post-operatively and how such discussions are documented, and 3) in how many subjects________________________/11.
- Major Finding 5: As this activity was originally reviewed in 2009, it would be appropriate to utilize the 5 Year Renewal Form to capture the scope of current, intended usage and associated processes for prospective consent, emergency use and notification of various parties prior to the time of continuing review (current approval expires 6/23/16). This should be requested at the time the Report Form is requested to ensure the committee has complete information.

Proposed IRB Action:

- The IRB and PI have had an ongoing dialogue regarding__________ use under this protocol. This dialogue was taken into consideration with respect to the proposed action.
- Recommendation 1:________________________ span many multiple medical specialties. Adequate expertise in those specialties, supplemented by appropriate consultations with Milana Solganik, IND/IDE Regulatory Director, should provide sufficient experience and expertise to provide review and oversight of such activities.
Recommendation 3: Information will be sought regarding the PIs current notification processes for see above).
Appropriateness of the remaining recommendation will be determined at the time of IRB review of the requested Report and Renewal Forms.

Proposed PI Requirement:
- Major Findings 1-3: Request PI complete Report Form commenting on current consent practices and affirming that consent documentation is happening in real time. With respect to Finding 2, here is no general requirement that oral presentation of a study be witnessed; as such, no follow-up is warranted. There is no information provided in Finding 3 to reasonably infer that any study intervention may have occurred prior to consent. As such, no follow-up is warranted with respect that finding.
- Minor Finding 1: Advise the PI at the time the Report Form is requested of mechanisms by which to complete files if such documents are not readily available in the current files.

Proposed IRB Action:
- Recommendation 2: The PI will be advised of the expectation for maintaining complete regulatory files.
- Appropriateness of the remaining recommendation will be determined at the time of IRB review of the requested Report Form.

Proposed PI Requirement:
- Minor Findings 1-3: None; event was an off-site/external event.

Proposed IRB Action:
- None.

Proposed PI Requirement:
- Minor Findings 1-2: None; questionnaires are validated.
- Minor Finding 3: PI should review the CITI module for GCP compliance and revise delegation logs accordingly.

Proposed IRB Action:
- Recommendations 1,3: The questionnaire is validated.
- Recommendation 2: HRPP administrative office will strongly urge the PI to review the CITI module for GCP compliance and will advise the PI of the need to revise the delegation log.

Proposed PI Requirement:
- Major Finding 1: As described, the incident does not rise to the level of a promptly reportable event.
• Major Findings 2-3: Request PI complete a Report Form 1) explaining why this event was not previously reported, 2) indicating whether the subject had previously granted approval to send questionnaires to his/her place of employment, 3) detailing a corrective action plan to prevent similar occurrences.

Proposed IRB Action:
• Future investigator and committee education could include discussion of best practices for clarifying the scope of and mechanisms for subject notification or re-consent when required.
• Recommendations 4 and 5: It is noted that the study consent form does already include the consequences of withdrawal, procedures for orderly termination of participation, and a statement regarding provision of new findings.
• Appropriateness of the remaining recommendations will be determined at the time of IRB review of the requested Report Form.

 Proposed PI Requirement:
• Major Findings 1-3: HRPP administrative office will advise the PI of the signature finding and request that the PI complete a Report Form indicating: 1) whether subject [___] was provided a copy of the revised consent, and 2) the corrective action plan for ensuring appropriate reconsent processes and documentation are followed to prevent similar occurrences.

Proposed IRB Action:
• Recommendation 1: The HRPP administrative office will review Policy 701.

This study was inactivated by the PI 1/27/16.

Proposed PI Requirement:
• Critical Findings 1-5: None; due to the length of time since enrollment of the noted subject, the current, inactive status of the study, the reporting requirements in place at the time of the noted deviations (which would not have required prompt reporting), and the history of the study as illustrated through the below noted FDA audit and PI response.
• Minor Finding 1: As this study is now inactive, the PI will be advised of the importance of appropriate use of delegation logs in general.

Proposed IRB Action:
• Audit findings from the FDA’s 10/13/15 review were submitted to the IRB by the PI on 11/3/15 and reviewed by the IRB on 11/19/05. The IRB concluded its review on 1/21/16 without requiring further response.
• Critical Finding Recommendations 1-2: None; given the above considerations, the PI will be advised as a means of general education but no further action will be taken.
• Minor Finding Recommendation HRPP administrative office will advise the PI of the importance of appropriate use of delegation logs in general but action with respect to this study is no longer pertinent.
Proposed PI Requirement:

- Critical Findings 1-5: None; at the time the single subject was treated, there should have been a plan for discussion of the administration. At the time of review of the formal protocol amendment, there should have been IRB discussion regarding the possible need for reconsent based on the new information. As this study is closed to accrual and subjects are being followed only, a reconsideration of the need for reconsent is no longer applicable and will not add to subjects’ understanding of the study or potentially impact their willingness to continue participation.
- Critical Finding 6: None; deviation was appropriately reported.
- Critical Finding 7: None; deviation was appropriately reported.
- Critical Findings 8-9: None; deviations were appropriately reported.
- Critical Finding 10: None; a single instance of a deviation not reported in a timely manner but also not otherwise rising to the level of immediate reporting does not, absent other significant findings of concern, warrant further action.
- Minor Finding 1: None.

Proposed IRB Action:

- Recommendations 1-3: As presented, recommendations are not in line with actual study findings and conduct. A PI always has the right to medically treat a subject as necessary to ensure safety and welfare with notification to the IRB and an adequate, safety-based rationale. The IRB has mechanisms to facilitate reporting and review of requests to do so. The PI should perhaps be reminded more strongly (than reflected in the language used in the IRB’s 3/8/13 letter) of those mechanisms to facilitate faster review. Protocol deviations were all reported appropriately to the IRB. No further action is necessary.
- The HRPP administrative office will ensure that committee education materials currently under development include robust information regarding reconsent assessment.

The IRB is currently seeking additional input from the Institutional Official regarding appropriate action with respect to this investigator’s body of studies.

Proposed PI Requirement:

- Critical Findings 1-4: Request PI complete Report Form 1) clarifying the age range of subjects being enrolled both locally and nationally, and 2) providing the ages of all subjects enrolled to date.
- All findings are reflective of the same incident: enrollment of a subject apparent conflict with the enrollment age range provided in the application. Of note, the application and protocol appear to contain potentially conflicting information regarding the lower age limit for enrollment.

Proposed IRB Action:

- Recommendations 1-2: As noted above, a Report Form reflecting the event was not submitted to the IRB. Appropriateness of the recommendation will be determined at the time of IRB review of the requested Report Form.
• IRB will review the totality of the investigator’s historical and current compliance-related concerns and take appropriate action to ensure human subjects’ protection.

Proposed PI Requirement:
• Major Findings 1-2: None. As indicated by the descriptions provided below, withdrawal and orderly termination information do not appear to be appropriate or necessary for the first two trials (an observational study and a study where the drug involved has a short half life and the protocol does not call out any withdrawal concerns).

Proposed IRB Action:
• Recommendations 1-2: None.

Proposed PI Requirement:
• Major Finding: None; no concerns were raised at the time of review and Appendix I is current.

Proposed IRB Action:
• Recommendations 1-2: None; findings are NA.

Proposed PI Requirement:
• None; see below.

Proposed IRB Action:
• Recommendation: As enrollment appears closed, the PI will be advised of the importance of appropriate use of delegation logs in general but action with respect to this study is no longer pertinent.

Proposed PI Requirement:
• None; transferred to Quorum; Quorum reviewed and approved the study 8/13/15.

Proposed IRB Action:
• Recommendation 1: None.
• Recommendation 2: None; per OHRP guidance, the University of Minnesota is not required to list all external IRBs upon which it may rely for review of human subjects research on its FWA.
Human Research Protection Program
Independent Review of Investigator Compliance
AND
Recommendations for Post Approval Review Program

FINAL REPORT OF REVIEW RESULTS, FINDINGS, OBSERVATIONS & RECOMMENDATIONS
MARCH 9TH, 2016
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EXECUTIVE SUMMARY

A recent and comprehensive external review of the University of Minnesota’s human subjects protections program provided opportunities for improvement related to Institutional Review Board policies, procedures, and practices. Recommendations made by the External Review Panel included expanding methodologies for internal review of investigator adherence with IRB requirements, post IRB approval. Thus, at the request of the University of Minnesota (UMN), Compass Point Research was engaged to conduct an independent review of investigator compliance with 21 CFR part 312 (drugs and biologics), 21 CFR part 812 (medical devices), relevant sections of 45 CFR Part 46 (Office of Human Research Protections), ICH-GCP guidelines, and UMN IRB and institutional requirements for investigator compliance.

Intent and Scope of the Engagement

With the primary intent of identifying unique and systemic opportunities for improvement in investigator compliance, the scope of the engagement allowed for the selection and evaluation of approximately 100 risk-based UMN IRB approved clinical trial protocols with at least one enrolled subject. A secondary goal of the engagement was to identify and recommend relevant metrics and methodologies in support of UMN’s Post-Approval Review (PAR) program for the ongoing surveillance of investigator compliance.

Methodology

In keeping with “Work Plan To Implement the Recommendations of the External Review of the University of Minnesota Human Research Protection Program”¹, a review of investigator compliance was conducted on 92 UMN IRB approved trials that were either actively enrolling or following subjects. Also, consistent with the recommendations of the external review panel, clinical trials were selected based on a relative risk-score or a risk-indicator as defined herein. Subjects selected for review were identified using a modified random sampling methodology. One hundred-eighty seven subjects (187) were selected for review.

Review Results, Findings and Observations

The methodology developed for this engagement aligns with the philosophy that targeted reviews of known or suspected areas of risk provide more effective output for considerations of isolated and systemic issues than limited reviews of diverse populations. Thus, more than minimal risk clinical trials conducted by investigators with the highest risk scores were selected. Clinical trials for investigators with a risk score of 5 or greater were initially selected for review. In addition, investigators with risk indicators were chosen. This included investigators conducting clinical trials requiring IND, IDE or under an HUD, investigators with a recent history of noncompliance with IRB policies, investigators naïve to clinical research, and/or investigators conducting investigator/CTSI sponsored research. Lastly, additional investigators were chosen to ensure the review included multiple service lines and/or therapeutic disciplines. A total of 92 distinct clinical trial protocols with at least one active subject in follow-up conducted by 58 investigators were reviewed.

To fulfill the goal of identifying systemic opportunities for improvement, error frequency rates were determined. Consistent with FDA methodology, frequency rates are based on the total number of “investigations” conducted. This is defined by the number clinical trials with enrolled subjects reviewed by Compass Point Research (reviews limited to the regulatory binder/IRB correspondence

were not included in the sample size). Also consistent with the FDA’s methods, for “investigations” with more than one finding, each finding was identified separately in the total findings. In addition, frequency rates are further delineated to understand the number of investigators, number of protocols and number of subjects with findings. A high level summary of review findings is summarized in the table below.

**Table 1: Summary of Review Findings**

<table>
<thead>
<tr>
<th>Finding Source</th>
<th>Protocol Violations</th>
<th>% Error Rate</th>
<th>Consent Issues</th>
<th>% Error Rate</th>
<th>Documentation In Study Record</th>
<th>% Error Rate</th>
<th>IP Accountability</th>
<th>% Error Rate</th>
<th>IRB Communication</th>
<th>% Error Rate</th>
</tr>
</thead>
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<tr>
<td>Number of Investigators With Finding</td>
<td>5</td>
<td>8.6%</td>
<td>9</td>
<td>15.5%</td>
<td>6</td>
<td>10.9%</td>
<td>3</td>
<td>5.2%</td>
<td>9</td>
<td>15.5%</td>
</tr>
<tr>
<td>Number of Distinct Protocols With Finding</td>
<td>6</td>
<td>6.5%</td>
<td>12</td>
<td>13.0%</td>
<td>10</td>
<td>10.9%</td>
<td>6</td>
<td>6.5%</td>
<td>15</td>
<td>16.3%</td>
</tr>
<tr>
<td>Number of Individual Subjects With Finding</td>
<td>11</td>
<td>5.9%</td>
<td>11</td>
<td>5.9%</td>
<td>6</td>
<td>3.2%</td>
<td>6</td>
<td>3.2%</td>
<td>12</td>
<td>6.4%</td>
</tr>
<tr>
<td>Total Findings Per Category*</td>
<td>14</td>
<td>15.2%</td>
<td>12</td>
<td>13.0%</td>
<td>10</td>
<td>10.9%</td>
<td>6</td>
<td>6.5%</td>
<td>15</td>
<td>16.3%</td>
</tr>
</tbody>
</table>

*Investigators with more than one finding in the same category (i.e., 2 protocol violations for the same subject).

