



# DATA AND SAFETY MONITORING GUIDANCE

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**Harvard Catalyst | The Clinical and Translation Science Center**  
Regulatory Foundations, Ethics, and Law Program

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## Section One: Overview of Data and Safety Monitoring<sup>1</sup>

### *Background*

A clinical trial depends upon a relationship between research participants and investigators; each must fulfill certain obligations for the effort to succeed. A clinical trial also relies upon a partnership between investigator and institution/sponsor; together they must ensure proper monitoring and conduct of the clinical trial, in accordance with applicable regulations and Good Clinical Practice (GCP).

To ensure the safety of research participants, federal regulations require provisions to monitor data collected in the course of a research study, where appropriate (see 45 CFR 46.111(a)(6); 21 CFR 56.111(a)(6)). Data and safety monitoring aims both to protect participants and ensure the integrity and validity of research data. All studies involving human subjects require some level of data and safety monitoring. This includes physiologic, toxicity, and dose-finding studies (phase I); efficacy studies (phase II); and efficacy, effectiveness, and comparative trials (phase III). The specific monitoring strategy will depend on the risk, size, and scope of the study, and may involve individuals or groups.

The method and level of monitoring should be commensurate with the degree of risk to subjects and the size and complexity of the study. Generally, minimal risk studies may only require a Data and Safety Monitoring Plan (DSMP) which outlines limited monitoring by the principal investigator (PI) at regular intervals. Higher-risk studies require more frequent monitoring, including outside monitoring. Outside monitors can include an independent safety officer, a sponsor-appointed monitoring committee or board, or an outside independent group of experts (often referred to as a Data Safety Monitoring Board (DSMB), or a Data Monitoring Committee (DMC)), which conducts interim monitoring, analysis, and oversight.

The PI must protect participants' health and safety, inform participants of information related to their continued participation, and pursue the research objectives with scientific diligence. The Food and Drug Administration (FDA) holds the PI responsible for the overall conduct of a research study, including the

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<sup>1</sup> Adapted from "Planning for Data and Safety Monitoring in Clinical Research Studies: Developing your Study-Specific DSMP," in Boston University Medical Center's *Clinical Research Times*, November 2006 issue (<https://wwwapp1.bumc.bu.edu/ocr/ClinicalResearchNewsletter/article.aspx?article=118>).

establishment of data and safety monitoring provisions (see regulation 21 CFR 312.60). The PI is responsible for developing DSMP before the study is initiated<sup>2</sup>. The plan must be reviewed by the IRB and adhere to NIH guidance on data and safety monitoring, outlined below (Table 1).

<b>Table 1: National Institute of Health (NIH) Guidance on Data and Safety Monitoring</b>
<b><u><a href="#">June 1979: NIH Guide, Volume 8, No. 8</a></u></b>
<ul style="list-style-type: none"> <li>• Every clinical trial should have a provision for data and safety monitoring.</li> <li>• A variety of types of monitoring may be anticipated depending on the nature, size, and complexity of the clinical trial.</li> </ul>
<b><u><a href="#">June 1998: NIH Policy for Data and Safety Monitoring</a></u></b>
<ul style="list-style-type: none"> <li>• All clinical trials require monitoring commensurate with risks, size and complexity.</li> <li>• The monitoring focus is on participant safety and on validity and integrity of the data.</li> <li>• Each NIH Institute or Center “should have a system for the appropriate oversight and monitoring of the conduct of clinical trials.”</li> </ul>
<b><u><a href="#">June 2000: Further Guidance on Data and Safety Monitoring for Phase I and Phase II Trials</a></u></b>
<ul style="list-style-type: none"> <li>• Investigators must submit a general description of the data safety monitoring plan (DSMP) as a part of the research application.</li> <li>• A detailed monitoring plan must be included as part of the protocol submitted to the Institutional Review Board (IRB).</li> <li>• Plans must include a description of the reporting mechanisms of adverse events (AEs) to the IRB, FDA, and NIH.</li> <li>• NIH Centers have the flexibility to determine AE reporting requirements.</li> </ul>

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<sup>2</sup> According to the NIH Policy for Data and Safety Monitoring, released June 10, 1998.

## *Using this Guide*

This guidance describes current principles and practices with respect to the creation of DSMB/Ps for clinical research trials involving human subjects. This resource was developed specifically for audiences who are unfamiliar with DSMB/Ps and/or those looking for DSMB/P templates.

This guidance does not establish legally enforceable rights or responsibilities, and the contents should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. Specific requirements imposed by those entities with authority to review and approve DSMPs and DSMBs (such as federal agencies (e.g. NIH), IRBs, scientific review committees (SRCs), study sponsors, or study coordinating centers must be respected, and supersede any recommendations included in this document.

## *Audience*

The following guidance and templates are designed with two audiences in mind:

- **Researchers and Research Staff**

The guidance has been developed to assist principal investigators and research staff in developing DSMP and DSMB procedures. These templates should be used as guides to develop materials that adhere to institutional policies and guidelines. Please refer to the links in this document and to the [NIH website](#) for applicable regulations.

