

CTSI Data Safety Monitoring Plan (DSMP) Instructions

Introduction to Data and Safety Monitoring Plan Requirements

The purpose of this section of the online CTSI application form is to provide the principal investigator (PI) and his/her staff the necessary background and guidance regarding Data and Safety Monitoring Plans (DSMPs).

Background

In June 1998, the National Institutes of Health (NIH) issued a policy on data and safety monitoring that requires oversight and monitoring of all intervention studies to ensure the safety of participants and the validity and integrity of the data. The National Center for Research Resources (NCRR), the funding agency for the Clinical and Translational Science Institute (CTSI), requires that all protocols conducted on the CTSI have a Data and Safety Monitoring Plan (DSMP) that is commensurate with the risks to human subjects. The DSMP is the responsibility of the PI, and it is subject to review and approval by the CTSI Scientific Review Committee (SRC). Research Subject Advocates (RSAs) are responsible for assuring that research carried out on the CTSI is in compliance with NIH, FDA, Good Clinical Practice (GCP) and local (e.g., IRB and CTSI) guidelines.

The Data and Safety Monitoring Plan (DSMP)

The DSMP is written in an effort to ensure the safety of study participants and the validity and integrity of study data. A DSMP must be submitted as part of the initial CTSI application and approved prior to the initiation of the study.

In the DSMP the PI provides the framework for data and safety monitoring, including the routine review and evaluation of enrollment data, outcomes, and adverse events (AEs). The DSMP can be as simple as the investigator submitting the annual report including safety and adverse event information to the IRB for minimal or low risk studies or as complex as having a Data and Safety Monitoring Board for high risk studies. The DSMP must be appropriate for the context of the disease, drug or device being studied, the level of risk to the patient, and the size and the complexity of the study. It should describe who is responsible for data and safety monitoring, what will be reviewed, frequency of reviews, and how adverse events will be reported, to whom they will be reported (e.g., CTSI, IRB, NIH, FDA) and when they will be reported. See the IRB website http://www.med.nyu.edu/irb/information_sheets/ae_rep.html for guidance on adverse event, serious adverse event and unanticipated adverse event reporting requirements.

The DSMP section of the CTSI application form can be used as a template to create a DSMP. The RSA can assist an investigator in preparing the DSMP.

Data and safety monitoring functions, including oversight of such activities, are distinct from the requirement for study review and approval by the Institutional Review Board. All correspondence to and from the IRB regarding patient safety issues (adverse event reporting, periodic reviews, etc.) should be forwarded to the CTSI RSA without delay.

Guidelines for conducting data and safety monitoring for studies conducted on the CTSI

1. All protocols involving human subjects must have a DSMP.
2. The creation and implementation of the DSMP is the responsibility of the PI.
3. The DSMP must be approved through a formal process (CTSI Scientific Review Committee).
4. The individual plan must be appropriate to an individual study's objectives, design and risks. The higher the risk of a study or the lower the certainty with which risk can be defined, the more frequent and intensive the interim data reviews.
5. Participant confidentiality must be maintained throughout the data and safety monitoring process, even if interim reviews are unblinded.

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6. The integrity of the DSMP process must be maintained and potential conflicts of interest avoided. This can include independent review, especially in higher risk situations.
7. Issues of unblinding during the review must be addressed. Monitoring must not compromise the scientific integrity of the study.
8. The DSMP has at least the following elements:
 - a. Brief description of the study
 - b. Selection criteria for the safety monitors/reviewers; a listing of their names, qualifications, potential conflicts, and contact information.
 - c. Designation of study contact person for communication with RSA/CTSI
 - d. Type of data to be reviewed at each monitoring periodic review and the rationale for selecting the data. Some examples are:
 - i. Number of subjects screened and enrolled
 - ii. Assessment of dropout rate
 - iii. Efficacy parameters such as primary/secondary endpoints (if appropriate)
 - iv. Categorization of adverse events using known criteria tools (e.g., use the National Cancer Institute CTC III scale or the WHO scale)
 - v. All serious adverse events (SAEs) and deaths
 - vi. Frequency of review and rationale for the recommended frequency
 - vii. Interim analysis (blinded, unblinded)
 - e. Preliminary criteria for decision making regarding continuation, modification or termination of the clinical study.

Definitions

Data and Safety Monitoring Plan (DSMP): A prospectively defined strategy to assess the assumptions made in the trial design while the study is in progress and to monitor and ensure safety of research subjects.

Data and Safety Monitor: The data and safety monitor must have expertise in the disease, drug or device being studied. This is separate and distinct from the monitor that some studies have (generally provided by the sponsor) to review study documents such as source documents, case report forms, pharmacy logs, etc.

Data and Safety Monitoring Committee/Board (Independent Data Monitoring Committee): An independent group of individuals who assess the progress of the study including the number of subjects enrolled, dropouts, adverse events and their severity, and the likelihood of achieving the anticipated results. The board's composition, meeting frequency, and its responsibilities should be tailored to the design and risks of the study.

