UNC | SCHOOL OF MEDICINE
North Carolina Translational and Clinical Sciences Institute

Developing an Appropriate Data and Safety Monitoring Plan

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Objectives

- Describe appropriate monitoring of research
- Differentiate between a monitoring plan (DSMP) and a monitoring board (DSMB)
- Identify what to include in a monitoring plan
- Identify roles and responsibilities of a DSMB
- Understand how to complete the monitoring section of the UNC IRB application

What is Study Monitoring?

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

1) **Safety of participants**
   - Monitor for adverse events
   - Assess risk/benefit ratio
2) **Integrity and quality of data**
   - Monitor trial data for accuracy, completeness, quality and ensure data is verifiable
   - Verify trial conducted in compliance with protocol & Good Clinical Practice

Policies on Oversight and Monitoring

- NIH policy stipulates that a system be in place for **appropriate oversight and monitoring** to ensure the safety of participants and the validity of the data in all NIH-sponsored or NIH-conducted clinical trials. http://grants.nih.gov/grants/guide/notice-files/not98-084.html

- NIH - All studies should have a **safety monitoring plan** that is **commensurate with the risk level** of the study

- FDA - The sponsor shall **monitor** the progress of all clinical investigations being conducted under its IND, 21 CFR 312.56a

- NIH - **Phase III clinical trials** require monitoring by a **DSMB or DMC** http://www.nih.gov/grants/guide/notice-files/not98-084.html

What is a Data and Safety Monitoring Plan?

A **Data and Safety Monitoring Plan (DSMP)** is a detailed plan outlining the steps the study team will take to provide **oversight and monitoring** of a study to ensure subject safety and data integrity. The level of risk to participants in the study will determine the level of monitoring required.

It's a requirement for NIH funded clinical trials but any study can benefit from a monitoring plan.

What to include in a DSMP?

Components may include some or all below:

1. Monitoring safety of participants to ensure risk is minimized (e.g., labs tests, physical exams, EKGs)
2. Reporting unanticipated problems or adverse experiences
3. Identification of individual subject stopping rules, if appropriate
4. Ensuring data accuracy and protocol compliance
5. Study wide stopping rules or an interim analysis
6. Independent monitoring groups or boards (i.e., SMC or DSMB) for additional oversight.

Options for Who Monitors a Trial

- **Principal Investigator** ultimately responsible for all aspects of trial safety, can monitor low risk, unblinded study (phase 1)
- **Clinical Monitor** to review study files for adherence to protocol, quality & accuracy of data (e.g., IND or IDE studies)
- **Safety Officer** (physician, medical monitor) to provide review of adverse events, in real time (not member of study team)
- **Safety Monitoring Committee** to review study progress, safety events, advise the PI
- **Combination of aspects of above** (e.g., PI, clinical monitor + SMC)
- **Data and Safety Monitoring Board** to review blinded data, assess safety and rule on meeting stopping point

Extent of monitoring should be commensurate with the level of risk in the study.

Continuum of Oversight - Monitoring Plan

	Lower Risk	Higher Risk
• **Who:**	PI, IRB	Medical Safety Officer, Safety Committee or DSMB
• **When:**	Initial & Annual Review	Every X Subject Every X month Interim analysis
• **What:**	Enrollment Withdrawal, AE & SAE	Enrollment, Efficacy, Safety, Withdrawals, AE & SAE Stopping points

Importance of Independent Monitoring

Independent monitoring groups review data in aggregate and make decisions about the ongoing safety of the study:

- Having independent group review unblinded data and adverse events, allows investigators to remain blinded and **reduce bias in trial**.
- Recommended when a study involves a blinded intervention, there is significant risk, or study is large with multiple sites.
- Independent means NOT part of the study team

Data Monitoring Committee or Board

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)
- Review un-blinded trial data regularly
- Assess reasonable risk/benefit ratio
- Recommend continue, modify or stop
- Preserve integrity / credibility of trial and scientific result

Phase III or high-risk trials required to utilize a DSMB

DSMB Review Example

Multicenter trial (30 sites) looking at investigational drug vs. placebo in 600 diabetic patients, study team blinded to drug assignments.

Stopping Rule: if 20% of subjects in one arm experience grade 3 or higher AE or SAE related to the intervention, study will be stopped.