- **IRBs, Human Research Protection Programs, and Office of Sponsored Programs**

IRBs, Human Research Protection Programs, and Offices of Sponsored Programs may use this guidance to assist in determining the requirements for, models of, and procedures relating to DSMPs and, more specifically, DSMBs. This document can also be provided to researchers as supplemental guidance on DSMB/P regulations and procedures, as described above.

## Section Two: Data and Safety Monitoring for Clinical Trials

To the extent possible, IRBs and the NIH must ensure the safety of study participants. Although study participants may benefit from taking part in clinical research, participants should not incur unnecessary risk in doing so. For this reason, a study's risk/benefit profile should be periodically reassessed throughout the study period.

The above aims are accomplished in part through data and safety monitoring. The method and intensity of monitoring for a clinical trial is directly related to the degree of risk involved and the size and complexity of the study. The appropriate DSMP for a particular study can range from episodic or continuous monitoring by the PI, to more rigorous monitoring by an independent DSMB.

## Single Center Clinical Trials<sup>3</sup>

### Risk Determinations

The following examples may be helpful when determining the degree of risk and appropriate level of monitoring for a single center clinical trial:

1. **Non-therapeutic observational studies using procedures generally considered as minimal/low-risk**

*For example* - collection of blood samples by finger stick, heel stick, ear stick, or venipuncture; nasal wash; nutritional assessments; questionnaires; behavioral surveys; imaging (not using sedation); EKGs; gait assessments; use of left over samples from clinically indicated procedures.

**Recommendation:** PI monitoring.<sup>4</sup> (See Appendix A for PI's responsibilities)

2. **Moderate- to high-risk non-therapeutic clinical trials, low-risk therapeutic clinical trials, and observational studies using procedures or treatments with well-established risk profiles**

*For example* - behavioral trials, psychiatric surveys, nutritional therapies, low-risk procedures (e.g., endoscopy, glucose-tolerance tests, induced sputum, skin or muscle biopsy, lumbar puncture, bone marrow biopsy, imaging requiring sedation, etc.). Also includes therapeutic trials involving licensed agents with known safety profiles, provided there is no reason to suspect the safety profile would differ for the proposed indication or age group.

**Recommendation:** Independent study monitor(s). (See Appendix B for more information on Independent study monitors and monitoring)

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<sup>3</sup> Adapted from the University of Washington – ITHS Partner Institutions Joint Tool for Data and Safety Monitoring Plans (DSMP) available: <https://www.iths.org/wp-content/uploads/Cross-institutionalDSMPguidelines.doc>

<sup>4</sup> This type of plan is appropriate when the study is conducted only at one site; involves a small number of subjects; and the range of possible study events that could have a significant impact on the risks and benefits to research participants is narrow. In such cases, continuous monitoring of events by the investigator, and prompt reporting of toxicity to the IRB and, when applicable, the FDA, the NIH, or others, may be adequate.

**3. Therapeutic intervention trials and observational studies using procedures or treatments generally considered to be moderate-risk**

*For example* - organ biopsy, insulin clamp studies, or Phase II studies of agents with available safety data in the same population. Also includes research in psychologically or neurologically impaired individuals.

