
Yale University Institutional Review Boards

420 GD.1 Data and Safety Monitoring Plan (DSMP)

Overview

This guidance is provided for the use of the investigators and research staff as a supplement to the policy on data and safety monitoring plans (Policy 420), as well as to further describe the application of the policy.

Content Requirements of the DSMP

The DSMP must describe how the investigator intends to provide ongoing supervision and evaluation of the activities of the study, including whether new risks have been identified and whether appropriate progress is being made.

The DSMP must document the procedures and means to protect the welfare and safety of subjects and to protect the integrity of the data. When the study sponsor is performing data and safety monitoring activities, the Yale investigator must provide a brief plan that describes how the local monitoring responsibilities will be integrated into the sponsor's DSMP and accomplished by the Yale investigator and how the IRB reporting requirements will be met.

The type and degree of monitoring must be commensurate with the degree of risk involved, the size and complexity of the study, and should be appropriate to the study population and research environment. The plan must include provisions for data review and performance of safety reviews, at a specified frequency appropriate for the level of risk undertaken by research participants. The plan must also include provisions for reporting unanticipated problems and adverse events as required by IRB policy and/or other internal and external organizations.

Required Elements of the DSMP

The following is a more detailed explanation of the elements required of a Data and Safety Monitoring Plan, as set forth in Policy 420:

A. Identification of the individuals who will be responsible for monitoring the data, assuring protocol compliance, conducting the safety reviews, and the specified frequency of the review(s).

1. The PI should identify who is responsible for monitoring the study.
Example: The principal investigator or named designee, e.g., co-investigator, will monitor the data and conduct safety reviews, at a specified frequency appropriate to the level of risk.
2. The PI should specify the frequency of reviews in the DSMP. During the review process the principal investigator will evaluate whether the study should continue unchanged, require modification/amendment, or close to enrollment.
3. The PI should define the parameters whereby the individual will analyze the monitoring and safety review data, (e.g., by time or per subject basis or any other specific and predetermined parameter or outcome). The focus of the analysis is to determine whether enrollment should continue or be closed, whether the trial should continue as originally designed or require modification/amendment.

It must be noted that the principal investigator, study sponsor, DSMB (if one exists), the IRB, and other University oversight committees e.g., QUACS, have the authority to stop or suspend the study or require modifications.

B. Explicit Statement of Risk:

The principal investigator must state the level of risk associated with participation in the study and must explain why that designation is appropriate. It is necessary to assess the risk associated with participating

in a study in order to facilitate consideration of safety issues and to design a DSMP appropriate to the level of risk presented. Risks considered should include not only physical risks but also the possible harm to the subject if confidential and sensitive data is inadvertently disclosed. Other considerations include whether vulnerable populations are included in the research study, if investigational agents or devices will be employed, the use of placebo in certain types of studies, and the underlying health of the study population(s).

C. Plan for Determining Relatedness of Adverse Events:

The principal investigator is responsible for determining the likelihood that an adverse event is related to the study and must assess the relatedness. (See IRB Policy 710, Reporting Adverse Events and Unanticipated Problems, and its associated Procedure.) A sample scale is provided below.

Example: Attribution of adverse events:

Definite: Adverse event is clearly related to investigational agent(s) or other study intervention(s)

Probable: Adverse event is likely to be related to investigational agent(s) or other study intervention(s)

Possible: Adverse event may be related to investigational agent(s) or other study intervention(s)

Unlikely: Adverse event is likely not to be related to investigational agent(s) or other study intervention

Unrelated: Adverse event is clearly not related to the investigational agents(s) or other study intervention(s)

Scales for attributing adverse events other than that specified above may be used so long as the criteria are clearly defined and/or referenced in the DSMP, e.g., National Cancer Institute's Common Toxicity Criteria (CTC), (<http://ctep.cancer.gov/reporting/ctc.html>)

D. Plan for Grading Adverse Events:

The principal investigator must provide a plan for categorizing/grading adverse events using a scale similar to the one provided below. The plan should indicate what sorts of events would be included in each category.

Example: Grades of Adverse Events:

1. Mild adverse event- discomfort noticed, but no disruption of normal daily activity
2. Moderate adverse event- discomfort sufficient to reduce or affect normal daily activity
3. Severe adverse event – incapacitation, with inability to work or perform normal daily activity

Scales for grading adverse events other than that specified above may be used so long as the criteria are clearly defined and/or referenced in the DSMP, (e.g., National Cancer Institute's Common Toxicity Criteria (CTC), <http://ctep.cancer.gov/reporting/ctc.html>).

Serious Adverse Events:

In addition to grading the adverse event, the PI must determine whether the adverse event meets the criteria for a Serious Adverse Event (SAE). An adverse event is considered serious if it 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, or any other Adverse Event that, based upon appropriate medical judgment, may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition.