DSMB Reviews:

DSMB reviews data / AEs after every 100 subjects enrolled. Looks at data separated by arm of study, monitors rate of events (e.g., cardiac death) to see if more in one arm than other

- 1st review – 10 subjects out of 100 enrolled experience sudden cardiac death (10%)
- 2nd review – 30 out of 200 enrolled subjects experience sudden cardiac death, several cardiac events (15%)
- 3rd review – 60 out of 300 enrolled experience sudden cardiac death events (20%)

Different Types of DSMBs

- **Industry-sponsored DSMB** for specific study intervention
  - May serve several studies using same product over time
  - Primary responsibility to sponsor/steering committee
- **NIH DSMB** for large multicenter clinical trials
  - Set up to be advisory to the NIH sponsoring institute/center
- **Association Specific DSMB** (e.g., cystic fibrosis foundation)
- **Project Specific**
  - Investigator assembles a DSMB for a specific project only
- **Standing Institutional DSMB**
  - Assembled to monitor multiple trials conducted at an AMC

Institutional DSMBs at UNC

- **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, frequency based on risk and complexity

- **NC TraCS DSMB:** review UNC Investigator-initiated trials requiring a DSMB or additional oversight
  - Standing board that monitors multiple trials of various investigational drugs, devices or disease entities
  - Available to UNC Investigator or faculty
  - Membership: UNC faculty with wide range of medical backgrounds, research experts, biostatisticians

TraCS DSMB Membership / Expertise

Name	Department/School	Area of Expertise
Ross Simpson, Jr, MD, PhD (Chair)	Medicine	Cardiology, Epidemiology
David Weber, MD, MPH	Medicine	Pediatrics, Infectious Disease, Epidemiology
David Couper, PhD	School of Public Health	Biostatistics
Elizabeth Geller, MD	Medicine	Obstetrics & Gynecology
Lori Carter Edwards, PhD	School of Public Health	Public Health, Community
William Fischer II, MD	Medicine	Pulmonary, Critical Care
Eliza Park, MD	Medicine	Psychiatry
Marie Rape, RN, BSN	NC TraCS / Medicine	Nursing, ER, Clinical Research

Types of Trials Reviewed by TraCS DSMB

The following types of investigator-initiated trials accepted for review:

- UNC led trials with **significant risk or safety concerns, blinded interventional studies**
- Typically Phase II, III or IV clinical trials **(single site trials)**
- **Select multi-center clinical trials (3-5 sites)** and UNC is coordinating center (IF DSMB determines it has adequate resources to conduct monitoring required of study)
- **No Cost** to use TraCS DSMB

Examples of Trials reviewed:

Single Center Clinical Trial

- Randomized, controlled trial, pregnancy prevention treatment in 112 subjects, study conducted only at UNC
- PI initiated project, foundation support
- Study run under an IND (already approved drug used for different condition)

Multicenter Clinical Trial

- Phase 2, double blind study to evaluate an investigational drug in treatment of autism
- 250 subjects, 5 site clinical trial - CTSA sites
- Funded by NIH
- UNC PI of multicenter project
- IND - sponsor-Investigator

NC TraCS Institute DSMB Meetings

Meeting Schedule:

- Meetings held monthly in person or via Zoom (e.g., COVID)
- Agenda consists of initial and interim reviews of accepted trials

Initial Review:

- Determine if trial needs a DSMB or if another option is better
- If needs DSMB review, is TraCS DSMB appropriate resource?
- Is study design / statistical plan adequate? Is a statistician involved?
- Are stopping rules defined? Is role of DSMB well defined?
- Recommendations to improve protocol and statistical plan

Interim Reviews:

- Exam data on regular basis (e.g., every 6 months) – blinded or unblinded
- Monitor recruitment / enrollment on quarterly basis
- Review adverse events, SAEs (at regular meeting or if concern arises)
- Recommend continue, modify, or stop trial

Table 2a: Serious Adverse Events, by arm and relationship to treatment/study drug

Subject Number	Study Arm or Treatment	Date of SAE	*Relationship to Treatment/ Study Drug	Study Discontinuation Y or N	Description of Event
006	**Active**	**4-5-2010**	**Possibly**	**Yes**	**Anaphylactic reaction within ½ hour drug admin.**
ID #	A or B				
ID #	A or B				
ID #	A or B				
ID #	A or B				
ID #	A or B				
ID #	A or B				
ID #	A or B				
ID #	A or B				

* ***Relationship:*** *Definitely Related, Probably Related, Possibly Related, Not Related, Unknown*