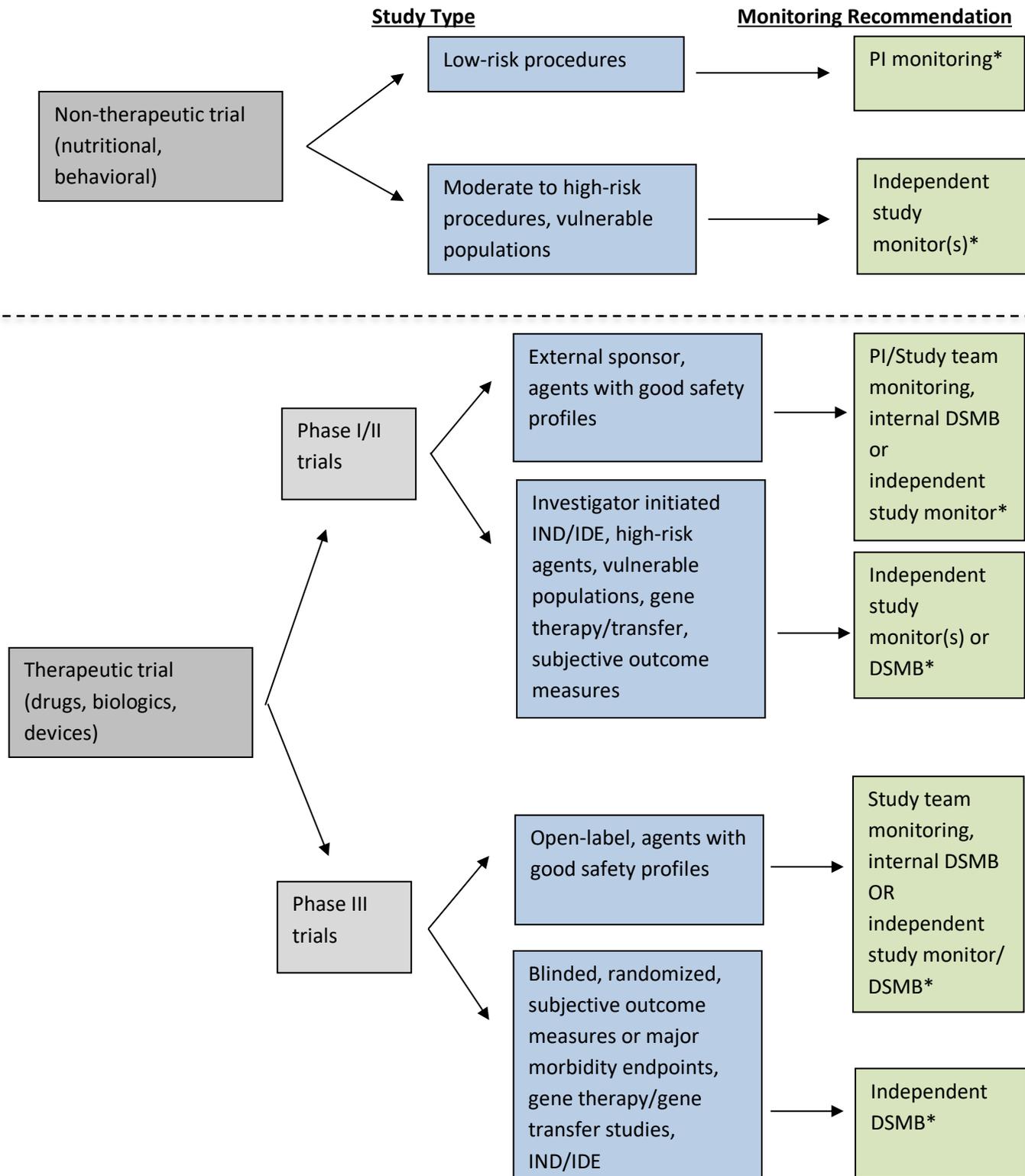
**Recommendation:** External monitor or DSMB generally required.

**4. Therapeutic trials involving investigational agents or devices that present substantial risk to study participants, or observational studies with high-risk clinical procedures**

*For example* - gene therapy, investigator-initiated INDs, Phase III randomized blinded comparative trials, high-risk clinical procedures performed solely for research purpose.

**Recommendation:** DSMB.

## Decision Tree<sup>5</sup>



<sup>5</sup>Adapted from the University of Washington – ITHS Partner Institutions Joint Tool for Data and Safety Monitoring Plans (DSMP) (<https://www.iths.org/wp-content/uploads/Cross-institutionalDSMPguidelines.doc>)

\* See Appendices A and B for more information on PI monitoring and independent monitors/monitoring.

## Multi-Center Clinical Trials<sup>6</sup>

### Risk Determinations

The following examples may be helpful when determining the degree of risk and appropriate level of monitoring for a multi-center clinical trial:

1. **Non-therapeutic observational studies using procedures generally considered as minimal/low-risk**

*For example* - collection of blood samples by finger stick, heel stick, ear stick, or venipuncture, nasal wash, nutritional assessments, questionnaires, behavioral surveys, imaging (not using sedation), use of discarded biospecimens from clinically indicated procedures, EKGs, gait assessments

**Recommendation:** PI or Study team monitoring.<sup>7</sup>

2. **Moderate- to high-risk non-therapeutic clinical trials, low-risk therapeutic clinical trials, and observational studies using procedures or treatments with well-established risk profiles**

*For example* - behavioral trials, psychiatric surveys, nutritional therapies, low-risk procedures (e.g., endoscopy, glucose-tolerance tests, induced sputum, skin or muscle biopsy, lumbar puncture, bone marrow biopsy, imaging requiring sedation, etc.). Also includes therapeutic trials involving licensed agents with known safety profiles, provided there is no reason to suspect the safety profile would differ for the proposed indication or age group.

**Recommendation:** Independent study monitor(s); internal or independent DSMB. (See Appendix B for more information on Independent study monitors and monitoring)

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<sup>6</sup> Adapted from the University of Washington – ITHS Partner Institutions Joint Tool for Data and Safety Monitoring Plans (DSMP) available: <https://www.iths.org/wp-content/uploads/Cross-institutionalDSMPguidelines.doc>

<sup>7</sup> This level of monitoring is appropriate for minimal risk studies and certain single-site studies that have greater than minimal risk. Reportable events and other study-related safety information must be promptly reported to the sponsor, federal agencies, and any other required entities as outlined in the approved protocol. The PI must report protocol deviations that involve a safety issue and proposed amendments. Examples of study activities appropriate for this level or review are: open-label, single-site clinical trials; small pilot studies with drugs/devices; phase 4 drug or device studies.