Lastly, comparison of UMN identified findings to published information by the FDA on the frequency of clinical investigator deficiencies may be instructive in confirming systemic opportunities for improvement as well as developing prospective review plans. UMN frequency rates were lower than FDA data, based on post inspection correspondence following 356 domestic inspections initiated in 2014, with the exception of two categories: consent issues and IRB communication.

**Process Improvement Recommendations**

Monitoring activities should focus on preventing or mitigating important and likely sources of error in the conduct, collection, and reporting of critical data and processes necessary for human subject protection and trial integrity. The investigator is at the front-lines of the actual conduct of a clinical trial and is operationally responsible for the protection of research subjects including selection/development of the clinical trials for participation, identification, consenting, screening and enrollment of subjects, compliance with protocol requirements, and the clinical care of the subjects. Thus, investigators are likely sources of error.

Currently, PAR’s monitoring/auditing plan for risk-based reviews are protocol based. Criteria for supplemental compliance reviews are limited to “random or targeted selection” of IRB approved studies. A methodology for assessing, scoring and selecting investigator versus individual protocols for review was employed in this scope of work. Adopting a similar framework for risk assessment for post approval monitoring is recommended.

According to the External Review Report, the PAR program is under resourced in terms of staff. In addition, it may lack the necessary technology and training to effectively promote research compliance. This implies knowing organization issues and monitoring or auditing plans for smaller and more targeted audit investigations. Thus, it is recommended that PAR monitoring of informed consent form completion and documentation of the consent discussion/process as well as IRB communications be considered as priorities for audit planning.

Lastly, implementing a metrics driven approach to the review function requires the ability to track and report activities and results in near real-time. Thus deployment of a database solution is recommended to create statistically valid output such as representative sample size for audit planning, establishing and monitoring error rates over time, trend analyses, and outcomes of PAR initiatives.
INTRODUCTION AND ENGAGEMENT BACKGROUND

Clinical research is an inextricable link between advances in medical research and technology, physician engagement, and quality healthcare delivery. In addition, the conduct of research is integral to the University of Minnesota’s (UMN) mission as “Minnesota’s Research University”².

In October of 2014, the University commissioned a comprehensive independent review and assessment of its human research policies and practices. The external review was logistically managed by the Association for the Accreditation of Human Research Protection Programs (AAHRPP) who assembled a panel of experts with deep content knowledge of human research protections. As part of its charge of examining fundamental components of UMN’s research protections program, post-approval monitoring was assessed. The review team obtained program descriptors, policies, procedures and audits tools for the various monitoring or internal audit functions for human subjects research at UMN.

In 2011, under the direction of the Vice President for Research and the Institutional Review Board (IRB) Executive Committee, the continuing review procedures of the IRB were expanded to include a Post Approval Review (PAR) function. This function is housed within the Human Research Protection Program (HRPP) office, the administrative home of the IRB (Figure 1). The PAR component of HRPP is designed to enhance the oversight of approved research involving human subjects and provide a mechanism for assuring the quality of human subjects research.

Figure 1: Operational Structure of University of Minnesota’s Human Research Protections Program

² https://twin-cities.umn.edu/about-us
The external review panel found PAR policies, procedures, review tools, and sample reports of findings to be “impressive and potentially valuable tools to promote compliance with human subjects protections.” However, the reviewers raised concerns regarding the prioritization methodology for PAR monitoring as no clear process or procedure was delineated for assessing human subjects or organizational risk. Also, the reviewers questioned the effectiveness of the PAR monitoring in addressing concerns about research at Fairview. Thus, the reviewers posed expansion of the monitoring conducted through the PAR program, with specific emphasis on PAR efforts for research conducted at Fairview.

As a result of the recommendations made by the External Review Panel (March, 2015), UMN has implemented a work plan developed by an implementation team made up of faculty, university leaders and external experts. In addition to the strategic intent to strengthen its human research protections, the work plan outlines the steps, timelines and resources needed to address recommendations from the external review. Faculty and staff from across the university, serving as team leads, established specific action plans to address each recommendation and maintain accountability for completion.

To assist in addressing action items related to PAR monitoring, UMN engaged Compass Point Research to conduct an independent review of Investigator compliance with 21 CFR part (312 drugs and biologics), 21 CFR part 812 (medical devices), relevant sections of 45 CFR Part 46 (Office of Human Research Protections), ICH GCP guidelines, and UMN IRB and institutional requirements for Investigator compliance. Additional goals of the engagement were to identify opportunities for systemic process improvement, if applicable, as well as provide recommendations for relevant metrics and risk based prioritization methods for prospective surveillance of investigator compliance.

To achieve these objectives, the scope of work was to independently select and review 100 clinical trials that were either enrolling or following subjects as of the last IRB continuing review. The clinical trials were selected based on a risk scoring methodology described herein. The selected clinical trials were reviewed for the following elements of regulatory and UMN IRB policy requirements and ICH/GCP guidelines:

- Significant and Unanticipated Adverse Event Reporting
- Informed Consent (Form, Documentation and Process)
- Subject Enrollment/Randomization
- Delegation of Authority
- Medical/Clinical Oversight and Management
- Investigational Product (Dispensing, Accountability and Storage)

Following the review of the selected clinical trials, an analysis of findings, corrective action recommendations and suggestions for UMN’s PAR program were to be provided to UMN’s leadership in written format. Given the retrospective nature of the review, the major emphasis of this engagement was to assist HRPP’s resource constrained PAR team to conduct a large number of reviews to evaluate individual investigator risk and provide suggested corrective actions as applicable. In addition, and in keeping with the external review panel’s recommendations, the analysis of findings were also for the intended purpose of providing methodology for identifying human subjects and organizational risk in near real-time to optimize functionality and outcomes of prospective reviews of investigator compliance.

METHODOLOGY

In recent past, human subjects protections and clinical research compliance was a minor component of an institution’s broader compliance auditing/monitoring program. Today, given the regulatory, organizational, and business complexities, the participation in human subjects research is an activity that can no longer be managed reactively or with only periodic auditing focus. However, given this engagement was a retrospective review of investigator compliance, the methodology was designed to reflect outcome orientation, enhance risk identification processes as well as demonstrate an ability for data driven findings to offer valued input to strategic research initiatives.

Virtual Review Preparation
Following the receipt of the External Review Panel’s assessment report of UMN’s Human Subjects Protections Program (HRPP), a detailed action plan was created by an implementation team led by the Vice President for Research and Vice President for Health Sciences. Prior to finalizing the methodology, workflow and review tools for this engagement, the published work plan was reviewed in detail.

The key components of the work plan that are most relevant to the review methodology for this engagement as well as the process improvement recommendations for assisting UMN in maximizing investigator adherence to Institutional Review Board (IRB) policies, governing regulations and protocol compliance are:

- Create opportunities for advanced training in human subjects protections for all individuals involved in human subjects protections including investigators, IRB members and staff, research personnel, and clinical staff on units that conduct research (3.3.2).
- Evaluate whether additional mandatory training requirements, comparable to the new mandatory training for sponsor-investigators, should be implemented. Careful attention should be given to areas of research that are considered to be “high-risk,” including those involving vulnerable populations such as individuals with the potential for limited decision-making capacity (3.3.3).
- Institute a more substantive requirement for advanced level training for investigators and research teams when a determination has been made by the IRB of serious or continuing noncompliance, and develop a mechanism for ensuring compliance with this requirement. (3.3.4).
- Efforts to expand monitoring conducted through the PAR program and/or via the application of its methods to other HRPP monitoring efforts should be considered. Specific emphasis should be placed on increasing PAR monitoring efforts for research conducted at Fairview with an active dialogue with the Fairview staff so that they can be actively engaged in the process (3.3.18).
- Best practices regarding consent and capacity to consent should be introduced and made routine (3.5.2).

Additional actions items in the work plan addressed virtual communication of policies related to post-approval monitoring, including information regarding risk-based selection of protocols for review. Requirements for formal reporting of findings as well as Governance structure for the post-approval review function are also outlined in the work plan.
IRB policies were reviewed via electronic repository at irb.umn.edu. The following policies were considered most relevant to the review methodology:

- IRB Policy 402: Criteria for Approval
- IRB Policy 403C: Minnesota State Law that Affects Research
- IRB Policy 411: Reporting Events Including Unanticipated Problems Involving Risks to Subjects
- IRB Policy 416: Federally Funded Research (DHHS)
- IRB Policy 501: Vulnerable Populations
- IRB Policy 501D: Requirements for Research Involving Children
- IRB Policy 506: Adults Lacking Capacity and/or Adults with Diminished Capacity to Consent
- IRB Policy 603: Transfer of IRB Authority
- IRB Policy 700: Consent Process
- IRB Policy 701: Documentation of General Requirements of Consent
- IRB Policy 800: Principal Investigator Responsibilities
- IRB Policy 800A: Additional Investigator Responsibilities for Federally Funded Research: Department of Defense
- IRB Policy 800F: IRB: Additional Investigator Responsibilities for Federally Funded Research: Food and Drug Administration
- IRB Policy 800G: Investigator Responsibilities for Industry-Sponsored Research: ICH-GCP E6
- IRB Policy 802: Principal Investigator Signature Requirements
- IRB Policy 903: Post Approval Review

Risk Stratification of Clinical Trials
Following the initial review of the work plan and IRB policies an inventory of all IRB approved clinical trials with at least one enrolled subject was requested. The master study selection list was generated by Office for the Vice President of Research (IT Request #68645). OVPR-IT provided a list of 695 clinical trials for which the last submission was continuing review and, on that submission, the investigator reported that the study was active (either enrolling and/or following subjects).

A risk assessment of the list of clinical trials provided was conducted in order to develop a targeted review plan. The methodology described below may also support ongoing prospective monitoring plans to manage risks across clinical trials. Criteria utilized by Compass Point Research for the selection of clinical trials for review employed the following standardized methods:

1. An FDA failure analysis of recent cases of serious scientific misconduct of clinical investigators revealed seriously noncompliant investigators may work on multiple clinical trials for multiple sponsors. Therefore, the initial list of 695 clinical trials was first organized by principal investigator to allow visibility of the number of studies conducted by each investigator that were either enrolling or following subjects at the time of the last continuing review.

2. Each clinical trial was then categorized by minimal risk or greater than minimal risk. The definition of minimal risk referenced is “the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests.” Note that federal regulations only define minimal risk (45 CFR 46.102(i); 21 CFR 56.102(i)). Therefore,

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greater than minimal risk was defined as anything to be above minimal risk. Thus, consistent with commitments the following considerations were evaluated in determining risk category:  

a.) estimates of risk were uniformly applied across the general population and not indexed to the experience of the study population alone;  
b.) the general population standard was defined in terms of healthy persons living in safe environments;  
c.) age-indexed criteria was used for determining the probability and magnitude of harms or discomfort in the daily life of, and in routine medical, psychological, or educational examinations, tests, or procedures of, infants, children, and adolescents (if the Common Rule minimal risk definition remains the default criterion for risk categorization of research involving children);  
d.) the probability and magnitude of harm and discomfort when determining whether research meets minimal risk criteria for domain-specific areas of research was assessed.  

3. Once the clinical trials were categorized by minimal risk or greater than minimal risk, factors that may have the highest likelihood of placing subjects at increased risk were evaluated and scored. Trials in this category consider the relative safety of the investigational product as well as the clinical complexity of the study population. For example, a study of a product that has significant safety concerns, for which there is no prior experience in human clinical trials (e.g., a phase 1 pharmaceutical investigation or a device feasibility study), and/or involves a vulnerable population may require more intensive monitoring to ensure appropriate investigator oversight of subject safety. Therefore, the following items were weighted as a “1” per occurrence in risk scoring for study selection.  

- Clinical trials that determined to be more than minimal risk  
- Clinical trials that are investigator and/or UMN department initiated (minimal/no external oversight)  
- Clinical trials that may include vulnerable subjects  
- Clinical trials that require an IND or IDE  
- Clinical trials that are Phase I  

Subsequently, factors that may have a modest to moderate affect on subject safety were evaluated and weighted as a “0.5” per occurrence:  

- Clinical trials determined to be minimal risk  
- Clinical trials that are Phase II  

Lastly, factors that may create increased organizational risk were also weighted as a “0.5” per occurrence. These items included:  

- Clinical trials that are Federally funded  
- Clinical trial that are funded by UMN Foundation  
- Clinical trials that had more than 20 subjects enrolled at the time of the review  

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6 http://www.hhs.gov/ohrp/archive/irb/irb_chapter3.htm
4. From the initial list, clinical trials requiring an IND and/or and IDE were also categorized. Given that the vast majority of IND and IDE clinical trials are interventional, involve an investigational product and have a higher degree of subject safety concerns, a minimum of 50% of the more than minimal risk clinical trials with an IND or IDE were targeted for review by Compass Point Research.

