

**TraCS Institute**  
**Clinical and Translational Research Center**  
**Protocol Risk Assessment and Monitoring Guidelines**

**Definitions of Levels of Risk:**

There are four levels of protocol risk, number one representing no more than minimal risk (as defined in federal regulations research), and numbers two, three, and four representing greater than minimal risk. Criteria for each and examples are given below. Various factors are taken into consideration when determining the level of risk and are described below. Additional factors may include potential for invasion of privacy/breach of confidentiality, the psychological impact of the protocol, social implications, experience of research team, or potential for conflicts of interest. Some studies may not clearly fit into one category and instead have elements of two or more categories. In that case, the highest risk category should be selected. The various levels of risk include:

**1. No Greater than Minimal Risk** – “Minimal Risk” means that the probability and magnitude of harm or discomfort anticipated in the research are not greater than those ordinarily encountered in daily life or during the performance of routine physical and psychological examinations or tests and where confidentiality is adequately protected. This category includes protocols that pose “no greater than minimal risk” according to federal regulations. **Requires Minimal Intensity Monitoring.**

Examples of risk level 1:

Study poses no more risk than expected in daily life (blood draw, physical exam, routine psychological testing).  
Non-interventional studies (e.g., observational studies of behavior or nutrition).  
Survey/questionnaire studies of a non-sensitive nature.

**2. Minor Increase over Minimal Risk** – Research involves a minor increase over minimal risk. There is medium to high probability of the occurrence of a low-severity event that is completely reversible (e.g., headache from lumbar puncture) or the likelihood of serious harm occurring is low (e.g., fatal anaphylaxis from allergy skin testing). **Requires Low Intensity Monitoring.**

Examples of risk level 2:

Studies of normal volunteers using well-described research procedures and/or single dose of experimental agent.  
Post-marketing study - phase IV drug study or device (as defined by FDA) with minor safety concerns.  
Interventions or invasive procedures present low risks, reasonably commensurate with those expected in medical or dental practice.  
Studies that involve sensitive information or a potential risk of breach of confidentiality

**3. Moderate Risk** - Risks are recognized as being greater than minimal, but are not considered high. There is a medium to high probability of a moderate-severity event occurring as a result of study participation (e.g., reversible worsening of a non-fatal disease such as seasonal allergy while receiving placebo or pneumonia from a bronchoscopy), but there is adequate surveillance and protections to identify adverse events promptly and to minimize their effects. **Requires Moderate Intensity Monitoring.**

Examples of risk level 3:

Subjects treated with placebo for a recognized disease  
Substantial risk (>5%) of a Serious Adverse Event originating from the underlying condition of the enrolled subject  
Involves subjects with serious viral, autoimmune, and malignant illness in a treatment study of moderate risk  
Phase I or II, clinical trial with available safety data in humans  
Minimal risk studies involving vulnerable populations (e.g. subjects with impaired capacity to give informed consent)

**4. High Risk** - The study risk is greater than a moderate risk study due to the increased probability for generating serious adverse events. There is a high probability of an event that is serious and prolonged or permanent occurring as a result of study participation. In situations where there is the prospect of direct benefit to the subject, study risks are high or there is significant uncertainty about the nature or likelihood of adverse events. **Requires High Intensity Monitoring.**

#### Examples of risk level 4:

- Clinical trials of interventions to prevent or treat diseases that lead to death or irreversible morbidity
- Involves an intervention or invasive procedure with substantial risk or potential for severe toxicity
- An investigator-initiated IND trial
- Implantation of a device with an IDE
- Involves the use of a new chemical or drug for which there is limited or no available safety data in humans
- A gene transfer study or research involving recombinant DNA molecules
- An investigator initiated, phase III, clinical trial
- Industry sponsored, multi-center, randomized, clinical trials (phase 2b, 3, and 4)

#### **Monitoring Recommendations Based on Level of Risk:**

Safety monitoring for a protocol must be appropriate for the level of risk identified. The combination of factors used in assessing the level of risk drives the intensity of monitoring required for a protocol. The requirements outlined below represent the minimum amount necessary to assure subject safety. The CTRC Protocol Review Committee may require more frequent and/or additional monitoring to include Quality Assurance Reviews by the Office of Research Subject Advocacy. Standard reporting to the IRB of unanticipated problems and adverse events is required regardless of the level of monitoring.

**Minimal Intensity Monitoring** – The PI or co-investigator will monitor the study with prompt reporting of adverse events and other study related information to the IRB, CTRC, sponsor, and other agencies as appropriate. A Modified Safety Monitoring Plan that describes appropriate safety-monitoring procedures will be reviewed and approved by the CTRC Protocol Review Committee.

**Low Intensity Monitoring** –The PI or co-investigator will monitor the study with prompt reporting of adverse events and other study related information to the IRB, CTRC, sponsor, and other agencies as appropriate. Team meetings by the PI and his/her staff will be conducted on a routine basis to discuss protocol issues and review adverse events. A Safety Monitoring Plan that addresses each of the questions, approved by the CTRC Protocol Review Committee, will be revised and updated if the risk/benefit ratio changes.

**Moderate Intensity Monitoring** – The PI or co-investigator monitors the study on a day-to-day basis and includes all monitoring activities described above in low intensity monitoring. In addition, most protocols will require well-described criteria for dose escalation, criteria defining maximum tolerated dose (MTD), and/or criteria for stopping the trial or involvement of a subject. Surveillance and protections are in place to adequately identify adverse events promptly. An independent medical monitor or safety monitoring committee may also be utilized to review adverse events as they occur and make recommendations to the protocol team.

**High Intensity Monitoring** – The PI or co-investigator monitors the study on a day-to-day basis and includes all monitoring activities described above in low intensity monitoring. Most high-risk protocols will also require a Data Monitoring Committee to monitor the safety and efficacy of the study. An independent Data Safety Monitoring Board (DSMB) is required by NIH Guidelines for all Phase III clinical trials. Based on the level of risk, the complexity of the protocol, and the patient population, the CTRC Protocol Review Committee or SOM-IRB may determine that a clinical trial or protocol requires an independent DSMB or DSMC. Some single institution, investigator initiated, clinical trials or protocols deemed of significant risk may also fit these criteria. If no other DSMB is in place for a single institution clinical trial, the PI may use the SOM-DSMB as an independent board to fulfill this function.