Useful Websites [THESE NEED TO BE UPDATED]

1. <http://qcrc-www.med.nyu.edu/researcher/rsso/monitoring.html>
2. <http://www.ncrr.nih.gov/clinical/qcrcpatientsafety20010622.asp>
3. <http://grants1.nih.gov/grants/guide/notice-files/not98-084.html>
4. <http://grants2.nih.gov/grants/guide/notice-files/NOT-OD-00-038.html>
5. <http://www.fda.gov/cber/gdlns/clindatmon.htm>

Instructions for Completing the Data and Safety Monitoring Plan

Risk Level

This section is a guide to help you understand the basis for assigning the risk level for a study and that the risk level affects the type of oversight or monitoring that is appropriate for the study.

I. Monitoring and Safety Reviews

1. Who will do Data and Safety monitoring for this study?

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Data and safety monitoring must continue throughout the progress of a study until all patients have completed their treatment and for an additional month after their last visit. The data and safety monitor is different from the study monitor who typically reviews subject study records, regulatory documents, and study drug or device management. The data and safety monitoring can be done only by qualified persons with expertise in the disease, drug or device being studied.

Identify the person/s, committee or Data and Safety Monitoring Board (DSMB) that will perform the data and safety review. If the study has a DSMB, check the appropriate box and submit a copy of their charter and membership information, including a description of the planned meeting frequency and how information will be distributed to investigators.

2. Primary Data and Safety Monitor contact information

Provide the name, contact information and qualifications for the primary data and safety monitor. Does the study monitor have a conflict of interest? If yes, describe.

3. Plan for what will be monitored

Check appropriate boxes and provide additional information on what the data and safety monitor will evaluate.

4. Frequency of Monitoring

Check the appropriate box or describe the plan for frequency of monitoring. If this changes during the course of the study, submit the modification to the Research Subject Safety Office and note the change on the CTSI renewal form at the time of annual renewal.

5. Describe plans for interim analysis

Describe plans for interim analysis. If no interim analysis is planned check none. Interim analysis is recommended to evaluate whether or not the study should proceed based on available data and safety information.

II. Adverse Events

1. Scale for grading adverse event and serious adverse event severity and attribution

It is the Investigator's responsibility to evaluate Adverse Events (AEs), Serious Adverse Events (SAEs) and unanticipated adverse events for severity and attribution to study drug/device/procedure. Use of an accepted rating scale is required. Please indicate the scale that will be used.

CTC II and III can be found at <http://ctep.info.nih.gov/reporting/ctc.html>. The **WHO scale** and others can be found at <http://www.accessdata.fda.gov/scripts/cder/onctools/toxicity.cfm>. For the **General Severity scale**, the definitions below may be used for guidance in selecting the AE/SAE grade:

Grade	Event Severity	Description
1	Mild	Mild discomfort, no limitation in activity; no medical intervention/therapy required
2	Moderate	Moderate discomfort, limitation in activity-some assistance usually required; no or minimal medical intervention/therapy required
3	Severe	Marked discomfort, marked limitation in activity-some assistance usually required; medical intervention/therapy required, hospitalization possible
4	Life-threatening or disabling	Extreme and possibly permanent discomfort, extreme and possibly permanent limitation in activity-significant assistance required; significant medical intervention/therapy required, hospitalization possible
5	Death	

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For the **General Attribution scale**, the definitions below may be used for guidance in selecting relationship to the study article:

Category	Definition
Definite	Events occurring within a timely manner after administration of the study drug(s), which are known sequels to the administration of the study drug(s), and follow a previously documented pattern of reaction but for which no other explanation is known. This category applies to those AEs that the investigator believes are incontrovertibly related to the study(s).
Probable	Any event occurring in a timely manner after administration of the study drug(s), that follows a known pattern of reaction to the study drug(s), and for which no other explanation is known. This category applies to those AEs that, after careful medical consideration at the time they are evaluated, are believed with a high degree of certainty to be related to the study drug(s).
Possible	Any event occurring in a timely manner after administration of the study drug(s) that does not follow a known pattern of reaction and for which no other explanation is known. This category applies to those AEs that, after careful medical consideration at the time they are evaluated, are considered to be unlikely to be related but cannot be ruled out with certainty.
Unlikely	In general, this category can be considered applicable to those AEs that, after careful medical consideration at the time they are evaluated, are considered to be unrelated to administration of the study drug(s).
Not related	Any AE for which there is evidence that an alternative etiology exists or for which no timely relationship exists to the administration of the study drug(s) and the AE does not follow any previously documented pattern. This category applies to those AEs that, after careful medical consideration, are clearly and incontrovertibly due to causes other than the study drug(s).