5. A list of determinations by the IRB of investigator non-compliance was requested and obtained. The risk scoring methodology described above was repeated for the clinical trials contained in the master review list. The investigators with the highest overall risk scores were selected for review.

6. To identify any external regulatory action that may affect review list/strategy, a search of the FDA and OHRP websites for UMN clinical investigators was conducted.

7. A review of ClinicalTrials.Gov by study title and/or investigators was conducted to determine study phase, enrollment numbers for completed trials, verify registrations, identify funding sources, etc. This informed risk scoring as applicable.

8. Lastly, the relative experience of the investigator was considered. Investigators who may lack significant experience in conducting and overseeing investigations, using a novel or innovative medical device or investigational drug were considered for review.

Together, the above steps determined the list of clinical trials for review and relative risk scores of the respective investigators. Hence, as estimated in the scope of engagement, a risk-based selection of 100 studies for targeted review was recommended. The proposed clinical trial review list acknowledged by UMN prior to on-site work.

**Development of Data Collection Instruments for UMN On-Site Review**

To ensure that review efforts were focused on identifying important and likely sources of error in clinical trial conduct for risk mitigation, process improvement and future prevention, the types of data and specific activities required to collect these data were considered. Thus, consistent with FDA’s guidance for risk-based auditing, errors were assessed and prioritized by considering the following:

- the likelihood of errors occurring;
- the impact of such errors on human subject protection and trial integrity;
- the extent to which such errors would be detectable.

Also, prior to finalizing the data collection instruments to be utilized by the on-site reviewers, organizational risks specifically related to investigator responsibilities and protocol compliance were evaluated. Understanding current challenges that may be unique to UMN informed implications of a specific risk area being left unchecked that could manifest itself in a way that impacts brand, affects image, suggests a lack of competency or insufficient institutional controls. In addition, an assessment of how individual risks interrelate enables further delineation of systemic versus localized findings.

The steps used in defining organizational risk and interrelatedness includes *event identification, categorization, prioritization and development of event specific data collection tools*. (Figure 2)

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Figure 2: Organizational Risk Assessment Methods

- Event Identification
  Identify the meaning of each risk event, how it can be tested, and what the impact may be on the institution.
- Categorize each risk event by using a methodology applied to all events
  - Risk and exposure
  - Impact to institution
  - Likelihood of detection
  - Frequency of occurrence
- Using the approved categories, prioritize each risk event before the events are placed into a risk assessment audit plan.

Assemble Identified Risks, Score and Prioritize

Risk Event Identification
In creating the event matrix, potential risk event categories were defined by published metrics on the most common deficiencies during FDA inspections of clinical investigators.8 Risk events were further delineated by specific findings as defined by FDA 483 observations.9 The most common deficiencies and findings included:

- Failure to adhere to investigational plan (21CFR 812.100 / 110(b), 21 CFR 312.60)
  - Subjects were enrolled that did not meet inclusion/exclusion criteria
  - Failure to report serious adverse events or serious adverse device effect
- Failure to obtain proper informed consent (21CFR50.20, 21CFR812.100,110, 312.60)
  - Missing elements of informed consent (21CFR50.25)
  - Consent form is not dated by subject or dated by someone other than subject
- Failure to personally conduct or adequately supervise the clinical trial (21CRF312.60, 2CFR812.100)
  - Employee training, documentation and delegation of authority
  - Lack of documentation of investigator supervision
- Failure to protect the rights, safety and welfare of subjects (21CFR312.60, 21CFR812.100)
  - Protocol deviations for safety monitoring
  - Protocol deviations with procedures to ensure compliance
- Failure to maintain accurate, complete and current records relating to study. 21CFR 812.140 (a), 312.62(b)
  - No source documentation to verify eligibility criteria of enrolled subject
  - Documentation in the “case history” that informed consent was obtained prior to subject participation in the study.
- Study Agent Accountability Records 812.140(a)(2),312.62(a)
  - Drug accountability logs are incorrect, incomplete or missing

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Risk Event Categorization
Risk events were categorized by ranking them based on organizational impact and probability of occurrence and/or detection during the on-site review. Probability of occurrence or detection was determined by: 1) identified gaps and/or discrepancies in UMN IRB policies related to consent process, documentation of general requirements of consent and principal investigator responsibilities; 2) published metrics on most common findings during FDA investigations of clinical investigators\(^{10}\); and, 3) relevant audit and monitoring experience of the reviewers. The External Review Panel report, UMN work plan, monthly reports to the Board of Regents and lessons learned from reputable Academic Medical Centers that have faced recent challenges related to human subjects protections also informed the Organizational impact risk prioritization for UMN.

Prioritization of Risk Events
Following the completion of the above virtual procedures, risk events were prioritized and review elements were determined. Examples of specific review items include:

- Informed Consent Form and Documentation review of:
  - required elements of consent
  - accurate completion of consent form (including assent as applicable)
  - adherence to UMN/FDA/OHRP policies for consenting subjects with diminished capacity or fluctuating capacity to consent
  - documentation of consent process in study or EPIC record

- Regulatory Binder/Trial Master File review of
  - delegation of authority log
  - subject screening and enrollment logs
  - IRB correspondence (approvals, communications, etc.)
  - sponsor correspondence (monitoring letters, safety reports, etc.)

- Protocol Compliance review of:
  - subject eligibility (ie. inclusion and exclusion criteria were met)
  - documentation of completion of protocol required procedures/visits
  - investigator oversight (ie., documentation of randomization, dosing, clinical care, etc.)
  - timely SAE/UAE reporting to IRB and Sponsor as applicable

- Management and Oversight of Investigational Product (IP) review of
  - IP accountability logs, shipping records, etc.
  - storage requirement logs as required by protocol.

Development of Review Tools
Compass Point Research review tools were revised to ensure collection of prioritized items. Tools utilized by reviewer included: (1) informed consent document (required elements); consented subject; enrolled/dosed subject; and, adverse events. Template tools are provided in Appendix III.

\(^{10}\)http://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/UCM438250.pdf
**On-Site Review Methodology**

UMN communicated notice of the upcoming review to selected investigators. On-site reviews were performed by a team of three to four full-time reviewers at various campus and hospital locations beginning October 26, 2015 and ending November 13, 2015.

Once the reviewers were able to determine the availability of the investigator and/or study personnel as well as the study records, screening and enrollment logs were requested to confirm the number of enrolled subjects. A random number generator was then used to select subject records for review within each study.

UMN customized review tools were used by all reviewers. The reviewers completed the forms by systematic evaluation of documents and informal interviews of personnel connected to the administration and conduct of the study. All completed review forms were de-identified, password protected, and provided to the senior project manager for analysis.

**Virtual Review of EPIC Medical Records**

Given the time constraints imposed by the volume of clinical trials requested for review, on-site access to the EPIC records was not feasible. Thus, all review forms were analyzed and a list of subjects for an additional virtual review of their EPIC record was generated. The list was provided to the EPIC access team for inclusion in the authorized remote access workspace. Subjects were selected for EPIC review when additional documentation for key metrics was necessary to supplement study specific source documents. Specifically, the EPIC record was utilized to verify: (1) documentation of informed consent; (2) subject eligibility; (3) appropriate reporting of adverse events affecting subject safety; and, (4) investigator oversight. Access to EPIC for virtual reviews of medical records for select subjects was acquired by an additional reviewer on December 29th, 2015.

Concurrently with analysis of the review tools, obtaining EPIC access, and query generation and feedback among reviewers and HRPP team, the compilation of the results, findings and observations were in progress. Also, recommendations consistent with the UMN established work plan were formulated as specific and general findings were better understood. The timeline of engagement activities are depicted below. *(Figure 3).*

**Figure 3: Timeline of Engagement Deliverables**

![Timeline Diagram](image-url)
Limitations of Methodology and Interpretation of Findings

The stated deliverables of the engagement were to select and evaluate approximately 100 risk-based UMN IRB approved clinical trial protocols with at least one enrolled subject to assess investigator compliance with the IRB approved protocol, IRB policies, and governing regulations. Although risk-scoring for trial selection as well as a review of the prior findings of organizational gaps in human subjects protections were completed, large-scale audits of specific metrics such as this are most effective when there is an inherent and stated knowledge of the key issues.

The design methodology of this engagement can be characterized a retrospective “look-back”, without a defined period. Thus, this review is best described as a non-statistically valid, baseline probe sample of risk-based trials. This type of design is typically utilized when targeting/addressing one specific area of concern, such as informed consent documentation for minors requiring assent. However, by clearly defining metrics and adapting review tools, findings discussed herein may provide insight and direction for further process improvement.

In addition, in assessing the risk profile of each clinical trial, a determination of minimal risk versus more than minimal risk was made by the review team. This decision was made based on described methodology, available information, and prior to on-site review of study documents. The IRB determination of minimal risk versus more than minimal risk was unknown and may be contradictory. Also, the adherence to IRB policy was based on the policies available at the time of review, which may have been revised since the date the action occurred which resulted in the finding. The reviewers did not request or conduct inspections of the IRB regulatory files to clarify inconsistencies or obtain missing regulatory documents identified in the investigator’s study records.

Lastly, it is usual and customary to perform quality checks or re-review of documentation related to critical and major findings and provide provisional findings to investigators. Investigators are then given the opportunity to provide additional documentation and/or explanations of findings prior to making final determinations of non-compliance with FDA, OHRP, GCP/ICH guidelines and/or the institution’s policies. However, given the scope of work, provisional findings are reported based on available documentation at the time of the review.

Development of Process Improvement Recommendations

The intent of this report will serve as a quality support measure. Additional goals of the review are to potentially identify both random and systemic errors occurring during the conduct of clinical trial as well as provide analytical input for real-time post-approval monitoring planning. The metrics driven approach to the risk-based review was designed to offer process improvement recommendations that:

- Provide output that is productive and not punitive in nature;
- Lead to enhanced processes and prescriptive, achievable corrective actions;
- Assist UMN in anticipating future risk, regulatory pressures, and compliance challenges;
- Demonstrate methodology that will allow a shift from conducting routine audits based upon research risk profiles from previous years;
- Provide data that will allow for future engagement and collaboration with UMN leadership and research teams;
- Assist with opportunity analysis rather than respond, look back, and assess failures “after the fact.”
- Provide analytical feedback on metrics, performance, and data.
REVIEW RESULTS, FINDINGS, AND OBSERVATIONS

Conducting clinical studies is a complex endeavor, involving oversight of clinical investigators with respect to the protocol, Good Clinical Practices (GCP), governing regulations, and IRB and institutional policies, during the conduct of a study. The study data that are generated must be of high quality, accurate and evaluable, and collected in a manner that protects the rights, safety and welfare of properly consented trial participants.

Both internal monitoring and auditing/reviewing are necessary to provide synergistic oversight of the overall quality and integrity of the clinical research activity. For the purposes of this scope of service, this summary report represents an independent, review/audit of specific elements of clinical trial conduct as a quality assurance function. As such, this review was not required by Federal regulations, but voluntarily requested by UMN. Therefore, during the course of a regulatory inspection by the FDA and/or OHRP allowing access to review materials, results, findings, and observations is not required.

REVIEW RESULTS—UMN INVESTIGATOR AND TRIAL RISK PROFILES

A master study selection list, generated by Office for the Vice President of Research, contained 695 clinical trials that were either enrolling or following subjects at the last continuing review. Using pivot tables, the clinical trials were divided into 4 research “portfolios”: pediatrics (all), adult psychiatry, adult medicine/surgery, and adult hematology and oncology. These portfolios were further categorized by minimal or more than minimal risk. A total risk score was calculated for each investigator using the methodology described above. Risk scores for each portfolio are incorporated below.

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* Unable to verify prior research experience
** Unable to verify as Coordinating Center
*** No NCT Registration Found
### Table 3: Principal Investigator Risk Score—Adult Psychiatry Research Portfolio

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*NO NCT Found
**UMN CTI acting as Coordinating Center
***UMN Foundation Funded Clinical Trial
****DOD Funded Trial

### Table 4: Principal Investigator Risk Score—Adult Medicine/Surgery Research Portfolio

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**Unable to verify prior research experience
***IDE/Emergency Use Trial

### Table 5: Principal Investigator Risk Score—Adult Hematology and Oncology Research Portfolio

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<td>TOTAL SCORE</td>
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| 15 | 14.5 | 9.5 | 21 | 12.5 | 10.5 | 6 | 6 | 7.5 |
Summary of Risk Based Review List Selection

The methodology developed for this engagement aligns with the philosophy that targeted reviews of known or suspected areas of risk provide more effective output for considerations of isolated AND systemic issues than limited reviews of diverse populations. Thus, more than minimal risk clinical trials conducted by investigators with the highest risk scores were selected. **Clinical trials for all investigators with a risk score of 5 or greater were initially selected for review.** Table 6 below summarizes the risk scores as a rationale for clinical trial selection by investigator.