**3. Therapeutic intervention trials and observational studies using procedures or treatments generally considered to be moderate-risk**

*For example* - organ biopsy, insulin clamp studies, or Phase II single- or multi-site trials of agents with available safety data in the same population. Also includes research with cognitively impaired individuals.

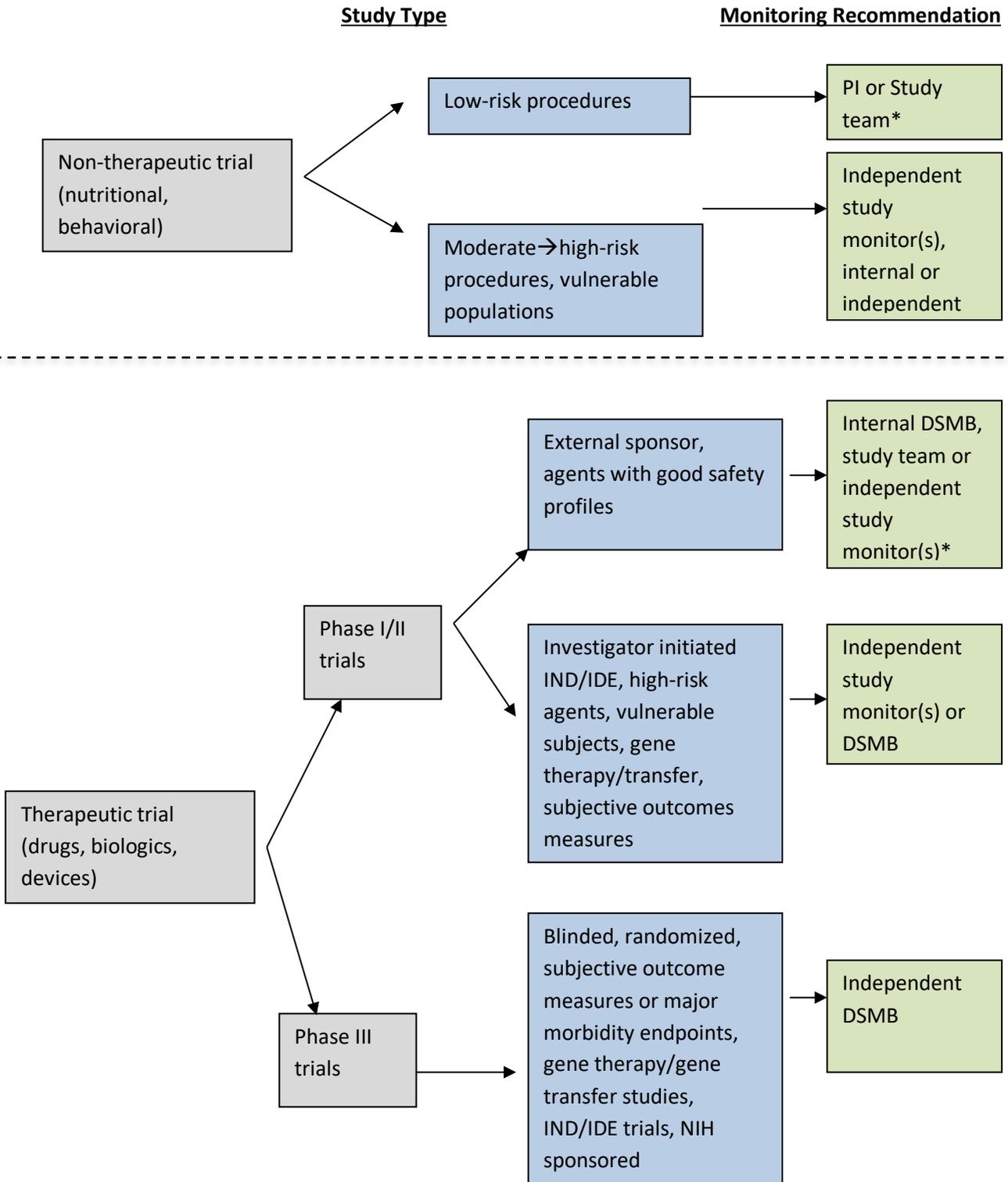
**Recommendation:** external monitor or DSMB generally required.

**4. Therapeutic trials involving investigational agents or devices that present substantial risk to study participants, or observational studies with high-risk clinical procedures**

*For example* - gene therapy, investigator-initiated INDs, Phase I multi-site trials, Phase III randomized blinded comparative trials, high-risk clinical procedures performed solely for research purposes.

**Recommendation:** DSMB generally required

Decision Tree<sup>8</sup>



<sup>8</sup> Adapted from the University of Washington – ITHS Partner Institutions Joint Tool for Data and Safety Monitoring Plans (DSMP) <https://www.iths.org/wp-content/uploads/Cross-institutionalDSMPguidelines.doc>

\* Reference Appendices A and B for more information on PI monitoring and Independent monitors/monitoring.

