UCH Clinical Translational Research Center Policy

Study Monitoring

Introduction

NIH policy regarding the appropriate oversight and monitoring of the conduct of clinical trials established a requirement for Data and Safety Monitoring Plans (DSMPs) as a means of ensuring that all clinical research have a level of monitoring commensurate with the risks, nature, size and complexity of the trial. Furthermore, a detailed monitoring plan must be an integral part of the research plan.

A DSMP is a written plan whose purpose is to delineate how the safety of clinical research subjects and the validity and integrity of research data will be monitored. Additionally, the DSMP allows for the monitoring of study data to determine if early termination of a study is warranted for safety or efficacy reasons, or when it appears that the study cannot be concluded successfully.

All studies conducted on, or using the resources of the UCH Clinical Translational Research Center (CTRC) are required to have a Data and Safety Monitoring Plan. The UCH CTRC requirements for data and safety monitoring are based on overall requirements from NIH and the National Center for Research Resources (NCRR). These requirements apply to all investigations regardless of source of funding, (NIH, foundations, local, etc.). Since the requirements for safety monitoring may not be readily apparent for a particular study, investigators are encouraged to contact the Research Subject Advocates (RSAs) on the UCH CTRC for consultation during the development of the DSMP.

Oversight

A plan may include the following types of monitoring:

- Principal Investigator

- Safety Monitor – an individual independent from the study that is responsible for data and safety monitoring activities and advises the Principal Investigator, the UCH CTRC Study Monitoring Committee (SMC), and the Colorado Multiple Institutional Review Board (COMIRB) regarding participant safety, scientific integrity and ethical conduct of a study.

- Data and Safety Monitoring Board (DSMB) – an independent committee that provides safety review and trial guidance, including advice on continuing, modifying, or

terminating the study. Committee members may not participate in the study as principal or co-investigators, or as study physicians.

The level of oversight required for a UCH CTRC study will vary depending on the degree of risk. For studies that present a minimal or low risk to subjects, safety monitoring may be conducted continuously by the PI. For studies that present a moderate degree of risk, safety monitoring may be conducted by a single independent monitor or possibly a DSMB. NIH funded phase III clinical investigations (or any multi-site clinical trial) involving interventions that entail potential risk to participants are required to have a DSMB. In addition, a DSMB may be appropriate for earlier trials (phase I and II) that are either (1) multi-center; (2) blinded to the researcher; (3) employ particularly high risk interventions (gene therapy, cancer treatments, AIDS treatment); or (4) include vulnerable study populations (pediatric, pregnant, prisoners, cognitively impaired, economically or educationally disadvantaged). The NCRR requires a DSMB for any investigation that places participants at significant risk.

The ultimate decision regarding the level of risk of the investigation, and therefore the monitoring requirements, will be made by the Scientific Advisory and Review (SARC) and the Colorado Multiple Institutional Review Board (COMIRB).

Risk Related to Study Intervention and Monitoring Guidelines
Minimal Risk
Defined in the federal statutes as a risk where "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" (45 CFR 46, Section 102 (i))

Examples: routine physical tests; peripheral blood draws; routine X-rays; routine psychological examinations or tests when low risk to confidentiality; use of surveys or questionnaires when low risk to confidentiality; non-invasive radiology or imaging studies; observational studies; nutritional studies that do not involve radioactive isotopes; behavioral studies; gait assessments; anthropometric evaluations.

Minimal Risk Study Monitoring: can be monitored appropriately for safety by the investigator. These studies will be reviewed at least annually by the UCH CTRC Study Monitoring Committee (SMC) using information that the investigators have already submitted to COMIRB. Unanticipated problems reported to COMIRB will also be reported to the RSA.

Low Risk:
Involves a minor increase over minimal risk- the intervention or procedure presents experiences that are reasonably commensurate with those inherent in actual or expected medical, dental, psychological, social or educational situations (45 CRF 46.406).

*Examples***:** studies of normal volunteers using well described research procedures such as intravenous infusions of non-vasoactive drugs; euglycemic clamp; indirect calorimetry; muscle and fat biopsy; low risk exercise tests; indwelling catheter < 24 hours; oral glucose tolerance test;

minimal anticipated drug/treatment related adverse events with minimal or no anticipated medical intervention; meets the requirements for minimal risk but include special populations.

Low Risk Study Monitoring: can be monitored appropriately for safety by the investigator. These studies will be reviewed at least annually by the SMC using information that the investigators have already submitted to COMIRB. Unanticipated problems reported to COMIRB will also be reported to the RSA.

Moderate Risk:
Risks are reasonable in relation to anticipated benefits, if any, to subjects and the importance of the knowledge that may reasonably be expected to result (45 CFR 46.111). Risks are recognized as being greater than low, but are not considered as serious as high risk, and their surveillance and protections are adequate to identify adverse events promptly and keep their effects minimal

Examples: participants treated with placebo for a recognized disease or a multi-arm study where there is the potential for increased risk in one or more arms; disease orientated participants exposed to non-FDA approved drug or drug combinations; reasonable level of baseline knowledge from which it is feasible to extrapolate risk of adverse events; only anticipated mild/moderate adverse events or low probability of SAE; microneurography in normal participants; low risk studies in vulnerable populations; procedures involving the collection of sensitive information (e.g. illegal activities); invasive sampling, invasive diagnostic testing.

