

# General Clinical Research Center Protocol Risk Assessment and Monitoring Guidelines

(Adapted from the GCRC's at University of North Carolina and Wake Forest University)

## DEFINITIONS OF LEVELS OF RISK:

This document is intended as a guide for defining the level of risk for clinical research protocols in order to recommend the appropriate level of monitoring. Each protocol's final risk assessment and monitoring recommendation will depend on a case-by-case review.

In line with federal regulations and the Weill-Cornell IRB, the GCRC divides risk levels into two main categories: 1) **No Greater than Minimal Risk** and 2) **Greater than Minimal Risk, with** the latter category divided into three subcategories: Low, Moderate and High risk.

1. **No Greater than Minimal Risk:** (as defined in federal regulations, 45CFR46.102) *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.*  
For example:
  - Non-invasive studies.
  - Studies that involve low risk procedures (e.g., blood draw, physical exam).
  - Survey/questionnaire studies of a non-sensitive nature.
2. **Greater than Minimal Risk:** sub-divided into three levels for monitoring purposes:
  - A. **Low Risk or Minor Increase over Minimal Risk:** involves probability of the occurrence of a low-severity event that is reversible (e.g., headache from lumbar puncture) and very low probability of a serious adverse event (e.g., fatal anaphylaxis from allergy skin testing). Requires Low Intensity Monitoring, for example:
    - Normal volunteers using a well-described, low risk procedure.
    - Interventions that are reasonably commensurate with those expected in medical practice.
    - Survey/questionnaire studies that involve sensitive information or a potential risk of breach of confidentiality.
  - B. **Moderate Risk:** increased probability of a moderate-severity event that is reversible (e.g., hypoglycemic episode, bronchoconstriction, infection), with adequate surveillance and protection to identify adverse events promptly and to minimize their effects. The probability of a serious adverse event is very low, for example:
    - May include Phase I, II or III multi-institutional studies
    - Studies involving healthy volunteers with low probability for irreversible adverse events
    - Invasive procedures (e.g., hemodynamic monitoring)
    - Off-label use of FDA approved of low risk drug or device
    - Blood drawing for genetic testing real time or stored (may fall into any of the Greater Than Minimal Risk categories)
  - C. **High Risk** increased probability for the occurrence of a study-related adverse event that is serious and/or prolonged or permanent, or significant uncertainty about the nature or likelihood of adverse events, for example:
    - Use of a new investigational drug or device for which there is limited or no available safety data in humans
    - Investigator initiated, or industry-sponsored phase III, clinical trials.

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- Intervention or invasive procedure with known substantial risk.
- Gene transfer studies or research involving recombinant DNA molecules
- Clinical trials of interventions to prevent or treat diseases that lead to death or irreversible morbidity.
- Studies involving vulnerable populations

### **MONITORING RECOMMENDATIONS BASED ON LEVEL OF RISK:**

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 and will help the SAC in evaluating sections 2A and 2B of the Data and Safety Monitoring Plan (DSMP). The SAC may require more frequent and/or additional monitoring by the Research Subject Advocate (RSA) or other individuals of the research team. Standard reporting to the IRB of unanticipated problems and adverse events is required regardless of the level of monitoring.

1. **Monitoring for “No Greater than Minimal Risk” protocols (Minimal Intensity Monitoring)** – The PI or appropriate designee monitors the study, reporting adverse events and other study related information to the IRB, GCRC, sponsor, and other agencies as appropriate within the required time frame. The DSMP describing appropriate safety-monitoring procedures is reviewed and approved by the SAC.
2. **Monitoring for “Greater than Minimal Risk” protocols**
  - A. **Low Intensity Monitoring**: The PI or appropriate designee monitors the study reporting adverse events and other study related information to the IRB, GCRC, sponsor, and other agencies as appropriate, within the required time frame. Meetings of the research team are conducted by the PI on a routine basis to discuss monitoring and review adverse events. If the risk/benefit ratio changes, the DSMP must be revised and updated and approved by the SAC.
  - B. **Moderate Intensity Monitoring**: The PI or appropriate designee monitors the study on a day-to-day basis using all monitoring tools described above in low intensity monitoring. In addition, most protocols will require well-described criteria for dose escalation, maximum tolerated dose (MTD), and 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 necessary to review adverse events as they occur and make recommendations to the protocol team.
  - C. **High Intensity Monitoring**: The PI or appropriate designee monitors the study on a day-to-day basis using all monitoring activities described above in low intensity monitoring. Most high-risk protocols will also require a Data Monitoring Committee to follow the data being generated. Based on the level of risk, the complexity of the protocol, and the patient population, the SAC and/or IRB may determine that a clinical trial or protocol requires an independent DSMB. An independent Data and Safety Monitoring Board (DSMB) is required by NIH Guidelines for all Phase III clinical trials. If no DSMB is in place for a single institution clinical trial or protocol of significant risk, the PI may use the Cornell-DSMB as an independent board to fulfill this function. The SAC may recommend monitoring of the informed consent process by the RSA for some high-risk protocols.