## Section Three: Data and Safety Monitoring Plans (DSMPs)

### *When is a DSMP Required?*

When conducting a clinical trial, data safety monitoring is integral to ensuring the safety of all research participants. A DSMP is a written plan for monitoring study data and participant safety. The DSMP ordinarily appears in the study protocol or other document submitted to the IRB and assures that the research study has a system for appropriate oversight and monitoring.

DSMPs are required for all clinical studies that pose minimal or greater than minimal risk. A DSMP should delineate who is responsible for reviewing and reporting adverse events, to whom events are reported, and on what schedule this monitoring and reporting will occur. When an NIH agency requests a copy of the final DSMP for agency approval prior to an award, these plans require approval from your institution.

## *DSMP Elements*

Generally, a written description of a DSMP (either included as part of the human subjects protocol or as a separate document) should contain the following elements:

1. **For a clinical trial requiring only a DSMP, include<sup>9</sup>:** The entity (person or committee) responsible for monitoring the overall investigation (as distinct from individual site monitoring for data completeness and accuracy); options include:
  - a. PI-only; may be sufficient for minimal/low-risk investigations;
  - b. Study team; appropriate for most observational trials and some multi-center trials;
  - c. External monitor; an individual not directly involved in the study; may be sufficient for some moderate-risk investigations; and/or
  - d. Internal Data Monitoring Committee; comprised of two or more individuals from the home institution (but independent of the study team) who have familiarity with the condition under study; may be appropriate for moderate to high-risk single-center investigations.
2. Description of the aspects of the study to be reviewed (e.g. enrollment, adverse events, data completeness, outcome data, protocol non-compliance, new and relevant information, etc.).
3. Frequency of data review and frequency of written reports (if different from the review periods).
4. Plan for adverse event identification and reporting, including:
  - a. Grading scales,
  - b. Attribution scale,
  - c. Methods used to capture adverse events (e.g. subject interview, lab tests), and
  - d. To whom adverse events will be reported, and time frame for reporting.

Note: At a minimum, review of adverse events should occur annually, and reports should go to the IRB, with unexpected and serious adverse events reported and reviewed immediately, as they occur. Office for Human Research Protections (OHRP) regulations require adverse events and unanticipated problems be promptly reported to the IRB of record; guidance specifies reporting these events within five business days. Be aware that some studies may have more stringent monitoring and reporting mechanisms and requirements.

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<sup>9</sup> DSMPs for low-risk observational studies may not need to specifically address all of the following elements.

5. Data and safety monitoring criteria for decision-making regarding continuation, modification, or termination of the individual participant or clinical study, including interim statistical analysis/early termination rules (if applicable).
6. Plan for monitoring of data quality and accuracy.

**A clinical trial that requires a DSMP *and* a DSMB** should include the elements listed above in the DSMP, along with the appropriate elements in the following section. Though every study will have a DSMP, only a subset of studies will have a DSMB as one of several components of their safety monitoring plans. The DSMP should specifically indicate whether a formal DSMB will be convened.

*DSMP Template*

General DSMP for Low-Risk Study

**See Appendix C**

## Section Four: Data and Safety Monitoring Boards (DSMBs)

### *What is a DSMB?*

A DSMB is made up of members from a variety of disciplines who are knowledgeable about, and responsible for, the conduct of research. Membership must include representatives with backgrounds in biostatistics, experimental design, bioethics, and the medical field(s) of concern.

DSMBs are responsible for reviewing data and endpoints on a timeline set forth by the DSMP in the approved protocol. DSMBs are typically required for the following:

1. Studies that pose greater than minimal risk
2. Blinded studies
3. Studies involving a vulnerable population (e.g., pediatric, geriatric, cognitively impaired)
4. Studies involving new therapies or science
5. Studies involving highly toxic therapies or dangerous procedures
6. Studies involving high expected rates of morbidity or mortality in the study population
7. Studies involving a high chance of early termination
8. Multi-site studies—It is more difficult for an investigator to recognize a pattern of increased or unusual problems when he or she sees only a small fraction of study participants

## *DSMB Elements*

### **DSMB Charter**

A DSMB charter is a set of written policies that describes the roles, rules, and functioning of the DSMB.

Generally, a charter will include:

- The purpose of the DSMB;
- Responsibilities of the members;
- The operation and format of the DSMB meetings;
- Monitoring guidelines;
- Reporting processes (to and from the DSMB);
- Research data to be monitored, and how data will be provided; and
- The responsibilities of DSMB administrators.

The charter is intended to be a living document that members may review at any time to determine whether changes in procedure are necessary.

### **External Data Safety Monitoring Boards**

For studies requiring an external DSMB, such as industry-initiated and sponsored studies, the PI may follow the procedures delineated by the sponsor. In this case, the sponsor usually drafts the DSMB charter. However, the PI must be prepared to describe to the IRB of record the composition of the DSMB, frequency of meetings and reports, and the plan to provide such reports.