**Table 6: Risk Score of Investigators Conducting More Than Minimal Risk Trials**

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In addition, all investigators conducting clinical research requiring an IND, IDE and/or an HUD were identified. A delineation of investigator-sponsored versus industry sponsored INDs and IDEs was also performed. Sixty percent (60%) of these identified investigators were selected for review as indicated in the table below.

Table 7: Number of clinical trials requiring IND, IDE and HUDs conducted by investigators.

<table>
<thead>
<tr>
<th>Investigator Name</th>
<th>Investigator IND</th>
<th>Sponsor IND</th>
<th>Investigator IDE</th>
<th>Sponsor IDE</th>
<th>HUD</th>
<th>Totals</th>
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</table>

*Investigators not reviewed during engagement. Consider conducting PAR monitoring for all investigator sponsored IND and SR IDE trials.*
Also, a list of recent IRB determinations of non-compliance was obtained. Risk scoring methodology was applied to ensure unbiased selection of trials for review within this category. From this, the investigators with the two highest risk scores were initially chosen for review.

### Table 8: Risk Score of Principal Investigator with Recent IRB Determination of Non-Compliance

<table>
<thead>
<tr>
<th>Major Risk Criteria (Weight 100%)</th>
<th>0</th>
<th>2</th>
<th>0</th>
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<th>0</th>
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<tbody>
<tr>
<td>More Than Minimal Risk Clinical Trial</td>
<td>0</td>
<td>1</td>
<td>0</td>
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<td>1</td>
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<tr>
<td>Vulnerable Subjects</td>
<td>0</td>
<td>0</td>
<td>0</td>
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<tr>
<td>Investigator/Department Initiated</td>
<td>0</td>
<td>0</td>
<td>0</td>
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<tr>
<td>No. Trials Requiring and IN/ID/DE</td>
<td>0</td>
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<tr>
<td>No. of Phase I Trials</td>
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<tr>
<td>Major Risk Score</td>
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<td>4</td>
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<tr>
<td>Confounding Variable Risk Score (Weight 50%)</td>
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<td>Minimal Risk Trials</td>
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<tr>
<td>No of Phase II Trials</td>
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<td>Confounding Variable Risk Score</td>
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<td>Confounding Variable—Organizational Risk (Weight 50%)</td>
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<tr>
<td>No. of Government Funded Research Projects</td>
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<tr>
<td>No. of Foundation Funded/Internally Supported Research</td>
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<tr>
<td>No. of Clinical Trials with more than 20 subjects enrolled</td>
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<tr>
<td>Confounding Variable—Organizational Risk Score (Weight 50%)</td>
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**TOTAL SCORE** | 1.5 | 6 | 0 | 4.5 | 1.5

*No NCT Registration Found*

Further, a review of FDA and OHRP websites for regulatory inspections, establishment inspection reports, 483s and/or warning letters revealed an inspection of [link] with no findings on 12/12/11.11

An OHRP determination letter of non-compliance was issued to R. Timothy Mulcahy, Ph.D., Vice President, UMN OVPR on November 28, 2012. This determination letter was in reference to the

[link]

After receiving the UMN response to findings, all determinations of non-compliance were documented by OHRP as unproven, with the exception of the UMN IRB-approved consent document for this study failed to include the risk of... required by HHS regulations at 45 CFR 46.116(a)(2). Subsequently, UMN IRB corrected this deficiency and the OHRP letter dated July 8, 2013 confirmed no further action required.12

Lastly, additional confounding variables that may increase the likelihood of risk to subjects or the organization were also considered for review inclusion. Examples included:

- Investigators that may be research naive conducting more than minimal risk research;
- CTSI sponsored multi-center trials;
- Inability to locate NCT registration for interventional, more than minimal risk

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11 [link]
12 [link]
The final list of selected and reviewed trials is attached as Appendix II. Although 100 trials were selected, a total of 97 trials were reviewed due lack of availability of study teams during the review period. In addition, only 92 trials were either actively enrolling or had active subjects in follow-up available for subject record review (e.g. trials closed since last continuing review, all subjects discontinued or completed since last continuing review, etc.), however, regulatory binders/trial master files were reviewed. A total of 187 subject records were reviewed.

**REVIEW RESULTS—AGGREGATE SUMMARY OF INVESTIGATOR FINDINGS**

In an effort to provide an aggregate summary of specific review observations, findings are categorized utilizing the same nomenclature defined by FDA’s Bioresearch Monitoring Program. Thus, findings are defined as:  

- **Protocol violations**
  - enrollment violations
  - failure to follow protocol required steps and instructions
  - violations related to the use of the drug or device

- **Consent**
  - use of a deficient form
  - lack of appropriately signed informed consent
  - not obtaining consent prior to performing a study related procedure

- **Documentation in Study Records**
  - missing documentation
  - discrepant documentation
  - missing correspondence
  - documentation that has been altered

- **IP accountability**
  - discrepancies in product control records
  - lack of control of the receipt, use and disposition of investigational drugs, devices or biologics

- **IRB communication**
  - failure to report adverse events to IRB
  - failure to submit annual progress reports to the IRB
  - failure to obtain IRB approval of consent forms, protocol amendments, advertisements, rating instruments, etc. prior to using

Thus, for a systemic view and comparison purposes with available industry metrics of clinical investigator deficiencies, investigators with identified findings, are classified as above (Table 9). Specific review findings of investigator noncompliance are described in the following section.

---

13 http://sitesolutionssummit.com/wp-content/uploads/2015/10/Podium_An-FDA-Update-on-Clinical-Trial-Site-Inspections_1115-12-pm_10Oct15_FINAL.pdf
Table 9: Summary of Review Findings Categorized by FDA Published Metrics

<table>
<thead>
<tr>
<th>Investigator Name</th>
<th>CATEGORY OF FINDING</th>
<th>Protocol Violations</th>
<th>Consent Issues</th>
<th>Documentation in Study Record</th>
<th>IP Accountability</th>
<th>IRB Communication</th>
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To further identify systemic opportunities for improvement, frequency rates were determined. Consistent with FDA methodology, frequency rates are based on the total number of “investigations” conducted. This is defined by the number clinical trials with enrolled subjects reviewed by Compass Point Research (reviews limited to the regulatory binder/IRB correspondence were not included in the sample size). Thus, our sample size was 92 as described above. Also consistent with the FDA’s methods, for “investigations” with more than one finding, each finding is listed separately in the table above. The frequency rate of investigator related deficiencies identified at UMN are provided in Figure 4.

Figure 4: Frequency Rate of Review Findings of Investigator Related Deficiencies
Lastly, **comparison of UMN identified findings to published information by the FDA on the frequency of clinical investigator deficiencies may be instructive in developing prospective review plans** (Figure 5). The FDA data is based on post inspection correspondence following 356 domestic inspections initiated in 2014. Potential confines to this comparison are: (1) the reviews conducted by Compass Point Research were limited in scope as only a small number of subject records per study were randomly selected for review. Conversely, it is not uncommon for the FDA to conduct a review of 100% of subject records, especially for pivotal trials supporting an IND application; (2) given the volume of reviews conducted by Compass Point Research over a three week period, the time allotted for each review precluded a full investigation of all study related records that an FDA inspection may encompass; and lastly, (3) Compass Point Research targeted reviews were based on a pre-determined investigator risk score versus a general sampling of investigator’s conducting clinical trials at UMN. While the FDA also uses risk-based criteria to guide inspection priorities, for FY 2014, 20% of the audits were referrals (complaints, IRB/Sponsor notifications, internal referrals from branches of Office of Scientific Investigation) which may have inherently higher risk of investigator noncompliance while 80% were data audits to source verify clinical trial results reported by sponsors in support IND applications.15

Figure 5: UMN versus FDA Published Frequency of Investigator Deficiencies

![](http://sitesolutionssummit.com/wp-content/uploads/2015/10/Podium_An-FDA-Update-on-Clinical-Trial-Site-Inspections_1115-12-pm_10Oct15_FINAL.pdf)
REVIEW FINDINGS OF INVESTIGATOR NON-COMPLIANCE

The review findings contained in this report are classified in terms of severity and categorized with respect to impact on specific processes. Specifically, the findings were graded to be critical, major or minor, based on the following definitions:

1.) Critical: conditions, practices or processes that adversely affect the rights, safety or well being of the subjects and/or the quality and integrity of data. Critical observations are considered totally unacceptable. Findings classified as critical may include a pattern of deviations classified as major, poor quality of the data and/or absence of source documents. Fraud belongs to this group.

2.) Major: Conditions, practices or processes that might adversely affect the rights, safety or well-being of the subjects and/or the quality and integrity of data. Major observations are serious deficiencies and are direct violations of GCP principles. Findings classified as major, may include a pattern of deviations and/or numerous minor observations.

3.) Minor: Conditions, practices or processes that would not be expected to adversely affect the rights, safety or well being of the subjects and/or the quality and integrity of data. Findings classified as minor, indicate the need for improvement of conditions, practices and processes. Many minor observations might indicate poor quality and the sum might be equal to a major finding with its consequences.

In addition, prior to assigning a grade, the seriousness/impact (potential or actual) on subject safety and/or data integrity, frequency of occurrence, resolvability, and whether issues had already been identified were considered. For critical and major findings, the relevant Code of Federal Regulations (CFR) references are provided, as applicable.

Principal Investigator:

Psychiatry

A. IRB Study Number:

B. Study Title:

C. Investigator Risk Score:

Critical Findings for

Identified potential failure to obtain informed consent by the use of a written consent form approved by the IRB and signed and dated by the subject or the subject’s legally authorized representative at the time of the consent. [21 CFR 50.27(a)]

Finding 1: Documentation of subject’s capacity to consent was not located in the study records at the time of the review. (Category of Finding: Documentation in Study Record)

Finding 2: The signature date of subject on the informed consent document is more than 5 months after the signature date of caregiver of the subject and person obtaining informed consent. [Subject signed IRB approved informed consent form (Version 3, February 21, 2014) on [____] /14. Caregiver
Finding 3: Although “living with (or has substantial periods of contact with) a caregiver who is willing and able to attend visits when required….” is a mandate of the protocol for study inclusion, caregiver is not required to be the subjects legally acceptable representative. At the time of the review, documentation that the caregiver is also the subject’s legally acceptable representative was not located. Thus, the reviewer was unable to discern if a valid consent was obtained.

Finding 4: A note to file located in the study records states “the participant was verbally notified of the changes in the ICF on [____-14]”. However, there is no indication that the caregiver was also notified of changes in the ICF. (Category of Finding: Documentation in Study Record)

Finding 5: The note to file located in the study records appears to be a scanned signature of a research study team member with no signature date but a typed date of [____-15].

Finding 6: At the time of the review, documentation of the information that was conveyed to the subject that may be relevant to his willingness to continue participation in the trial was not located in the study records.

Observations and Recommendations for [____-____]

Observation 1: Documentation of the consent process was not located in the study records.

Observation 2: IRB/IEC approval date of a main informed consent form is March 21, 2014. However, the footer information on the consent form states “Main Informed Consent” Final Version 4.0, 04 September 14”, which is greater than 5 months after the IRB/IEC approval date.

Observation 3: IRB/IEC approval date for caregiver consent states “pending”. However, footer information on the consent form states “Caregiver Informed Consent, Final Version 3.0 dated 14 October 2014”.

Observation 4: UMN has transitioned IRB oversight for this ongoing study to Quorum Review. Quorum IRB first approved the UMN application for this study on July 13, 2015.

Recommendation 1: Confirm and/or ensure appropriate documentation of subject’s capacity to consent is documented in the study record. This should include ongoing documentation of subject’s ability to understand new information about the trial, especially any potential safety issues.

Recommendation 2: Confirm adherence with IRB Policy 506 (Adults Lacking Capacity and/or Adults with Diminished Capacity to Consent).

Recommendation 3: Confirm and document the relationship of “caregiver” is also the subject’s legally authorized representative, in the event the subject is determined to have diminished capacity to consent.

Recommendation 4: Perform live consent monitoring for future re-consent of this subject.
UMN IRB Policy References Relevant to this Finding

[University of Minnesota IRB Policy 500: Principal Investigator Responsibilities—PIs whose research involves human subjects are responsible for ensuring that informed consent is obtained from each subject or the subjects legally authorized representative, unless waived by the IRB.]

