

Protecting Human Subjects Involved in Research

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Agenda

- Responsibility for Protecting Subjects
- Oversight and Monitoring of Research
- Developing a Data and Safety Monitoring Plan
- Data and Safety Monitoring Boards (DSMBs)
- Human Subject Protection – NIH Grants
- Practical Examples of Trials that used a DSMB

Ethical Conduct in Clinical Trials

The ethical conduct of a clinical trial does not end with the formulation of study design and a signature on the informed consent form. Protecting the rights, interests, and safety of research subjects must continue **throughout** the study duration (during the conduct of the research).

H. Silverman, Ethical Issues during the conduct of clinical trials

Proc Am Thorac Soc, 2007 May 4

Investigator Responsibilities

PI responsible for protecting the rights, safety, and welfare of subjects involved in the research

Main Investigator Responsibilities

- Ensure adequate IRB review
- Ensure adherence to the protocol
- Conduct protocol according to Good Clinical Practice
- Maintain appropriate control of drugs and devices
- Ensure informed consent obtained
- Ensure adverse events are appropriately reported
- Ongoing monitoring of the study

Investigator and Study Team

- Study teams may be large or small, depending on size and complexity of research:
 - PI, co-investigators, study coordinator, nurse, data manager, biostatistician, pharmacist
- Common practice for PI to **delegate** certain study-related tasks to co-investigators and study staff.
- When tasks are delegated by an investigator, the investigator is still responsible for providing adequate **supervision** of those to whom tasks are delegated.

Appropriately Delegating Tasks

When delegating study-related tasks to co-investigators and study staff, PI must ensure that

1. Designated individuals are **qualified** to perform such tasks (qualified by education, training, and/or experience to perform the delegated task)
2. Study staff receive **adequate training** on how to conduct the delegated tasks and are provided with an adequate understanding of the study
3. Recommend **keeping a list** of appropriately qualified persons to whom significant study related tasks have been delegated and the training/education they received.

Oversight of Study Team

Investigator should remain involved in the ongoing conduct of the clinical trial:

- After delegate tasks, offer periodic supervision to ensure staff remain capable of performing the tasks.
- Hold regular team meetings status updates on subjects
- Review of Inclusion/Exclusion criteria before enrollment
- Stay in frequent communication with staff
- Evaluation adverse events
- Involvement with investigational drug dosing

PI is accountable for regulatory violations resulting from **failure to adequately supervise** the conduct of the study.

Key Responsibility of the Investigator - Ongoing Monitoring of the Study

What is Study Monitoring:

Assuming responsibility for reviewing events and outcomes during the implementation of a study in two domains:

- 1) safety of participants**
- 2) integrity and quality of data**



Ongoing Monitoring of Research

Ensures Safety of Participants:

- Protect rights of human subjects (informed consent signed)
- Monitoring for safety, occurrence of adverse events
- Assess continued reasonable risk/benefit ratio

Ensures Integrity and Quality of data

- Monitor trial data for accuracy, completeness, ensure verifiable (reported data match source documents)
- Verify trial conducted in compliance with protocol, good clinical practices, local regulatory requirements and approvals

Data and Safety Monitoring Plans

Detailed plan outlining the steps the Investigator will take to provide oversight and monitoring of a study to ensure subject safety and data integrity.

DSMP should be outlined in advance (before the study begins).

Written document submitted to the **funding agency** (e.g., NIH) and **IRB** for review, it becomes part of the working protocol.

All research should have a system for the appropriate oversight and monitoring of the study

Specific Components of a Data and Safety Monitoring Plan (DSMP)

1. Monitoring safety of participants to ensure risk is minimized
2. Reporting unanticipated problems or adverse experiences
3. Individual subject and study wide stopping rules, if appropriate
4. Ensuring data accuracy and protocol compliance
5. Independent monitoring groups or boards (i.e. DSMB) for oversight when appropriate

Monitoring Safety of Participants

Data and Safety Monitoring Plan should outline procedures to promptly detect harm and minimize risk of adverse effects from study intervention