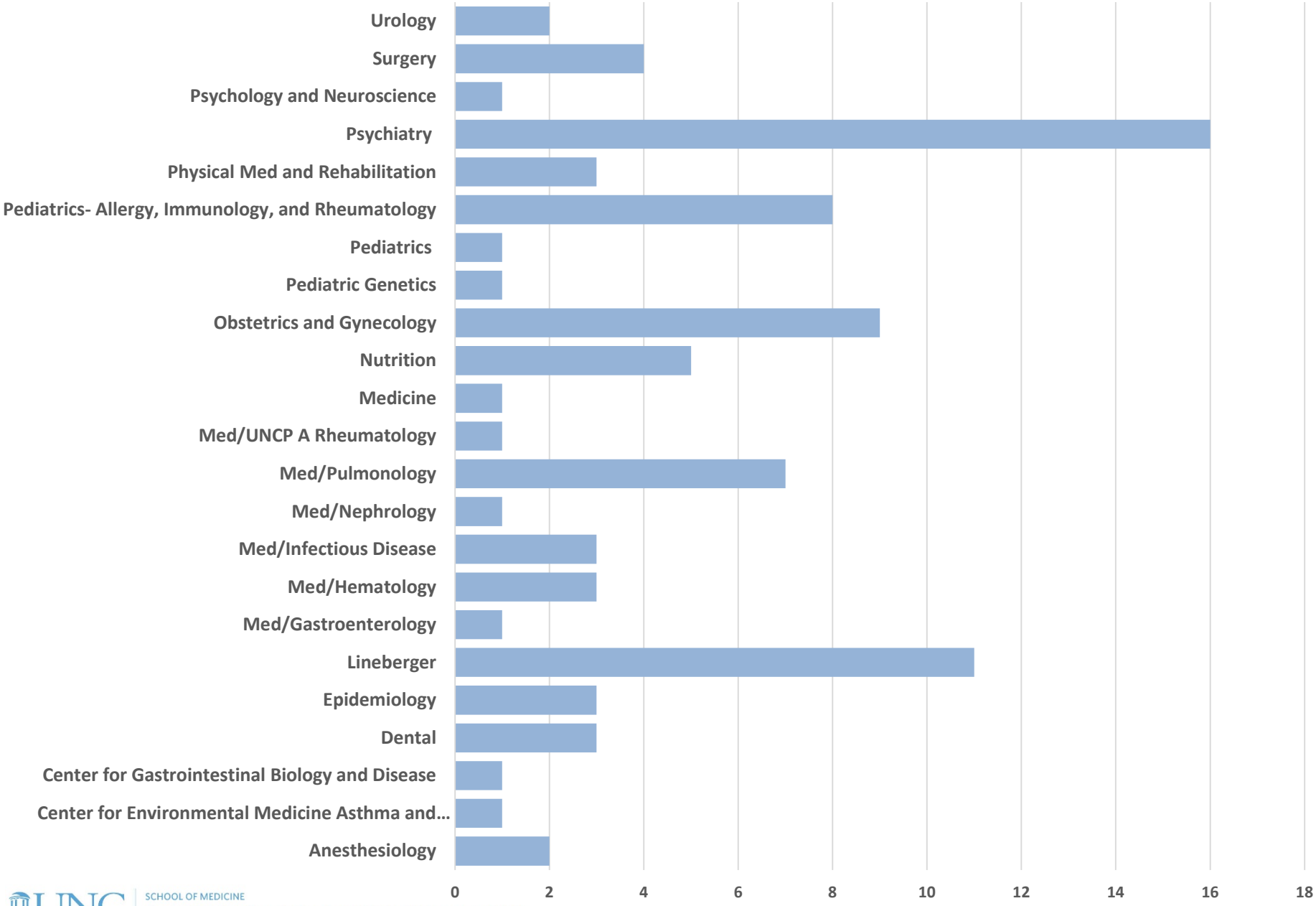
Table 1b: Subject Disposition

	Active (Arm A) N = #	Placebo (Arm B) N = #	Total N = #
Subject Disposition (all subjects)			
Screened (consented)			#
Randomized	#	#	#
Currently in trial	# (%)	# (%)	# (%)
Completed trial	# (%)	# (%)	# (%)
Discontinued trial	# (%)	# (%)	# (%)

SOM / TraCS DSMB Metrics over 18 years

- 75 + investigators provided guidance
- 90 + studies overseen or guided by DSMB
- 25 UNC Schools, Departments and Divisions served, heavily SOM
- 16 multisite studies provided oversight
- 21 studies currently under review
- 4-8 projects per month reviewed by TraCS DSMB

NC TraCS DSMB Studies Per Department



Contacting the TraCS DSMB

- **Marie Rape** (Administrator, TraCS DSMB)
  - Phone: 919-966-6844
  - Email: marie_rape@med.unc.edu