[University of Minnesota IRB Policy 800G: Additional Investigator Responsibilities for Industry Sponsored Research: ICH-GCP E6 (1.8.2 and 1.8.12) ……The subject or the subject’s legally acceptable representative should be informed in a timely manner if new information becomes available that may be relevant to the subject’s willingness to participate in the trial. The communication of this information should be documented.]

[University of Minnesota IRB Policy 800G: Additional Investigator Responsibilities for Industry Sponsored Research: ICH-GCP E6 (1.8.12). When a clinical trial (therapeutic or non-therapeutic) includes subjects who can only be enrolled in the trial with the consent of the subject’s legally acceptable representative (e.g., minors, or subjects with severe dementia), the subject should be informed about the trial to the extent compatible with the subject’s understanding and, if capable, the subject should sign and personally date the written informed consent.]

Principal Investigator:

Surgery

A. [ ] 3
B. Study Title:
C. Investigator Risk Score:

Major Findings for

Identified potential violation of IRB Policy 702: Waiver or Alteration of the Informed Consent Process. The IRB reviews and documents a waiver or alteration of informed consent by reviewing the application submitted by the researcher, deliberating and determining that the criteria for the waiver is met and justified according to the research. It should be noted that only the IRB may determine when a waiver is acceptable. No independent decision by an investigator to waive consent is permitted.

Finding 1: [ ] IRB approval is required, with the exception of emergency use. Although [ ] do not require consent, the UMN IRB made the determination to require informed consent prior to use. The investigator failed to obtain informed consent [ ] (Category of Finding: Consent Issue X 3)

Finding 2: The investigator notified the IRB of the failure to obtain informed consent and requested a “waiver” of the consent requirement. The IRB declined this request and made the determination that consent can reasonably be obtained [ ] Regulatory documents in the study records identified communication to the IRB in which the investigator acknowledged consent requirement and confirmed that he would obtain consent.

Finding 3: The investigator again disclosed failure to obtain informed consent to the IRB. At the time of the review, further action or communication from the IRB was not located in the study records. (Category of Finding: IRB Communication)

Finding 4: At the time of the review, no documentation [ ] (Category of Finding: Documentation in Study Record x 3)
Finding 5: Study records state FDA has made a determination of safety and probable benefit for

FDA recommends that the physician obtain informed consent from the subject and ensure that reasonable subject protection measures are followed, such as devising schedules to monitor the subject, taking into consideration the subject's specific needs and the limited information available about the risks and benefits. FDA further recommends that the physician submit a follow-up report on the subject's condition first check with the IRB.

Observations and Recommendations for

Observation 1: The reviewer verified documentation of IRB approved informed consent for 13 subjects.

Recommendation 1: Ensure the IRB has among its members (or consultants) the appropriate experience and expertise to perform a complete and adequate review.

Recommendation 2: Review IRB Policy 408: Managing Allegations of Non-Compliance with IRB Policies and Procedures to ensure violations of IRB policy 702 do not constitute serious non-compliance and/or continuing non-compliance in which further action may be required.

Recommendation 3: 

FDA references relevant to these findings
[21 CFR 814.124(a): IRB approval. The HDE holder is responsible for ensuring that a HUD approved under this subpart is administered only in facilities having an Institutional Review Board (IRB) constituted and acting pursuant to part 56 of this chapter, including continuing review of use of the device. In addition, a HUD may be administered only if such use has been approved by the IRB located at the facility or by a similarly constituted IRB that has agreed to oversee such use and to which the local IRB has deferred in a letter to the HDE holder, signed by the IRB chair or an authorized designee. If, however, a physician in an emergency situation determines that approval from an IRB cannot be obtained in time to prevent serious harm or death to a subject, a HUD may be administered without prior approval by the IRB located at the facility or by a similarly constituted IRB that has agreed to oversee such use. In such an emergency situation, the physician shall, within 5 days after the use of the device, provide written notification to the chairman of the IRB of such use. Such written notification shall include the identification of the subject involved, the date on which the device was used, and the reason for the use.]

[21 CFR 814.124: A physician must report the emergency use within five days; provide written notification of the use to the IRB chair person including identification of the subject involved, the date of the use, and the reason for the use.]
Potential failure to obtain informed consent which shall be documented by the use of a written consent form approved by the IRB and signed by the subject or the subject's legally authorized representative. [45 CFR 46.117]

Finding 1: A consent note states that [ ] was contacted by telephone on [ ] to discuss the study. The consent form and research authorization form were then mailed to the prospective subject. The signed study consent and HIPAA authorization forms were returned to the research coordinator on [ ] 2010 with a subject signature date of January 05, 2010. The study coordinator signed and dated on [ ] 2010 as the person conducting consent discussion. Correspondence and/or documentation from the IRB approving the use of telephone consent procedures was not located at the time of the review.

Finding 2: At the time of the review, no documentation was found to confirm the presence of a witness during the oral presentation of the study. (Category of Finding: Consent Issue)

Finding 3: The subject was randomized on [ ] 2010 to the interventional arm of the study vs. the standard of care group. It is difficult to confirm from the study record that no study related procedures occurred prior to receiving the signed subject informed consent form, as according to note in study record, the individual obtaining consent signed 2 days after receiving the consent, via mail, from the subject.

Minor Findings for
Potential violation of IRB Policy 800: Principal Investigator Responsibilities

Finding 1: There are 10 versions of the protocol with 4 of the revisions occurring prior to enrollment of the first subject. The chain of IRB correspondence and action on each submitted amendment and the corresponding informed consents are missing from the study records (regulatory binder/trial master file). (Category of Finding: Documentation in Study Record)

Observations and Recommendations for

Observation 1: IRB policies for obtaining and documenting consent via telephone are not well defined.

Recommendation 1: Consider IRB policy revision or providing additional guidance to investigators regarding the requirements for obtaining and documenting informed consent via telephone or other proxy methods.
Recommendation 2: Encourage study team to obtain all versions of the IRB protocol and informed consent form and any other applicable regulatory documents and maintain in an organized and easily retrievable manner for future review and/or reference.

**UMN IRB Policy Reference Relevant to this Finding**

[IRB Policy 700: The Consent Process: In reviewing a proposed research study, the IRB determines if the setting, timing, and procedures for soliciting informed consent are acceptable and whether the consent process should be monitored. The IRB should know the nature and circumstances of the consent process, and determine whether the consent process meets the regulatory criteria for approval (45 CFR §46.116 and in 21 CFR §50.20).]

[IRB Policy 800: Principal Investigator Responsibilities The PI is required to ensure that copies of all amendments, advertisements, consent documents, and IRB communication documents, are in the researcher’s study files.]

**OHRP references relevant to these findings**

[A written consent document that embodies the elements of informed consent are required by §46.116. This form may be read to the subject or the subject’s legally authorized representative, but in any event, the investigator shall give either the subject or the representative adequate opportunity to read it before it is signed; or A short form written consent document stating that the elements of informed consent required by §46.116 have been presented orally to the subject or the subject’s legally authorized representative. When this method is used, there shall be a witness to the oral presentation.]

**Principal Investigator: |**

A. IRB Study Number: |
B. Study Title: |

C. Investigator Risk Score: |

**Minor Findings for**

**Potential violation of IRB Policy 411: Reporting Events Including Unanticipated Problems Involving Risks to Subjects or Others (UPIRTS0)**

Finding 1: Per the study record, a death occurred on a study subject during active trial participation on [__] 12. The investigator became aware of the death and filed an initial report determined the death to be “NOS” and possibly related to study treatments on [__] 12. Additional information and/or documentation of a written report to the IRB to provide further details regarding this unanticipated problem involving risks to subjects was not located during the review. *(Category of Finding: IRB Communication)*

Finding 2: The investigator signed the initial report on [__] /12 (reference [_______________]) and the IRB reviewed and acknowledged the submission on [__] /12. A final report was not located during the review. *(Category of Finding: IRB Communication)*

Finding 3: Observation: The investigators made the determination that the subject’s death was possibly related to study treatments. Rationale for this causality was not located in the study record at the time of review.

**Recommendations for**


Recommendation 1: Although IRB procedures were outside the scope of this engagement, a review of the policy regarding UPIRTSO reporting should be considered to ensure prompt receipt of adequate documentation of the event is available, following the initial report meeting the timeline specifications, for IRB determination of subject safety.

Recommendation 2: Provide further education to investigator regarding documentation of unanticipated problems and rationale for causality in the study/medical record as well as requirements for prompt filing of required supporting materials.

**UMN IRB Policy References Relevant to this Finding**

[UMN IRB Policy 411: Reporting Events Including Unanticipated Problems Involving Risks to Subjects or Others (UPIRTSO) Researchers must promptly report to the IRB unanticipated problems that may involve risks to subjects or others. Reports must be submitted to the IRB within five (5) working days of knowledge of the event.]

**OHRP references relevant to these findings**

[The HHS regulations at 46.103(b)(5) require written procedures for ensuring prompt reporting of unanticipated problems to the IRB, appropriate institutional officials, any supporting department or agency head (or designee), and OHRP. The purpose of prompt reporting is to ensure that appropriate steps are taken in a timely manner to protect other subjects from avoidable harm. The regulations do not define prompt. The appropriate time frame for satisfying the requirement for prompt reporting will vary depending on the specific nature of the unanticipated problem, the nature of the research associated with the problem, and the entity to which reports are to be submitted. For example, an unanticipated problem that resulted in a subject’s death or was potentially life-threatening generally should be reported to the IRB within a shorter time frame than other unanticipated problems that were not life-threatening. Therefore, OHRP recommends the following guidelines in order to satisfy the requirement for prompt reporting: Unanticipated problems that are serious adverse events should be reported to the IRB within 1 week of the investigator becoming aware of the event.]

**Principal Investigator:**

A. IRB Study Number:

B. Study Title:

C. Investigator Risk Score:

**Minor Findings for**

Finding 1: There is no documentation found in the investigator file that the IRB reviewed or approved the “Reported Outcomes Questionnaire” administered to Subjects. *(Category of Finding: IRB Communication)*

Finding 2: The Investigator name and contact information is absent from the Reported Outcomes Questionnaire administered to Subjects. It appears this information was never completed on the template form and submitted for IRB approval.

Finding 3: One delegation of authority log was used by more than one principal investigator as the principal investigator changed during the conduct of the trial. Authorization signatures are crossed out, and multiple signatures and dates are present in the fields of the form. In addition, multiple corrections are made to the task sections of the form and corrections are not dated. Thus, the reviewer was unable to determine delegation and/or appropriateness of assigned duties to study team members. *(Category of Finding: Documentation in Study Record)*
Recommendations for

Recommendation 1: Confirm the Reported Outcomes Questionnaire is a commercially available validated instruments cited in the protocol that is used without modification and thus does not require unique approval and/or be listed individually as an approved item on the IRB approval letter.

Recommendation 2: Complete a delegation of authority log for current investigator and study team members according to ICH/GCP guidelines.

Recommendation 3: Consider revising Reported Outcomes Questionnaire to include name and contact information of the investigator as provided in the template document.

ICH/GCP/Ibid Guidance reference relevant to these findings

[ICH/GCP 4.4.1. Before initiating a trial, the investigator/institution should have written and dated approval/favorable opinion from the IRB/IEC for the trial protocol, written informed consent form, consent form updates, subject recruitment procedures (e.g., advertisements), and any other written information to be provided to subjects.]

[ICH/GCP 4.3.1 The investigator should ensure that any individual to whom a task is delegated is qualified by education, training, and experience (and state licensure where relevant) to perform the delegated task.

[Ibid. 4.1.5 The investigator should maintain a list of the appropriately qualified persons to whom significant trial-related duties have been delegated. This list should also describe the delegated tasks, identify the training that individuals have received that qualifies them to perform delegated tasks.]

Principal Investigator:

A. 

B. Study Title:

C. Investigator Risk Score:

Major Findings for

Potential violation of 45 CFR 45.116 subjects right to withdraw from research at any time.

Finding 1: According to study records, a subject discontinued participation in the clinical trial due to relapse of his clinical condition. Subsequently, a new ICF was mailed to subject advising of new safety information. Per a note in the study record, the subject stated he did not understand why he was presented with ICF when he was no longer on study, and didn't want to sign because he felt he would be giving up his rights. The study coordinator advised the subject that new ICF was to inform him of new safety information, but she would document the subject received the ICF and did not wish to sign the revised ICF.