### **Internal Data Safety Monitoring Boards**

#### 1. Responsibilities

- a. Pre-enrollment meeting: The DSMB may meet prior to the enrollment of the first subject to review the research protocol, informed consent documents, and DSMP. This review allows the DSMB to:
  - (1) Determine the study's risks and benefits, protections in place, and safety of research subjects;
  - (2) Offer suggestions for improving the study design;
  - (3) Reach agreement on the data that will be required for review;
  - (4) Determine the schedule of future meetings

- (5) Appoint the chair and voting members;
    - (6) Decide who receives minutes; and
    - (7) Sign conflict of interest statements.
  - b. The above issues must be addressed, regardless of whether the DSMB formally convenes for a pre-enrollment meeting.
2. This meeting may result in modification of the safety plan provided in the IRB application. If the DSMP is revised, the new plan should be submitted to the institution's IRB and, any applicable advisory committees.
- a. Interim data review: The DSMB reviews interim data to detect evidence of efficacy or adverse effects and determines if the trial should continue as originally designed, or whether it should be changed or stopped.
  - b. Progress evaluation: The DSMB evaluates the progress of the trial, including periodic assessments of data quality/completeness, achievement of recruitment goals, protocol adherence, accrual and retention of participants, and other factors that may affect the study outcome.
  - c. Protection of confidentiality: The DSMB protects the confidentiality of study participants, trial data, and the results of the monitoring.
3. Membership
- a. Appointment: The investigator may independently appoint the DSMB; institution leadership may appoint DSMB members at their institution.
  - b. Composition: The Board should include three or five members in total (always an odd number). If an efficacy assessment is part of the monitoring plan, a statistical monitoring plan is necessary to ensure the validity of the study and so the board should include a biostatistician. Investigators are encouraged to consider appointment of individuals from different units or divisions from within their institution, and beyond. Board membership must be determined and described prior to submitting a project for scientific and human subjects review.
  - c. Qualifications and responsibilities: Qualifications for membership are:
    - (1) Expertise in the field,
    - (2) Experience in conduct of human subjects research and statistical knowledge,
    - (3) Independence from the direct management of the research study, and
    - (4) Absence of conflict of interest or other conflicting commitment (i.e., must not be a

co-investigator, should not be a direct report of any PI or co-investigator).

4. A chairperson will be appointed, and will be responsible for overseeing the meetings, developing the agenda, and summarizing the meeting. The chairperson is the contact person for the DSMB.

### **Timing and Frequency of Meetings**

DSMB meetings will take place at least annually. The board may choose to meet periodically (e.g., quarterly or semiannually) if the risk to the subject is high, the population is vulnerable, there is a large volume of data to review, and/or after a pre-determined number of subjects have accrued. The chair may also call ad hoc meetings depending on safety or efficacy concerns. Meetings may be conducted by teleconference at the request of the board members.

### **Meeting Agenda**

1. The board will review required data (determined at the pre-enrollment meeting) provided by the investigator.
2. As per the DSMP, The board will:
  - a. Determine if the study has adhered to the treatment plan
  - b. Review interim analysis, if applicable, and determine specific data to be analyzed
  - c. Evaluate end point/stop point rules
  - d. Review protocol violations and deviations to assess adequacy of the protocol
  - e. Ensure appropriate documentation of informed consent
  - f. Review current enrollment information to:
    - (1) Determine whether enrollment has followed eligibility criteria
    - (2) Ensure accrual is on target
    - (3) Assess visit compliance
    - (4) Review screening failure information
  - g. Review IND/IDE information
  - h. Discuss investigator or key personnel changes
  - i. Review completeness and quality of data collection forms
  - j. Evaluate the aggregate analysis of adverse events/serious adverse events
  - k. Review vital signs, clinical tests, etc.
  - l. Review confidentiality

## **Meeting Outcomes**

The major outcomes following data review include:

1. *Continuation* of the trial, unchanged
2. *Modification* of the protocol and/or consent form (for example, it may be unethical to continue giving a placebo after a new treatment has been proven to be effective, or to continue a new treatment when there is no chance the trials will be positive)
3. *Termination* of the trial

## **Minutes and Reporting**

Minutes from each meeting will be maintained.

The investigator should not be present for at least part of the meeting. Following the meeting, a report should be provided to the investigator, the IRB, the sponsor, and if necessary, study participants. The report should indicate whether the study should continue as originally designed, be modified to protect patient safety, or be terminated.

### ***DSMB Template***

This template covers the range of information that may be required when planning a study that includes a DSMB.

### **Multi-Center Clinical Trial**

**See Appendix D**

## **Training Curriculum for DSMB Members**

One challenge DSMBs face is ensuring adequate member training. Below is a sample outline of recommended training elements to provide individuals with the expertise necessary to serve on a DSMB. Video trainings for DSMB members are available [here](#).