- **Ross Simpson** (Chair, TraCS DSMB)
  - Email: rsimpson@med.unc.edu

- **TraCS Website**: https://tracs.unc.edu/index.php/services/regulatory/data-and-safety-monitoring-board
  - Helpful information about DSMBs in general
  - Explains who is eligible to use the TraCS DSMB
  - Contains forms and instructions for submitting requests and interim reports to TraCS DSMB

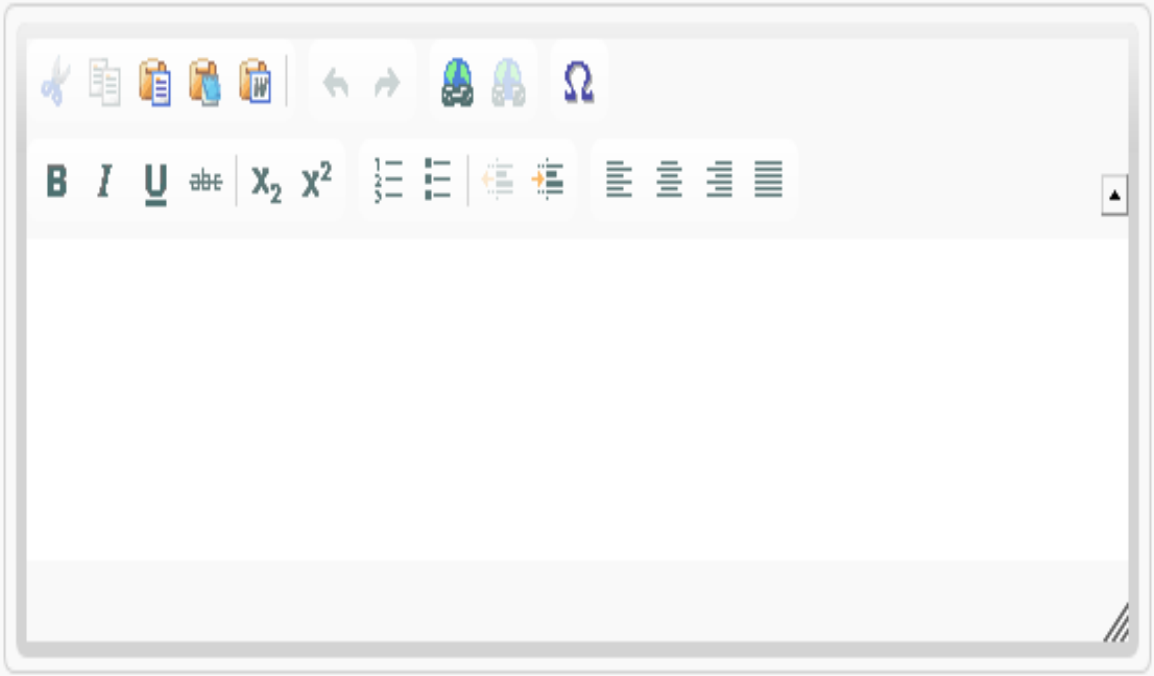
- **For a TraCS consult:** https://tracs.unc.edu/index.php/consultation
  - Advice on whether project needs a DSMB
  - Is the TraCS DSMB an appropriate option for your trial

IRB Applications & Renewals

IRB application Section A.7

Plan for monitoring the data to ensure safety

1. When appropriate, describe the plan for monitoring the data to ensure the safety of participants. These plans could range from the investigator monitoring subject data for any safety concerns to a sponsor-based data and safety monitoring board or committee (DSMB, DSMC, DMC), depending on the study. For studies that do not raise obvious safety concerns, you may still describe your plans for monitoring the study as it progresses. *