2. Plan for Reporting Adverse Events (AEs), Serious Adverse Events (SAEs) and Unanticipated Adverse Events

2a. Plan for reporting AEs, SAEs and Unanticipated AEs to the IRB

Please follow the IRB guidelines for submission of AEs, SAEs and unanticipated AEs to them. When you send the report to the IRB also submit a copy directly to the CTSI. If you have questions about what has to be submitted or the timeframe for submission, please call the IRB at (212) 263-4110. IRB general guidelines are listed below or can be found at <http://www.med.nyu.edu/irb/policies.html> or http://www.med.nyu.edu/irb/information_sheets/ae_rep.html.

Definitions

Serious Adverse Event means any adverse experience that results in any of the following outcomes: death, a life-threatening experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening or require hospitalization may be considered a serious adverse event when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

Unexpected Adverse Event is any adverse experience associated with the study article for which the specificity or severity is not consistent with the current investigator brochure, or, if an investigator brochure is not required or available, the specificity or severity of which is not consistent with the risk information described in the general investigational plan or elsewhere in the current application, as amended. "Unexpected" refers to an adverse drug experience that has not been previously observed.

Associated with the Study Article means that there is a reasonable possibility that the experience may have been caused by the study article.

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ADVERSE EVENT REPORTING REQUIREMENTS

Responsible Person	Event	Timeframe	Regulatory Cite
INVESTIGATOR:			
To the IRB:	Unanticipated problems involving risks to subjects or others.	Promptly.	45 CFR 46.103(b)(5); 21 CFR 56.108(b)(1)
	Any serious adverse event in human gene transfer protocols.	Immediately.	NIH Guidelines on Recombinant DNA, Appendix M-VII-C.
	Unanticipated adverse device effects.	No later than 10 working days after the investigator first learns of the effect.	21 CFR 812.150.
	All adverse drug reactions that are both serious and unexpected.	Within 15 calendar days of the Investigator learning of the event.	ICH Guideline for Good Clinical Practice §3.3.8.
To Sponsor:	Any adverse event that may reasonably be regarded as caused by or probably caused by the drug.	Promptly, except if the event is alarming, it should be immediately reported.	21 CFR 312.64(b).
	Unanticipated adverse device effects.	No event later than 10 working days after the investigator first learns of the effect.	21 CFR 812.150.
	Serious adverse events, except for those that the protocol or other document (i.e., Investigator's Brochure) identifies as not needing immediate reporting.	Immediately.	ICH Guideline for Good Clinical Practice §4.11.1.
SPONSORS:			
To the FDA:	Any adverse experience associated with the use of the drug that is both serious and unexpected.	Within 15 calendar days after the sponsor's initial receipt of the information.	21 CFR 312.32(c). See also, Expedited Reporting Rules, p.8.
	Any unexpected fatal or life threatening experience associated with the use of the drug.	As soon as possible but no later than 7 calendar days after the sponsor's initial receipt of the information.	21 CFR 312.32(c). See also, Expedited Reporting Rules, p.8.
	Results of sponsor's evaluation of unanticipated adverse device effects.	Within 10 working days of receipt of the information.	21 CFR 812.150.

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	Applicant having approved application under 314.50, must report any adverse drug experience that is both serious and unexpected, whether domestic or foreign.	Within 15 calendar days of receipt of new information.	21 CFR 314.80(c).
	Any person having a product license under 601.20 (biological product), must report any adverse experience that is both serious and unexpected, whether domestic or foreign.	Within 15 calendar days of initial receipt of the information by the licensed manufacturer.	21 CFR 600.80(c).
To Other Investigators:	Any adverse experience associated with the use of the drug that is both serious and unexpected.	Within 15 calendar days after the sponsor's initial receipt of the information.	21 CFR 312.32(c).
	Any unexpected fatal or life threatening experience associated with the use of the drug.	As soon as possible but no later than 7 calendar days after the sponsor's initial receipt of the information.	21 CFR 312.32(c).

2b. Reporting SAEs and Unanticipated AEs to the CTSI

SAEs and unanticipated AEs must be reported immediately to the CTSI Research Subject Safety Office. A written copy of the written report submitted to the IRB should be submitted directly to the CTSI.

2c. Other entities who will be notified of AEs, SAEs and Unanticipated AEs

AEs, SAEs and unanticipated AEs may need to be reported to other groups, organizations or agencies for your study. Some examples may include but are not limited to the study sponsor, NIH, FDA, NYU Cancer Center, AGTG and PACTG. Check all that apply. At least one box must be checked.

IV. Additional Information

1. Insert or attach any additional information related to the DSMP. This may include information on the investigator's or sponsor's plan to review study data and safety issues for this study or anything that relates to data and safety monitoring for this study.

People to call or email with questions regarding

CTSI application process and protocol review status, contact the CTSI Research Grants Coordinator, Hal Rosenblatt, 263-8040 or 263-7900, hal.rosenblatt@nyumc.org.

Data and Safety Monitoring Plans - contact Halia Melnyk, RN, Research Subject Advocate at 263-2584, halia.melnyk@nyumc.org or Anna Nolan, MD at anna.nolan@nyumc.org