Finding 2: According to the study records, the study team sent follow-up questionnaires via fax to the subject's place of employment after subject's discontinuation from the study and refusal to sign revised informed consent form. (Category of Finding: Protocol Violation)
Finding 3: Documentation of IRB report of subject’s concern and/or the protocol violation was not study records. (Category of Finding: IRB Communication)

Recommendations for

Recommendation 1: Ensure study related procedure for termination and/or subject discontinuation were followed.

Recommendation 2: Provide further guidance to investigator and study team regarding subject’s right to withdraw consent versus requirement for providing ongoing safety updates through revisions to the informed consent.

Recommendation 3: Ensure no further requests are made to obtain protocol required information from study subject, unless the subject voluntarily consents for further participation.

Recommendation 4: Review IRB approved informed consent and ensure the consent describes consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject.

Recommendation 5: Review IRB approved informed consent and ensure the consent contains a statement that significant new findings developed during the course of the research which may relate to the subject’s willingness to continue participation will be provided to the subject.

OHRP references relevant to these findings
[Subjects have the right to withdraw from (i.e., discontinue participation in) research at anytime (45 CFR 46.116(a)(8)). If a subject decides to withdraw from all components of a research study, the investigator must discontinue all of the following research activities involving that subject’s participation in that study (45 CFR 46.116(a)(8));]

OHRP required elements of Informed consent most relevant to these findings:
[(4) The consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject;
(5) A statement that significant new findings developed during the course of the research which may relate to the subject's willingness to continue participation will be provided to the subject]

Principal Investigator: [________________________] Department of Pediatrics,

A. IRB Study Number: [______]
B. Study Title: [________________________]  
C. Investigator Risk Score: [________________________]

Major Findings for

Finding 1: A revised IRB approved informed consent form was signed by subject [______] but the person conducting the re-consent discussion failed to sign or date the subject informed consent form. (Category of Finding: Consent Issue)

Finding 2: No documentation of the re-consent discussion to confirm the subject’s understanding of the new information provided that required a revision to the informed consent or the subject’s desire to
continue participation was located in the study record. *(Category of Finding: Documentation is Study Record)*

Finding 3: No documentation that subject was provided a copy of the revised informed consent form was located in the study record.

Observations and Recommendations for

Observation 1: Original and revised informed consent forms were signed by both the subject and the individual conducting the consent discussion for the reviewed subjects.

Observation 2: IRB policy 701: Documentation and General Requirement of Consent states “the FDA requires the signing and dating of the consent form document by the participant as well as the individual obtaining consent.

Recommendation 1: Consider revising IRB policy 701 to clarify UMN IRB’s requirement of the person conducting the consent discussion to sign and date the consent document. By regulation, FDA and OHRP do not require the person conducting the consent discussion to sign and date the consent document.

*FDA references relevant to these observations and findings*

[21 CFR 50.27(a) Except as provided in § 56.109(c), informed consent shall be documented by the use of a written consent form approved by the IRB and signed and dated by the subject or the subject's legally authorized representative at the time of consent. A copy shall be given to the person signing the form.]

[45 CFR 46.117: Except as provided in paragraph "c" of this section, informed consent shall be documented by the use of a written consent form approved by the IRB, and signed by the subject or the subject's legally authorized representative. A copy shall be given to the person signing the form.]

**Principal Investigator:**

______________________________ Department of Pediatrics, ________

A. IRB Study Number:  
B. Study Title:  

C. Investigator Risk Score:

*Potential failure to ensure that the investigation was conducted according to the investigational plan [21 CFR 312.60].*

*Potential failure of the investigator to assure that he or she will promptly report to the IRB all changes in the research activity and all unanticipated problems involving risk to human subjects or others, and that he or she will not make any changes in the research without IRB approval, except where necessary to eliminate apparent immediate hazards to human subjects [21CFR312.66].*

*Potential failure to personally conduct or supervise the clinical investigations [21 CFR 312.60].*

Critical Finding for
Finding 1: __________________________ prior to conducting required laboratory procedures for study entry. (Categories of Findings: Consent Issue, Protocol Violation)

Finding 2: ____________________________ is not allowed per study protocol. (Category of Finding: Protocol Violation)

Finding 3: ____________________________ lab draw for safety monitoring was not completed. (Category of Finding: Protocol Violation)

Finding 4: ____________________________ was calculated on incorrect weight ____________________________.
   This was corrected on the fifth day of dosing. (Categories of Findings: Protocol Violation, IP Accountability)

Finding 5: Documentation of IRB correspondence related to protocol violations was not located in the study record during the review. (Category of Finding: IRB Communication)

Observations and Recommendations for ____________________________

Recommendation 1: Ensure protocol violations have been reported to the IRB and appropriate actions have been taken.

Recommendation 2: Date of initial IRB approval was 6/13/06 and these findings reference subject _______. Consider further monitoring of additional subjects.

FDA references relevant to these observations and findings
[21 CFR 312.50 An investigator is responsible for ensuring that an investigation is conducted according to the signed investigator statement, the investigational plan, and applicable regulations: for protecting the rights, safety, and welfare of subjects under the investigator’s care; and for the control of drugs under investigation.]

21 CFR 312.66 The investigator shall also assure that he or she will promptly report to the IRB all changes in the research activity and all unanticipated problems involving risk to human subjects or others, and that he or she will not make any changes in the research without IRB approval, except where necessary to eliminate apparent immediate hazards to human subjects.]

Minor Findings for ____________________________

Finding 1: One delegation of authority log was used by more than one principal investigator as the principal investigator changed during the conduct of the trial. The first investigator of this trial was ____________________________.

   There are multiple authorization signatures, corrections that are not signed and dated and multiple corrections are made to the task sections of the form. Thus, the reviewer was unable to determine delegation and/or appropriateness of assigned duties to study team members. (Category of Finding: Documentation in Study Record)

Observation and Recommendations for ____________________________

Observation 1: This clinical trial was audited by ____________________________.
However, no documentation related to the outcome of these inspections was located in the study record.
Recommendation 1: Complete delegation of authority log for current investigator and study team members according to ICH/GCP guidelines.

Recommendation 2: If applicable, review correspondence from FDA inspection related to the approval If any findings requiring corrective actions were required, ensure maintained and sustained.

ICH/GCP/Ibid Guidance reference relevant to these findings

[ICH/GCP 4.3.1 The investigator should ensure that any individual to whom a task is delegated is qualified by education, training, and experience (and state licensure where relevant) to perform the delegated task.

[Ibid, 4.1.5 The investigator should maintain a list of the appropriately qualified persons to whom significant trial-related duties have been delegated. This list should also describe the delegated tasks, identify the training that individuals have received that qualifies them to perform delegated tasks.]

Principal Investigator: _____________________________________________________________________________

A. IRB Study Number: _____________________________________________________________________________
B. Study Title: ________________________________________________________________________________
C. Investigator Risk Score: _______________________________________________________________________

Potential failure to ensure that the investigation was conducted according to the investigational plan [21 CFR 312.60].

Potential failure of the investigator to assure that he or she will promptly report to the IRB all changes in the research activity and all unanticipated problems involving risk to human subjects or others, and that he or she will not make any changes in the research without IRB approval, except where necessary to eliminate apparent immediate hazards to human subjects [21 CFR 312.66].

Potential failure to personally conduct or supervise the clinical investigations [21 CFR 312.60].

Critical Findings

Finding 1: The investigator implemented changes contained in a pending protocol amendment (amendment 6) before receiving IRB approval for this version of the protocol. The amendment allowed for [ ] Prior versions of the IRB approved protocol [ ] (Category of Finding: Protocol Violation)

Finding 2: Version 5 of the IRB approved informed consent form does not discuss the risk of a [ ] (Category of Finding: Consent Issues)

Finding 3: The investigator submitted a written request to the IRB for a protocol deviation to allow for [ ] The subject was treated with [ ] 13.
Finding 4: Correspondence from the IRB to the PI dated March 6, 2013 asks the investigator to confirm if ‘the planned treatment deviation’ had been completed. A continuing review form later submitted by the PI states that “a deviation was requested on February 18, 2013 and was approved by the IRB on April 26, 2013.” (Category of Finding: IRB Communication)

Finding 5: Documentation of IRB approval of the protocol amendment or “planned treatment deviation” was not located in the study records at the time of the review. (Category of Finding: IRB Communication)

Finding 6: Two subjects were treated with the wrong starting dose in and again in before the error was detected. The deviation memo stated “the investigator was informed of the dosing error”, indicating he was not aware of the protocol deviations. (Categories of Findings: Protocol Violation X 2; IR Accountable X 2)

Finding 7: According to the protocol, treatment

Finding 8: Protocol deviations were identified during an audit on approximately 4/7/2015.

Finding 9: Deviations were classified by the investigator as minor/not affecting the safety of the subject. A deviation form was completed and reported to the IRB 4/7/2015.

Finding 10: Protocol requires treatment to be held for On subject was given treatment 12. Protocol deviation was identified by “nurse” and reported to the IRB on 1/18/12. (Category of Finding: Protocol Violation)

Minor Findings for

Finding 1: There is no evidence that a corrective action plan designed to prevent recurrence was implemented. (Category of Finding: IRB Communication)

Recommendations for

Recommendation 1: Require additional human subjects protections training for this investigator and his study team.

Recommendation 2: Consider requiring additional training on ICH/GCP guidelines to ensure further understanding of required supervision of personnel to whom tasks are delegated.

Recommendation 3: Conduct further and ongoing post-approval review of research activities for this investigator and study team to assist in safeguarding subjects, providing proactive opportunities for continued learning and mitigate organizational risk.
IRB Policy reference to these observations and findings
[IRB Policy 800: Principal Investigator Responsibilities: PIs must request approval for all amendments to or modifications of the research proposal, including the consent form, to the IRB prior to initiating the changes except when necessary to eliminate apparent immediate hazards to the subject.]

ICH/GCP/Ibid Guidance reference relevant to these findings
[ICH/GCP 4.3.1 The investigator should ensure that any individual to whom a task is delegated is qualified by education, training, and experience (and state licensure where relevant) to perform the delegated task.

[Ibid, 4.1.5 The investigator should maintain a list of the appropriately qualified persons to whom significant trial-related duties have been delegated. This list should also describe the delegated tasks, identify the training that individuals have received that qualifies them to perform delegated tasks.]

FDA references relevant to these observations and findings
[21CFR312.66 The investigator shall also assure that he or she will promptly report to the IRB all changes in the research activity and all unanticipated problems involving risk to human subjects or others, and that he or she will not make any changes in the research without IRB approval, except where necessary to eliminate apparent immediate hazards to human subjects.

[21CFR312.60 An investigator is responsible for ensuring that an investigation is conducted according to the signed investigator statement, the investigational plan, and applicable regulations; for protecting the rights, safety, and welfare of subjects under the investigator’s care; and for the control of drugs under investigation.]

Principal Investigator:

Neurology
A. IRB Study Number:______________________________
B. Study Title:______________________________
C. Investigator Risk Score:______________________________

Critical Findings for:______________________________

Potential failure to ensure that the investigation obtain documented approval/favorable opinion from the IRB/IEC of an amendment prior to implementing changes to the IRB approved investigational plan.

Finding 1: The investigator indicated in the protocol submission application that he intended to enroll subjects ______________________________ (Categories of Findings: Protocol Violation; IRB Communication)

Finding 2: The investigator documented that the subject ______________________________

Finding 3: According to the study record, the study subject ______________________________ required by the protocol.

Finding 4: Blood draws were performed on the study subject as required by the protocol.

Recommendations for:______________________________
1. Provide additional education regarding IRB policy 800

2. Confirm investigator reported protocol deviation to the IRB and appropriate actions were taken.

**IRB Policy reference to these observations and findings**
[IRB Policy 800: Principal Investigator Responsibilities: PIs must request approval for all amendments to or modifications of the research proposal, including the consent form, to the IRB prior to initiating the changes except when necessary to eliminate apparent immediate hazards to the subject.]

**ICH/GCP/Ibid Guidance reference relevant to these findings**
[ICH/GCP 4.5.2 The investigator should not implement any deviation from, or changes of, the protocol without agreement by the sponsor and prior review and documented approval/favorable opinion from the IRB/IEC of an amendment, except where necessary to eliminate an immediate hazard(s) to trial subjects, or when the change(s) involves only logistical or administrative aspects of the trial (e.g., change of monitor(s), change of telephone number(s).]

[ICH/GCP 4.5.3 The investigator, or person designated by the investigator, should document and explain any deviation from the approved protocol.]