### Data Safety Monitoring Board (DSMB) Training<sup>10</sup>

<b>Session A</b>
<b>8.20-8.30 Opening remarks</b>
<b>8.30-9.00 Perspectives: History and Responsibilities of DSMBs</b> <ul style="list-style-type: none"><li>• DSMB perspective</li><li>• Challenges associated with DSMB monitoring</li><li>• Rationale and purpose of DSMBs</li></ul>
<b>9.00-10.00 DSMB membership and responsibilities</b> <ul style="list-style-type: none"><li>• Where DSMBs fit in organizational flow</li><li>• Composition of DSMBs</li><li>• What members need to know and do (and need to know not to do)<ul style="list-style-type: none"><li>○ Conflict of Interest</li><li>○ Indemnification</li><li>○ Roles and responsibilities of the chair of a DSMB</li><li>○ Roles and responsibilities of the statistician member of a DSMB</li></ul></li><li>• Roles: Review protocol design, assess safety assessment, ensure trial integrity, assess efficacy and futility, make recommendations</li><li>• Understanding interim results</li><li>• Evaluation of study conduct</li><li>• Recruitment and study progress</li><li>• The DSMB charter</li></ul>
<b>10.00-10.15 Break</b>
<b>10.15-11.00 Guidance for Monitoring Clinical -Trials</b> <ul style="list-style-type: none"><li>• Meetings: Structure and Schedule</li><li>• Blinding (who is blinded, unblinded)</li></ul>

<sup>10</sup> Adapted from Data Safety Monitoring Training offered by the Multi-Regional Clinical Trials Center of Brigham and Women's Hospital and Harvard

<ul style="list-style-type: none"> <li>• Recommendations DSMBs can make <ul style="list-style-type: none"> <li>○ Modifying the protocol</li> <li>○ Stopping a trial</li> </ul> </li> <li>• Communicating DSMB recommendations</li> <li>• Regulatory Issues</li> </ul>
<p><b>11.00-11.15 Monitoring for Safety</b></p> <ul style="list-style-type: none"> <li>▪ How to evaluate safety data – what is important, what is likely spurious</li> <li>▪ SAE individual case reports</li> <li>▪ Aggregate tables</li> <li>▪ Quality of safety reports</li> </ul>
<p><b>11.15-12.00 Monitoring for Efficacy</b></p> <ul style="list-style-type: none"> <li>• Issues with multiple “looks”</li> <li>• Methods</li> <li>• Controlling for error rates</li> <li>• Operational issues</li> <li>• Bias</li> <li>• Methods for stopping for efficacy</li> <li>• Limitations of current methods</li> </ul>
<p><b>12.00-13.00 Lunch</b></p>
<p><b>13.00-13.45 Monitoring for Futility</b></p> <ul style="list-style-type: none"> <li>• Definition of futility</li> <li>• Data used</li> <li>• Metrics for low probability/conditional power</li> <li>• Case study</li> </ul>

<b>Session B</b>
<b>13.45-14.00 Multi-Regional Clinical Trials</b> <ul style="list-style-type: none"> <li>• Concept</li> <li>• Examples</li> <li>• Issues that can occur with MRCTs (sources of variability, heterogeneity, intrinsic or extrinsic factors, differences in treatment effects)</li> <li>• Region specific/site specific interim monitoring</li> <li>• Case study</li> </ul>
<b>14.00-15.00 Decision-Making in Multi-Regional Clinical Trials</b> <ul style="list-style-type: none"> <li>• Considerations for DSMB decision-making: Beyond stopping boundaries</li> <li>• Multi-regional clinical trials – How should DMCs look at interim data?</li> <li>• How should DMCs look at multi-national data?</li> </ul>
<b>15.00-15.15 Break</b>
<b>15.15-16.15 Case study</b>
<b>16.15-16.30 Closing Remarks</b>

## Frequently Asked Questions<sup>11</sup>

Below are a few of the most commonly asked questions regarding DSMPs and DSMBs.

### **I'm running an observational study. Does my protocol need a DSMP?**

Yes, however for observational studies the DSMP may be limited.

- Sample DSMP for an observational study with low-risk procedures: The PI will monitor the study, including review of study conduct, enrollment, adverse events with prompt reporting of AEs and other study-related information to the IRB, clinical research center (CRC), sponsor, and other agencies as appropriate. GCP will be followed for conduct of the study and modifications; deviations will be reported to the IRB and CRC (if applicable), along with an annual status report as per IRB guidelines.
- Observational study with moderate high-risk procedures: PI-monitoring required as described above. In addition, a detailed plan for oversight of the procedures by study staff should be provided and the PI or designee should review outcome of procedures on a regular basis and report any changes in risks or procedure to the IRB. The IRB or SRC may require additional monitoring by an independent safety monitor if study involves high-risk procedures or vulnerable populations.
- Multi-center observational studies: PI monitoring for local conduct of study is appropriate. In addition, the study team or central coordinating center should have a plan for regular review of study data and subject safety, and dissemination of reports to the sites and local IRBs.