Moderate Risk Study Monitoring: requires a level of oversight other than can be provided by the investigator. These studies will utilize, in addition to the investigator, additional monitoring by an individual not directly involved in the study such as a safety officer, and may require the oversight of a Data and Safety Monitoring Board. The determination that a study is moderate risk is the determination of SARC. A safety officer should be an expert in the field and experienced in clinical research, but independent of the study. He/she should be recommended by the investigator and approved by the SMC. The charter outlining the role of the safety officer in the study should be written by the investigator in conjunction with the safety officer and submitted to the SMC for review. This charter should include appropriate individual and study stopping criteria for safety. Wherever possible, a meeting should be scheduled with the investigator, safety officer and representation from the SMC prior to submission of the safety officer charter to the SMC. A written safety officer report should be sent to the RSAs and the COMIRB as predetermined by the DSMP and will be protocol specific. This report will be reviewed at the next scheduled SMC and any follow-up requests will be communicated to the investigator and safety officer in a timely manner. When appropriate, the report will be forwarded to the SARC with accompanying recommendations from the SMC with regard to possible action to be taken.

High Risk:
Studies that are of high levels of risk may result in permanent physical and/or mental changes, hospitalization, and/or death. In situations where the prospect of direct benefit to the study participant exists, the risks associated with study procedures are considered substantial; there is an increased probability for the occurrence of a study related event that is serious and prolonged or permanent, or there is significant uncertainty about the nature of likelihood of adverse event.

Examples: interventions or invasive procedures that involve substantial risk; blinded Phase I and II trials; studies involving the use of a chemical/drug/device for which there are little or no human toxicology data; gene transfer studies or research involving recombinant DNA; investigator-initiated phase III or multi-center clinical trials; studies where consent is waived such as in emergency circumstances or in populations unable to give informed consent (e.g., mentally incapacitated); potential anticipated for serious AE or frequent AE associated with the research requiring medical intervention; implantation of device with an IDE; Category III radiation risk (H_E (mrem) > 5000 mrem **or** organ limit of $H_T > 750/W_T$); surgical procedures; general anesthesia.

High Risk Study Monitoring: require a level of oversight other than can be provided by the investigator or a single independent safety monitor. These studies will utilize, in addition to the investigator, additional monitoring such as a formally established independent Data Safety Monitoring Board that has specific oversight of the safety monitoring of the study. A DSMB will be required for multi-center trials and all phase III clinical (interventional) trials. A monitoring board may be required for certain studies to determine safe and effective conduct and to recommend termination of the study when significant benefits or risks have developed or when the trial is unlikely to be concluded successfully. Earlier studies that involve vulnerable populations, are blinded to the researcher, or employ particularly high risk interventions may require a DSMB, depending on the nature of the study. The board should include a group of individuals with sufficient expertise to make safety decisions for the trial at hand. Clinicians, statistician, ethicists, epidemiologists, scientists from other fields, and members from outside the institution not directly affiliated with the study may be needed. The charter and membership of any independent DSMB must be provided by the investigator for review by the SMC. A written DSMB report should be sent to the RSAs and the COMIRB as predetermined by the DSMP and this will be protocol specific. This report will be reviewed at the next scheduled SMC meeting and any follow-up requests by the SMC will be communicated to the investigator in a timely manner. When appropriate the report will be forwarded to the SARC with accompanying recommendations from the SMC with regard to possible action to be taken.

Table 1- Assessment of Risk and Safety Monitoring

Risk Level	Definition	Examples	Safety Review
Minimal risk	Study poses no more risk than expected in daily life or in routine physical or psychological examinations	• blood draw, physical exam, routine psychological testing • Survey or Questionnaire studies • Observation studies • Nutrition studies • Behavior studies	Principal investigator
Low risk	Involves a minor increase over minimal risk- the intervention or procedure presents experiences that are reasonably commensurate with those inherent in actual or expected medical, dental, physiological, social or educational situations	• Studies of normal volunteers using well-described research procedures (e.g. IV infusion, euglycemic clamp, indirect calorimetry) • Studies which might meet requirements for minimal review but include special populations	Principal investigator
Moderate risk	Risks are reasonable in relation to anticipated benefits, if any, to subjects and the importance of the knowledge that may reasonably be expected to result. Risks are recognized as being greater than low, but are not considered as serious as high risk, and their surveillance and protections are adequate to identify adverse events promptly and keep their effects minimal	• participants treated with placebo for a recognized disease or a multi-arm study where there is the potential for increased risk in one or more arms • disease orientated participants exposed to non-FDA approved drug or drug combinations • reasonable level of baseline knowledge from which it is feasible to extrapolate risk of adverse events • only anticipated mild/moderate adverse events or low probability of SAE • low risk studies in vulnerable populations • procedures involving the collection of sensitive information (e.g. illegal activities)	Independent safety monitor
High risk	Involves an intervention or invasive procedure with substantial risk; there is an increased probability for the occurrence of a study related event that is serious and prolonged or permanent, or there is significant uncertainty about the nature of likelihood of adverse event.	• Phase III clinical study • complex multi-center study • intervention or invasive procedure with substantial risk • Implantation of device with IDE • Involves the use of a new chemical or drug for which there is little or no toxicology data in humans • A gene therapy study or research involving recombinant DNA molecules (gene transfer) • intervention related SAEs that might also be due to the underlying condition or disease	DSMB required