**Principal Investigator:**

Department of Pediatrics, ______

A. IRB Study Number:
B. Study Title:
C. Investigator Risk Score: ______

**Principal Investigator:**

A. IRB Study Number:
B. Study Title:
C. Investigator Risk Score: ______

**Principal Investigator:**

Department of Medicine,

A. IRB Study Number:
B. Study Title:
C. Investigator Risk Score: ______

Major Finding for:

Finding 1: An explanation regarding the consequences of a subject’s decision to withdraw from the research was not found in the subject’s informed consent form as reasonably appropriate for the these trials. *(Category of Finding: Consent Issues)*

Finding 2: Procedures for orderly termination of participation by the subject was not located in the informed consent for these studies but are likely appropriate for these studies.
Observations and Recommendations

Observation 1: Given that 2 of the 3 trials are placebo controlled, conducted under an IDE, investigator initiated, and/or the severity of the clinical status of the study subjects, this finding is conditionally considered a major finding.

Recommendation 1: Review appropriateness of including consequences of subject’s decision withdraw and/or procedures for orderly termination of participation.

Recommendation 2: If inclusion of these items is deemed “reasonably appropriate” by the investigator or IRB, revise informed consents forms and obtain IRB approval for subject re-consent of additional safety information.

FDA reference relevant to these observations and findings
[21CFR50.25 (b) Additional elements of informed consent. When appropriate, one or more of the following elements of information shall also be provided to each subject: The consequences of a subject’s decision to withdraw from the research and procedures for orderly termination of participation by the subject.]

IRB Policy reference to these observations and findings
[IRB Policy 701: Documentation and General Requirements of Consent—Additional information items which may be included on the consent form when applicable are as follows: Consequences of discontinuing participation and procedures for orderly termination of participation.]

Principal Investigator: ________________ Pediatrics, _________

A. IRB Study Number: ________________
B. Study Title: ________________
C. Investigator Risk Score: ______

Major Finding for ________________

Finding 1: The continuing review report located in the investigator regulatory file is missing Appendix 1. Vulnerable Populations and Additional Considerations. (Categories of Finding: IRB Communication; Consent Issues)

Observations and Recommendation for ________________

Observation 1: Given that this trial limited external oversight and thus, poses inherent subject safety and organizational risk, this is conditionally considered a major finding.

Recommendation 1: Although review of documentation maintained in the IRB study files is outside the scope of this engagement, consider ensuring investigator’s methods for ensuring additional safeguards of potentially vulnerable subjects not specifically protected by Subpart to 45CFR 46 and 21 CFR 56 have been review and approved during IRB continuing review procedures.

Recommendation: In the event the IRB determined additional protections were required during the
initial or continuing review, ensure the investigator has implemented appropriate safeguards to comply with IRB determination.

IRB Policy reference to these observations and findings
[IRB Policy 501-Vulnerable Populations. Procedures for Additional Protections: If through review, the IRB determines that additional protections are required of the researcher, these will be recorded in the minutes.]

**Principal Investigator:**

A. IRB Study Number:
B. Study Title:

C. Investigator Risk Score:

Minor Findings for

Finding 1: The Investigator has signed the delegation log authorizing personnel who have no tasks indicated. *(Category of Finding: Documentation in Study Record)*

Recommendations for

Recommendation 1: Complete delegation of authority log for current investigator and study team members according to ICH/GCP guidelines.

ICH/GCP/Ibid Guidance reference relevant to these findings

[ICH/GCP 4.3.1 The investigator should ensure that any individual to whom a task is delegated is qualified by education, training, and experience (and state licensure where relevant) to perform the delegated task.

Ibid. 4.1.5 The investigator should maintain a list of the appropriately qualified persons to whom significant trial-related duties have been delegated. This list should also describe the delegated tasks, identify the training that individuals have received that qualifies them to perform delegated tasks.]

**Principal Investigator:**

A. IRB Study Number:
B. Study Title:

C. Risk Score:

Observations and Recommendations for

Observation 1: Memo in study records states “UMN IRB agreed to transfer IRB review and oversight for this study to external IRB Review--Quorum Review.” April 17th 2015 Implementation Team Progress Update states: "The implementation team has retained an external, independent Institutional Review Board (IRB) to assess current Department of Psychiatry interventional drug studies."
Observation 2: Memo in study records from UMN Academic Health Center - Admin states "recruitment of new participants is suspended for all interventional drug protocols conducted by the Department of Psychiatry". April 17th 2015 Implementation Team Progress Update states: Enrollment in these particular studies has been suspended until the review by this external IRB is complete, which is expected in early May 2015.

Observation 3: UMN IRB Continuing Review approval date is 6/10/15. July 27, 2015 Report To Legislature states" following the March 19, 2015 report of the Office of the Legislative Auditor, VP Herman suspended enrollment and IRB review of all Department of Psychiatry interventional drug studies until re-reviewed by an independent IRB. Enrollment into 15 studies was suspended and 3 additional studies not yet approved by the IRB were forwarded to Quorum IRB for review. Of those: 2 were closed by UMN PIs, 2 are pending submission to Quorum, 7 were approved and suspension was lifted, 2 were approved but require further action per UMN requirements, 1 was approved pending modifications, and 1 was submitted and withdrawn by the UMN PI. (Category of Finding: IRB Communication)

Observation 4: July 27, 2015 Report To Legislature states "Approval for new applications for interventional drug trials in the Department of Psychiatry will continue to be outsourced to Quorum IRB. That practice will continue until all recommendations in the work plan have been implemented."

Recommendation 1: Confirm IRB of record and IRB approval for [______________ during enrollment suspension but active follow-up period.

Recommendation 2: Consider revising FWA's to include Quorum Review as an IRB linked to the Assurance. Review of formal transfer Agreements initiated by UMN IRB was outside the scope of this review.

IRB Policy reference to these observations
University of Minnesota IRB Policy 603: Transfer of IRB Review Authority (Rev. 5/29/2014)

FDA reference relevant to these observations and findings
[21 CFR 312.66] An investigator shall assure that an IRB that complies with the requirements set forth in part 56 will be responsible for the initial and continuing review and approval of the proposed clinical study.]
PROCESS IMPROVEMENT RECOMMENDATIONS

Used effectively, monitoring as a quality control function can ensure the protection of research subjects, verify the completeness and accuracy of trial data and establish that the trial was conducted in accordance with the protocol, GCP, and pertinent regulations at a clinical site. However, systematic review/audit is a higher-level process assessment, or quality assurance function, that provides an independent appraisal of data quality and integrity. Auditing critically evaluates the overall monitoring and regulatory compliance of a study by identifying potential system-wide problem areas. While monitoring and auditing are distinct functions, together, they can complement each other to create an additive impact on the overall quality, integrity and safety of clinical research programs.

Currently, regular and ongoing monitoring of research protocols for University sponsor-Investigators is conducted by the Clinical and Translational Science Institute (CTSI) clinical trial monitoring service. The PAR program is responsible for the audit/review of the conduct of a protocol at a single point in time. The PAR team seeks to identify protocol non-compliance, discrepancies in IRB review and/or approval process as well as problematic communications between the IRB and the investigators.

The External Review Panel concluded the PAR policies, procedures, review tools and a sample of reports of findings revealed “an impressive and potentially valuable tool to promote compliance with human subject protection priorities, including those related to the inclusion of subjects with impaired consent capacity and the use of legally authorized representatives. It is not clear, though, that reviews have been used effectively to address concerns about research at Fairview.” Thus, the following recommendations provide specific actions related to further review considerations as well as supportive solutions to expand excellent groundwork completed by the PAR program.

Recommendations for Post-Approval Review Function

Under the direction of the Vice President for Research and the IRB Executive Committee, the continuing review procedures of the IRB were expanded in 2011 to include a Post Approval Review (PAR) function. The purpose of the PAR program is to provide internal oversight on compliance issues associated with the performance of human subjects’ research by supplementing existing HRPP quality improvement and educational initiatives. Specifically, the PAR program has been developed to meet FDA requirements of continuing review provisions of the Federal Wide Assurances, and accreditation standards.

PAR review is primarily conducted via risk-based review, supplemental compliance review and researcher self-assessment. Criteria for selection of risk-based as well as supplemental compliance reviews (eg, directive or concern from the convened IRB, “high-risk” studies identified through the IRB Executive Committee’s defined risk profile, concerns identified by the IRB through the continuing review reports, etc.) are promulgated through information from IRB leadership. In addition, PAR

16 http://cdn2.hubspot.net/hub/149400/docs/auditingvsmonitoring.pdf
17 Implementing the Recommendations of the External Review of the University of Minnesota Human Research Protection Program (Work Plan-Public Comments DRAFT, May, 15, 2015)
18 An External Review of the Protection of Human Research Participants at the University of Minnesota with Special Attention to Research with Adults Who May Lack the Capacity To Consent.
20 IRB Policy 903: Post-Approval Review
reports associated with the completion of risk-based and supplemental reviews are prepared and forwarded to IRB for consideration. The IRB makes the final determination regarding required corrective actions related to PAR findings.

The established governance structure of PAR activities and reporting and limited resources to satisfy PAR’s charge may be limiting factors in the overall efficiency and effectiveness of the program. Thus, the following recommendations may be considered:

- Consider further delineating and clarifying HRPP functions (i.e., research compliance, research integrity and IRB)
- Continue PAR as human research protections function. However, within PAR, develop role clarity and expertise of the reviewers based on FDA/OHRP regulations:
  - Assign PAR resources that specifically audit IRB operations for compliance with IRB regulations.
  - Assign PAR resources that specifically audit for compliance with investigator regulations and ICH/GCP guidelines for protocol compliance\(^ {21} \), including 21CFR 312.66 (an investigator shall assure that an IRB that complies with the requirements set forth in part 56 will be responsible for the initial and continuing review and approval of the proposed clinical study.)\(^ {22} \)
- Select risk-based and supplemental compliance reviews based on a predetermined set of criteria, to include requirements for instituting a “for-cause” internal audit.

**Recommendations for PAR Work Plan**

Once what was only a minor component of a broader compliance auditing/monitoring work plan, research is an activity that can no longer be dealt with reactively or with only periodic auditing focus. A solid plan includes the following essential characteristics:

- Monitoring activities are pro-active and not reactive;
- Monitoring/auditing plans reflect outcome orientation;
- Audit outcomes are reported to appropriate level of management;
- Audit frequency is appropriate for level of risk to organization;
- Review methodology is appropriate for type of area being reviewed;
- Monitoring/auditing policy and strategy protects work papers and findings;
- Corrective actions include a timeline for completion and are verified;
- Re-audit/reviews occur at appropriate intervals to assure no re-occurrence of non-compliance.

In addition, research audit/monitoring plans must balance the needs of diverse stakeholders with the responsibility of measuring structural and systemic risk within the research program. Thus, a strategic paradigm shift in initial planning may assist in achieving and measuring sustainable improvements and ongoing compliance with human subjects protections. Specific considerations include:

\(^{21}\) [http://ichgcp.net/4-investigator]

\(^{22}\) [(21CFR312.66): An investigator shall assure that an IRB that complies with the requirements set forth in part 56 will be responsible for the initial and continuing review and approval of the proposed clinical study. The investigator shall also assure that he or she will promptly report to the IRB all changes in the research activity and all unanticipated problems involving risk to human subjects or others, and that he or she will not make any changes in the research without IRB approval, except where necessary to eliminate apparent immediate hazards to human subjects.]
Current Strategy/Focus
- Auditors/monitors issue reports and monitor progress against corrective actions;
- Auditing and monitoring functions have limited role in assisting investigators with implementing recommendations, design improvement plans or contributing to more prospective matters;
- Audits are standardized in approach with template driven reports designed to close the gap rather than provide “value-added” corrective actions;
- Preserves independence.

New Paradigm/Strategy
- Annual monitoring/auditing plans are developed through partnership with management to identify, define, measure, and create value for research;
- The monitoring/auditing program demonstrates an ability to offer valued input to strategic quality initiatives as they are being developed as opposed to after-the-fact;
- Monitor/audit program is able to provide analytical feedback on metrics, performance, and data;
- Monitoring/audit program is proactive, thoughtful, and focused on education;
- Monitors/auditors are assigned to research groups/programs to develop long-term relationships as well as content expertise in the therapeutic area, program goals, investigators, etc.;
- Monitoring/auditing processes are consultative and collaborative with research program leaders and investigators.

Recommendations for Risk Based Selection of Investigators and Clinical Trials for PAR Review
Monitoring activities should focus on preventing or mitigating important and likely sources of error in the conduct, collection, and reporting of critical data and processes necessary for human subject protection and trial integrity. The investigator is at the front-lines of the actual conduct of a clinical trial and is operationally responsible for the protection of research subjects including selection/development of the clinical trials for participation, identification, consenting, screening and enrollment of subjects, compliance with protocol requirements, and the clinical care of the subjects. Thus, investigators are likely sources of error.