IRB Application Section A.7

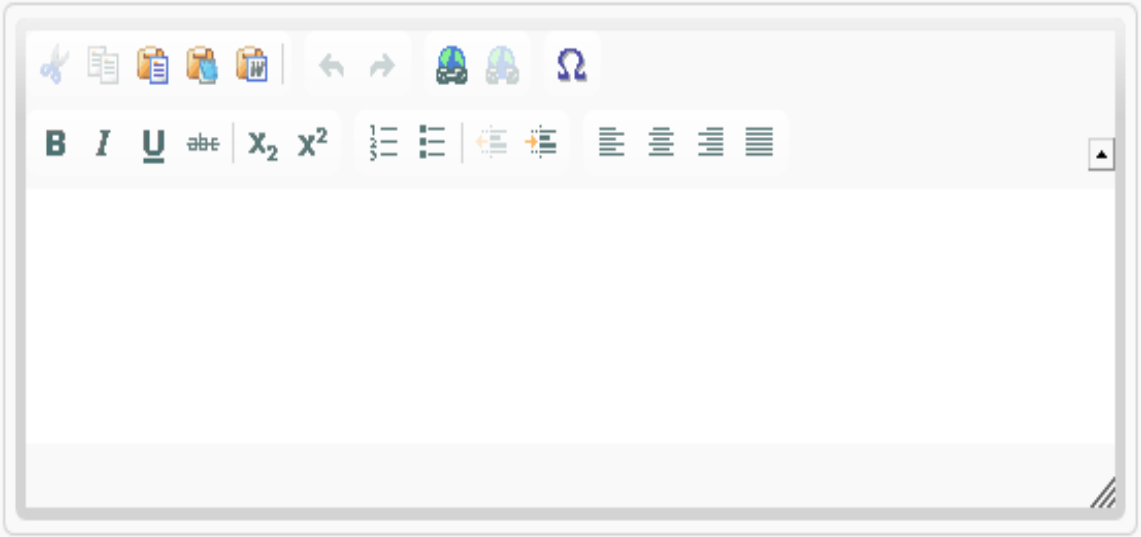
Plan for aggregate review of adverse events at all sites

2. If not already addressed above, describe the plans for aggregate review of unanticipated problems (including but not limited to adverse events) across all sites, in order to monitor subject safety.

IRB Application Section A.7

Subject and Study Wide Stopping Rules

3. What are the criteria that will be used to withdraw an INDIVIDUAL SUBJECT from this study or halt the research intervention (e.g., abnormal lab tests, allergic reactions, failure or inability to comply with study procedures, etc.)? *



Tips and Techniques on using the HTML Editor

4. Are there criteria that will be used to stop the ENTIRE STUDY prematurely (e.g., safety, efficacy, unexpected adverse events, inability to recruit sufficient number of subjects, etc.)? *

○ Yes ○ No

IRB Application Section A.7

Data and Safety Monitoring Board

5. Will this study involve a data and safety monitoring board or committee? *

(•) Yes ( ) No

Check all that apply

- [ ] TraCS Institute DSMB (formerly School of Medicine)
- [ ] Lineberger Cancer Center DSMC
- [ ] External DSMB (for example, established by sponsor or NIH)
- [ ] Other

If external or other, please identify here. You will be asked to attach charter and stopping rules later in the process. (limited to 200 characters)

Annual Renewal – Submitting DSMB reports

5. Have there been any relevant multi-site reports that have not been previously submitted to the IRB?

   No

6. If this study has a Data and Safety Monitoring Committee (DSMC or DSMB), is there a report that has not been previously submitted to the IRB?

   No

- Provide DSMB report with IRB renewal or when received
  - If significant finding, news, study trial stop – notify IRB promptly (don't wait for IRB renewal)

CTSA DSMB Training Manual

Online DSMB Training Manual with focus on investigator-initiated studies.

Provides information and training for Principal Investigators, DSMB members, IRB members, biostatisticians, and research staff.

- Monitoring of Clinical Research Studies (principals of monitoring, DSMP, methods of monitoring)
- DSMB Organization & Member Responsibilities
- DSMB meetings and Documents
- Data and Safety Review Process
- Role of Study Safety Officer & Study Monitoring Committees
- Forms & Templates: DSMP, DSMB charter, Safety Officer charter, Report forms, DSMB letter templates

CTSA DSMB manual – http://tuftsctsi.live/dsmb_manual

Links to More Information

- **TraCS DSMB Website** - https://tracs.unc.edu/index.php/services/regulatory/data-and-safety-monitoring-board and https://tracs.unc.edu/index.php/services/regulatory/monitoring-plan-development

- **Lineberger Comprehensive Cancer Center DSMC -** https://unclineberger.org/protocolreview/forms/

- **Research Coordination & Monitoring Unit (RCMU) –** to hire a clinical monitor to review study files: https://tracs.unc.edu/index.php/services/rcmu

- **NIH Policies and Websites with helpful guidance**
  - NIH Policy for Data and Safety Monitoring
  - Further Guidance on a Data and Safety Monitoring for Phase I and Phase II Trials
  - NCI Data and Safety Monitoring Guidelines
  - NIA guidance on Data and Safety Monitoring
  - NIDDK guidance on Data and Safety Monitoring Plans

Questions/Discussion

Thank you!