Examples of Adverse Events Reportable as Serious Adverse Events:

Any adverse experience that, even without detailed analysis, represents a serious unexpected adverse event that is rare in the absence of drug exposure (such as agranulocytosis, hepatic necrosis, Stevens-Johnson syndrome).

A series of adverse events that, on analysis, is both unanticipated and a problem for the study. There would be a determination that the series of adverse events represents a signal that the adverse events were not just isolated occurrences and significantly affected the rights and welfare of participants.

An adverse event that is described or addressed in the investigator's brochure, protocol, or informed consent documents, or expected to occur in study participants at an anticipated rate (e.g., expected progression of disease, occurrence of events consistent with background rate in participant population), but that occurs at a greater frequency or at greater severity than expected.

Any other adverse event that would cause the sponsor to modify the investigator's brochure, study protocol, or informed consent documents, or would prompt other action by the IRB to assure the protection of human participants.

E. Plan for reporting serious AND unanticipated AND related adverse events, anticipated adverse events occurring at a greater frequency than expected, and unanticipated problems involving risks to subjects or others to the IRB.

The IRB requires reporting only for serious AND unanticipated AND possibly, probably or definitely related events and anticipated adverse events occurring with a greater frequency than expected. The IRB also requires reporting for all unanticipated problems involving risks to subjects or others that are unexpected AND suggest that research participation places the subject or others at greater risk of harm than was previously known or recognized AND are related or possibly related to the subject's participation. Reports must be in writing and made in a timely manner (within 48 hours) using the IRB Form 710 FR 1/710 FR2 (as appropriate), which requires the investigator to assess the need for change to the protocol, the procedures or the consent document(s).

For more information on the reporting of adverse events and unanticipated problems involving risks to subjects or others see IRB Policy 710: Reporting Adverse Events and Unanticipated Problems

F. Plan for reporting adverse events to co-investigators on the study, and as appropriate the protocol's research monitor(s), e.g., industrial sponsor, Yale Cancer Center monitors, the Yale Center for Clinical Investigation RSAs (YCCI RSAs), Cancer Center's QUACS, DSMBs, study sponsors, funding and regulatory agencies, and regulatory and decision-making bodies.

Principal Investigators must review ALL adverse events. Principal Investigators must define plans for reporting and reviewing adverse events to fellow investigators and key study personnel, sponsors, research monitors and other oversight bodies. For Multicenter trials when Yale is the coordinating site, the Yale PI is responsible for reviewing safety reports forwarded by sponsors or cooperative groups. As the PI assesses these reports, they should be categorized as serious or non-serious, and unanticipated or anticipated. Reporting of such to the IRB should be based upon IRB Policy 710. Principal Investigators must define plans for reviewing and reporting **non-serious, unanticipated** and **anticipated** adverse events to fellow investigators, key study personnel and appropriate research monitors.

When is a DSMB/DSMC Required?

The IRB may, in certain circumstances, require a DSMB depending on the level of risk or if there is a potential for a significant conflict of interest.

A DSMB/DSMC may be appropriate:

- In any study where the risk level is moderate to high.

- When a Yale Principal Investigator holds the IND for the investigational agent being used in the study.
- For Phase I and II trials if the studies have multiple clinical sites, are blinded, or employ particularly high-risk interventions or enroll vulnerable populations.
- When Yale is the coordinating site of a multicenter study.
- As a mechanism of managing a real or potential Conflict of Interest.
- When a Yale Principal Investigator is the inventor of an intervention being tested.

DSMB Attributes:

- When a DSMB is involved, the DSMB's organization, membership, responsibilities and operations should be described. Membership should include appropriate scientific and biostatistical expertise.
- The DSMB generally should be independent from the sponsor and investigator team. The degree of independence required depends on the risk level associated with the trial.
- The DSMB should be responsible for reviewing comprehensive, cumulative, unblinded safety reports, and employing stopping rules if there is evidence of differential effects in either risk or benefit. The descriptions of standard operating procedures should include frequency and documentation of periodic reviews, and submittal of written summary or minutes to the principal investigator.
- The investigator, upon receipt, must submit the DSMB findings and recommendations to the IRB.
- When the Yale principal investigator is required by the IRB to constitute a DSMB, the following will likely be required:
 1. All DSMB members, or the majority of DSMB members do not have Yale appointments.
 2. DSMB members do not have interests, financial or otherwise, in the outcome of the study.
 3. DSMB members who may be internal to Yale do not have reporting relationships to members of the research team.
 4. DSMB members who are internal to Yale are not members of the same department or section as the Yale principal investigator.

The HRU and the Yale Cancer Center may have specific DSMP and DSMB requirements. The Principal Investigators should consult with these offices, if applicable, to ensure that these requirements are met.

DSMP Templates

DSMP Templates are available at <http://yale.edu/hrpp>