Currently, PAR’s monitoring/auditing plan for risk-based reviews are reactive and protocol based. Criteria for supplemental compliance reviews are limited to “random or targeted selection” of IRB approved studies. A methodology for assessing, scoring and selecting investigator’s versus individual protocols for review was employed in this scope of work. Adopting a similar framework for risk assessment for post approval monitoring is recommended.

Establishment and Implementation of Compliance Metrics
According to the External Review Report, the PAR program is under resourced in terms of staff. In addition, it may lack the necessary technology and training to effectively promote research compliance. Thus, efficiency and timeliness is more important than ever and value is created when audits and reviews are conducted across a spectrum of issues without increasing costs. This implies knowing organization issues and monitoring or auditing plans for smaller and more targeted audit investigations. Thus, unless a specific function or business unit requires a thorough analysis of data in order to evaluate risk, each review should be kept small and metric driven. Specific tools in identifying key metrics are recommended below:
- **Step 1:** Assemble identified research risks, score, and prioritize—A Risk Event Profile can be used to prioritize, categorize, and track the progress of evaluating the portfolio of risk events for non-compliance and exposure;
- **Step 2:** Determine what must be audited versus what can be monitored;
- **Step 3:** Establish thresholds levels for underperformance and/or minimum necessary performance metrics that can help calibrate situations that may justify investigations, audits, or further operational reviews;
- **Step 4:** Identify values within those metrics that could be classified as “normal” and ranges of values that may indicate the need for additional reviews, investigations, or audits;
- **Step 5:** Tracking performance measures and crafting reports that can survey trends that could be indicative of new risks or higher risks are crucial.

**Implementation of Database Solution for Near Real-Time Tracking of Compliance Metrics**

Deploying a metrics driven approach to the review function requires the ability to track and report activities and results in near real-time. In addition, developing statistically valid output such as representative sample size for audit planning, establishing and monitoring error rates over time, trend analyses, etc. requires consistent taxonomy and application of methodology. This is optimally accomplished through the development of a specific database for the HRPP’s compliance review function.

**Implementation of Immediately Accessible Educational Tools**

UMN currently conducts a wide spectrum of clinical research, with varying levels of inherent human subjects and organizational risk. UMN requires a basic level of human subjects’ protection training for all researchers and research personnel listed on an application. The Collaborative IRB Training Initiative (CITI) is the only IRB approved human subject protection training requirement for all medical/social researchers and research staff at the UMN. In addition, University of Minnesota faculty members who will serve as sponsor-investigators for research of a drug or device are required by the University of Minnesota to complete the CITI Sponsor-Investigator Training for drugs or devices. This training is recommended, but optional, for other personnel listed on the study.

The CITI human subjects protection modules were first developed at the University of Miami in 2000 to assist institutions fulfill the US Department of Health and Human Services mandate that all key personnel engaged in research must obtain human subjects protection training. Originally the CITI training consisted of single module basic course focused on biomedical content from experts at a single institution. Now in its tenth iteration, the CITI expanded their content experts across multiple institutions and expanded to three basic courses (i.e., biomedical, social, and behavioral), refresher courses, three good clinical practice courses, a health information privacy and security course (HIPS), a laboratory animal research course, six responsible conduct of research (RCR) courses, and a biosafety and bio-security course. Face and content validity is obtained through a peer review process of over 80 core developers across 65 institutions.

UMN IRB requires basic CITI training to be re-certified or refreshed every 3 years. The IRB recommends that researchers and research staff maintain their own records of CITI course completion. Sponsor-investigators are required to provide documentation of successful completion of the sponsor-investigator drug or device module before final IRB approval will be granted. However, IRB required

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23 IRB Policy 801: Researcher Education Requirements
documents and supporting information required from researchers for IRB initial review of research studies does not include certification of training.\textsuperscript{24}

Although investigator training through CITI is widely accepted, it is generalized and not specific to individual investigator’s needs, based on risk profile for his or her portfolio of clinical trials. Interactive educational series are also readily available. As an example, WCG Academy’s curriculum is scientifically designed to maximize the adult learner’s attention and retention, with course assignments tailored to meet each individual’s knowledge deficits. By filling specific knowledge gaps and insufficiencies, WCG Academy may provide a supplemental and more engaging learning experience (Figure 6).

\textit{Figure 6: WCG e-Learning Solution}

In addition, WCG Academy offers dashboards and metrics to allow for tracking and validating investigator training. With additional tools such as this, improvements in compliance metrics can be correlated with educational requirements for further refinement and ongoing measurement of quality assurance initiatives (Figure 7).

\textsuperscript{24} IRB Policy 301: Application Requirements
Appendix I: Recent IRB Determinations of Non-compliance with IRB Policies
### Appendix IIIA: Example of Audit/Review Tools (Informed Consent)

**CONFIDENTIAL QA Audit Tool: INFORMED CONSENT**

<table>
<thead>
<tr>
<th>Requirement fulfilled?</th>
<th>Explanation of n/a or N/A</th>
</tr>
</thead>
</table>

**Purpose of the research is explained accurately**
- Y
- N

**Statement that the study involves research.**
- Y
- N

**Approximate number of subjects involved in the study**
- Y
- N

**Expected duration of the subject’s participation**
- Y
- N

**Description of the procedures to be followed**
- Y
- N

**Identification of any procedures which are experimental**
- Y
- N

**Description of any reasonably foreseeable risks or discomforts to the subject**
- Y
- N

**Description of any benefits to the subject or to others which may reasonably be expected from the research**
- Y
- N

**Disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject**
- Y
- N

**Statement that the particular treatment or procedure may involve risks to the subject or to the embryo or fetus, if the subject is or may become pregnant, which are currently unforeseeable**
- Y
- N

**Statement that significant new findings developed during the course of the research which may relate to the subject’s willingness to participate will be provided**
- Y
- N

**Statement that participation is voluntary**
- Y
- N

**Statement that refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled**
- Y
- N

**Statement that the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled**
- Y
- N

**Consequences of a subject’s decision to withdraw from the research and procedures for orderly termination of participation by the subject**
- Y
- N

**Anticipated circumstances under which the subject’s participation may be terminated by the investigator without regard to the subject’s consent**
- Y
- N

**Any additional costs to the subject that may result from participation in the research**
- Y
- N

**Explanation as to whether any compensation and an explanation as to whether any medical treatments are available if injury occurs and, if so, what they consisted of, or where further information may be obtained (for research involving more than minimal risk)**
- Y
- N

**Does not include any exculpatory language that waive or appears to waive any of the subject’s legal rights or releases or appears to release the investigator, sponsor, or the institution or its agents from liability for negligence**
- Y
- N

**States to what extent, if any, confidentiality of records identifying the subject will be maintained**
- Y
- N

**Notes the possibility that the FDA may inspect the records**
- Y
- N

**Whom to contact for answers to pertinent questions about the research and research subjects’ rights**
- Y
- N

**Whom to contact in the event of a research-related injury to the subject**
- Y
- N

**Any additional requirements per state/local law**
- Y
- N

**Signature and date lines for the subject or for the legally authorized representative**
- Y
- N

*“When appropriate” (per FDA), however, because there is no FDA guidance re: this, these items should be included unless inappropriate to include

<table>
<thead>
<tr>
<th>n/a</th>
<th>Y</th>
<th>N</th>
</tr>
</thead>
</table>

*List other signature lines here (if any):*
### Appendix IIIB: Example of Audit/Review Tools (Consented Subject)

**CONFIDENTIAL**  QA Audit Tool: **CONSENTED SUBJECT**

<table>
<thead>
<tr>
<th>Original ICF in source documents?</th>
<th>Y</th>
<th>N: #</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subject consented before screening began? (SD = same day)</td>
<td>SD</td>
<td>Y: #</td>
</tr>
<tr>
<td>Correct ICF version used?</td>
<td>Y</td>
<td>N: #</td>
</tr>
<tr>
<td>Signed &amp; dated by subject or representative?</td>
<td>Y</td>
<td>N: #</td>
</tr>
<tr>
<td>If signed by representative, documentation that IRB policy was followed?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>If subject or representative is unable to read, documentation that IRB policy was followed?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>If subject is a minor, documentation that IRB policy was followed?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SD's support capacity to consent (e.g., meds, dx; cogni we fx., etc.?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Signed &amp; dated by person conducting informed consent discussion?</td>
<td>Y</td>
<td>N: #</td>
</tr>
<tr>
<td>Match between dates of subject/representative and person conducting discussion?</td>
<td>Y</td>
<td>N: #</td>
</tr>
<tr>
<td>All other signature &amp; date lines completed correctly by designated person(s)?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All other blanks throughout ICF completed correctly?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HIPAA valid authorization signed?</td>
<td>Y</td>
<td>N: #</td>
</tr>
<tr>
<td>Documentation of consent process in SD's by person conducting consent discussion?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>If consented in the hospital, documentation of consent process in the MR?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All other aspects of consent documentation proper (including corrections made properly)?</td>
<td>Y</td>
<td>N: #</td>
</tr>
</tbody>
</table>

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## Appendix IIIC: Example of Audit/Review Tools (Enrolled/Dosed Subjects)

### CONFIDENTIAL QA Audit Tool

**Enrolled/Dosed Subject**

<table>
<thead>
<tr>
<th>Sponsor</th>
<th>Auditor</th>
<th>CRC:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Protocol #:</td>
<td>Site</td>
<td>Ri</td>
</tr>
</tbody>
</table>

**All REI-approved enrollment requirements met?**

<table>
<thead>
<tr>
<th>Y</th>
<th>N</th>
</tr>
</thead>
</table>

**Phases/visits with no errors**

<table>
<thead>
<tr>
<th>Visit Type</th>
<th>Visit Date</th>
<th>Audit Date</th>
<th>Phases/visits with no errors</th>
<th>Visit Type</th>
<th>Visit Date</th>
<th>Audit Date</th>
<th>Did pt complete?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Y</td>
<td>N</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Phases/visits With One or More Errors**

<table>
<thead>
<tr>
<th>RE-CONSmts</th>
<th>MEDICAL CARE/PPI SUPERVISION</th>
<th>LK</th>
<th>PROTOCOL</th>
</tr>
</thead>
<tbody>
<tr>
<td>If new ICT approved, all &quot;consented subject&quot; audit criteria met?</td>
<td>Medical care documented?</td>
<td>IP dispensed, administered, returned per protocol?</td>
<td>Compliance with all other IRB-approved research activities?</td>
</tr>
<tr>
<td>Phase/Visit</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
</tr>
<tr>
<td>P/v date</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
</tr>
<tr>
<td>Audit date</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
</tr>
<tr>
<td>Phase/Visit</td>
<td>n/a</td>
<td>n/a</td>
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<tr>
<td>P/v date</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
</tr>
<tr>
<td>Audit date</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
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<tr>
<td>Phase/Visit</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
</tr>
<tr>
<td>P/v date</td>
<td>n/a</td>
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<td>n/a</td>
</tr>
<tr>
<td>Audit date</td>
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<td>n/a</td>
<td>n/a</td>
</tr>
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</table>

**NOTE:** This audit item applies only to study drug administered in a hospital.

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*Page 52 of 53*
## Appendix IID: Example of Audit/Review Tools (Adverse Events)

<table>
<thead>
<tr>
<th>Audit Date/AE date</th>
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</thead>
<tbody>
<tr>
<td>Subject # / Initials</td>
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<td>/</td>
<td>/</td>
<td>/</td>
</tr>
<tr>
<td>AE Type* (circle one/both)</td>
<td>S</td>
<td>U</td>
<td>S</td>
<td>U</td>
</tr>
<tr>
<td>Brief description of AE</td>
<td>/</td>
<td>/</td>
<td>/</td>
<td>/</td>
</tr>
<tr>
<td>Reported to IRB?</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Reported to IRB per Policy?</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Reported to sponsor?</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Reported to sponsor per Protocol?</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Comments</td>
<td>/</td>
<td>/</td>
<td>/</td>
<td>/</td>
</tr>
</tbody>
</table>

* S=Serious; U=Unanticipated

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<table>
<thead>
<tr>
<th>Audit Date/AE date</th>
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<th>/</th>
<th>/</th>
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<tr>
<td>AE Type* (circle one/both)</td>
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<tr>
<td>Brief description of AE</td>
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<td>/</td>
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<td>/</td>
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<tr>
<td>Reported to IRB?</td>
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<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Reported to IRB per Policy?</td>
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</tr>
<tr>
<td>Reported to sponsor?</td>
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<td>No</td>
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<td>No</td>
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<tr>
<td>Reported to sponsor per Protocol?</td>
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<tr>
<td>Comments</td>
<td>/</td>
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</tr>
</tbody>
</table>

* S=Serious; U=Unanticipated