- Labs and tests/procedures to monitor subjects (i.e., electrolyte levels, CBC, pregnancy tests)
- Schedule of events describes frequency tests ordered, study visits
- Plan how subject information will be relayed to and from researchers and staff (i.e., lab results)
- Describe communication among multi-center sites regarding safety issues, protocol changes

Reporting of Adverse Events

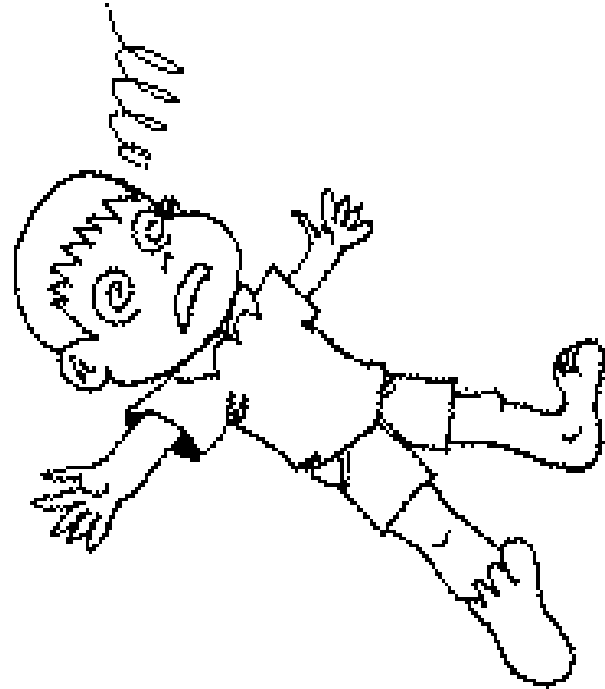
Data and Safety Monitoring Plan should describe the review and reporting of unanticipated problems (UPs) and adverse events.

- Describe **who** will receive and review adverse events and unanticipated problems (in real time)
- Describe **what** will be considered an Adverse Event or Unanticipated Problem for your study
 - Adverse Event - any unfavorable and unintended sign, symptom, or disease temporally associated with the subject's participation
 - Unanticipated Problem - incident, experience or outcome that is both *unexpected* (in nature, severity, or frequency) and *related or possibly related to the research*
 - Serious Adverse Event - fatal or life threatening, requires or prolongs hospitalization, results in significant or persistent disability, congenital anomaly/birth defect

Use a Consistent Method to Evaluate & Document AEs

Use a **classification scale** to grade the severity of adverse events (AE)

- Mild-Moderate-Severe Scale
- CTCAE v3.0 or 4.0 scale
- DAIDS AE Grading Table
- Other (specify scale)



Reporting of Adverse Events

Investigators are **only required to report** to the UNC IRB
“Unanticipated Problems involving risks to subjects or others”.

Funding Agency, Sponsor and FDA will have own reporting requirements for Adverse Events.

Whether or not reportable, still important to track adverse events in a study, communicate them to entire study team, watch for trends.

Decisions regarding AE reporting and management are the **responsibility of the PI, who makes the final decision** on causality, severity and relationship of adverse events

Individual Subject Stopping Criteria

The Data and Safety Monitoring Plan should describe the criteria that will be used to withdraw an individual subject from the study or halt the research intervention.

Examples of **subject stopping rules**:

- If subject develops allergic reaction, then study agent discontinued or held in subject
- If ALT increases 3 X ULN, drug administration held until ALT normalizes.
- Occurrence of any grade 3 or higher adverse event

Criteria to Stop Entire Study

The Data and Safety Monitoring Plan should describe the criteria that will be used to stop the entire study prematurely for safety or efficacy reasons, or inability to sufficiently recruit.

EXAMPLES:

Safety stopping rules:

- If 3 subjects develop Grade 3 Rash or one study related death occurs, study put on hold, re-evaluated

Interim analysis

- If data after first 10 subjects shows no improvement or worsening of condition, then stop entire study

Ensuring Data Accuracy & Quality

Data and Safety Monitoring Plan should detail quality control measures and procedures to ensure protocol adherence and quality and integrity of data generated and collected

- How will you ensure that data collected and entered in database is accurate, complete, and verifiable
- Monitoring and Auditing of Study:
 - Independent Monitor: reviews study files to ensure quality, accuracy of data collected; periodic checks conducted throughout study
 - Audits by Sponsors or FDA: comprehensive review of key aspects of a trial to assess compliance and ensure quality & integrity of data; typically retrospective and sample-based.

Monitoring Groups or Boards

The Data and Safety Monitoring Plan should describe the use of **independent** monitoring groups or boards to review data in aggregate and make decisions about the ongoing safety of the study, as applicable:

- Usually required when a study involves a blinded intervention, there is significant risk, or study is large with multiple sites.
- Group or board reviews data and adverse events at regular intervals to determine if safe to continue study.
- Options for Independent Oversight and Monitoring:
 - Independent Medical Monitor (physician or expert)
 - Industry/NIH Sponsored Data and Safety Monitoring Board
 - Institutional Safety Monitoring Committee or Board

Data Monitoring Committee or Board (DMC or DSMB)

DMC or DSMB: *Independent* committee of experts, objectively exam accruing data from a clinical trial, make decisions about the safety of continuing the study

- Members independent of those conducting trial (unbiased decisions)
- Assess reasonable risk/benefit ratio
- Recommend continue, modify or stop
- Review un-blinded clinical trial data
- Preserve integrity / credibility of trial and scientific result
- Phase III or high risk trials required to utilize a DSMB



Data and Safety Monitoring Boards and Committees at UNC

RMT1

NC TraCS DSMB: review UNC Investigator-initiated trials requiring a DSMB or additional oversight

- Provide oversight & monitoring of multiple trials involving various investigational drugs or disease entities
- **Membership:** UNC Faculty with wide range of medical backgrounds, biostatistician, Chair

Lineberger Cancer Center Data Safety Monitoring Committee:

Responsible for assuring data and safety monitoring of UNC oncology clinical trials

- Review studies on a regular basis, with frequency of review based on risk and complexity.
- PI is responsible for continuous monitoring of patient safety.

Slide 22

RMT1

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NIH Grants

Human Subject Protection

NIH grant applications must include a section titled Human Subjects Protection. This section describes specific risks to subjects who participate, and how risks will be minimized, and a **Data and Safety Monitoring Plan** for the research proposed.

Human Subject Protection:

1. Risks to Human Subjects
2. Adequacy of Protection Against Risks
3. Potential Benefits of Proposed Research
4. Importance of the Knowledge to be Gained
5. Data and Safety Monitoring Plan



Human Subject Protection Section

Data and Safety Monitoring Plan

5. If clinical trial, also include a Data and Safety Monitoring Plan describing:

- Who is responsible for monitoring study
- Frequency of monitoring data (every 6 months or every 20 subjects enrolled)
- Specific data to be monitored, procedures for analysis and interpretation of data
- Study wide stopping rules, if relevant
- Plan for review & reporting of adverse events and unexpected events to all sites, IRB, NIH, FDA
- Use of DSMB or Safety Monitoring Committee, when applicable

Continuum of Monitoring and Oversight

Lower Risk

Higher Risk



- **Who Monitors:** PI, IRB Medical Monitor, Safety Committee or DSMB
- **When to Monitor:** Initial & Annual Review Every X Subject
Every X month
Interim analysis
- **What to Monitor:** Enrollment Efficacy
Withdrawals Safety endpoints, AE & SAE
AE & SAE Stopping points



Are you sure you took the placebo?

Helpful Links & Websites

- NIH Policy on Safety Monitoring:
 - http://grants.nih.gov/grants/policy/hs/data_safety.htm
- NC TraCS Institute DSMB
 - <http://tracs.unc.edu/dsmb>
- Common Terminology Criteria for Adverse Events v.3.0
 - http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm
- Investigator Responsibilities – Protecting the Rights, Safety, and Welfare of Study Subjects
 - <http://www.fda.gov/cder/guidance/index.htm>
- International Conference on Harmonisation Good Clinical Practice E6
 - <http://www.ich.org/>
- Safety Monitoring Plan Template
 - <http://tracs.unc.edu/regulatory-services/data-and-safety-monitoring-plans.html>