### **When would I want to consider having an external monitor or independent monitoring committee?**

In general, use of an **external monitor or independent** monitoring committee is encouraged when:

- The study end point is one for which a favorable or unfavorable early result may require termination of the trial.
- There is a reason for a particular safety concern, (e.g., vulnerable population, high-risk procedures/interventions).

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<sup>11</sup> University of Washington – ITHS Partner Institutions Joint Tool for Data and Safety Monitoring Plans (DSMP)  
<https://www.iths.org/wp-content/uploads/Cross-institutionalDSMPguidelines.doc>

- The trial is large and of a long duration, thus exposing more study participants to risk.
- The assessment of risk is based on subjective outcomes.

### **When is a full independent Data Monitoring committee required?**

NIH guidelines<sup>12</sup> require DSMBs for multi-center Phase III clinical trials that involve interventions that entail potential risk to the participants. In particular independent DSMBs are recommended for large, randomized multisite studies:

- That evaluate interventions intended to prolong life or reduce risk of a major adverse health outcome;
- With mortality or major morbidity as a primary or secondary endpoint;
- In settings where trial participants may be at elevated risk of such outcomes;
- Where risk to study participants is best assessed by statistical comparison between treatment groups.

---

<sup>12</sup> <https://grants.nih.gov/grants/guide/notice-files/NOT-OD-00-038.html>

## **DSMB/P at Your Harvard Catalyst Institution**

Please refer to the requirements and guidance provided by your institution.

[Beth Israel Deaconess Medical Center](#)

[Boston Children's Hospital](#)

[Brigham and Women's Hospital](#)

[Dana-Farber Cancer Institute](#)

[Massachusetts General Hospital](#)

[McLean Hospital](#)

[Spaulding Hospital](#)

## Attribution, Sharing, and Adapting the Training Guidance

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- **Adapt** — modify the work to suit your needs

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- **Suggested citation:** *This material is the work of the Harvard Catalyst Regulatory Foundations, Ethics and Law's Regulatory Committee, affiliated with Harvard Catalyst | The Harvard Clinical and Translational Science Center.*

*Please see the acknowledgements section for other resources we used while developing this guidance.*

### With the understanding that:

- **We might contact you**— we are interested in knowing who is using the material and how they are using it. We may contact you by email to solicit information on how you have used the materials or request collaboration or input on future activities.
- **We ask that you share your templates/examples** — If you create DSMB/P templates or examples specific to your use, we would be grateful if you would share those with us so that your work will help to create a public library of case studies to support improved training.
- **When reusing or distributing, make clear these terms** — for any reuse or distribution, you must make clear to others the terms of this work. The best way to do this is with a link to the web page containing this guide.

## DSMB/P Templates and Examples

We are interested in growing our online catalog of DSMB/P templates and examples that will be openly accessible for researchers and IRBs to use for training purposes and in the development of study protocols.

If you would like to access the existing templates or have templates and/or examples of DSMB/P language to share, please contact [regulatory@catalyst.harvard.edu](mailto:regulatory@catalyst.harvard.edu)

All contributors will be acknowledged appropriately.

## Acknowledgements

The following resources were referenced or adapted for the development of this guidance:

<https://www.research.buffalo.edu/forms/hs/ubsop.pdf> (University of Buffalo)

<http://hub.ucsf.edu/data-and-safety-monitoring> (Marlene Berro, University of California, San Francisco)

[ITHS Partner Institutions Joint Tool for Data and Safety Monitoring Plans \(DSMP\)](#) (University of Washington)

<https://kb.wisc.edu/page.php?id=19538> (University of Wisconsin-Madison)

[https://www.rochester.edu/ohsp/documents/ohsp/pdf/policiesAndGuidance/Policy\\_506\\_Data\\_Safety\\_Monitoring.pdf](https://www.rochester.edu/ohsp/documents/ohsp/pdf/policiesAndGuidance/Policy_506_Data_Safety_Monitoring.pdf) (University of Rochester)

[Multi-Regional Clinical Trials Center | The MRCT Center of Brigham and Women's Hospital and Harvard](#)

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## Contact Us

Copies of all materials are freely available. Please send your requests, questions, and comments to [regulatory@catalyst.harvard.edu](mailto:regulatory@catalyst.harvard.edu) and visit the Harvard Catalyst Regulatory [web page](#).

## Resources

### *Links to DSMB/P NIH Policies<sup>13</sup>*

As previously announced in a series of notices within the NIH Guide for Grants and Contracts, applications for grants, cooperative agreements or contracts submitted to NIH since October 2000 should include a description of a data safety monitoring plan (DSMP) for any clinical trials to be conducted under the award. These policies can be found at the following websites:

- <http://grants.nih.gov/grants/guide/notice-files/not98-084.html>
- <http://grants.nih.gov/grants/guide/notice-files/NOT-OD-00-038.html>
- <http://deainfo.nci.nih.gov/grantspolicies/datasafety.pdf>

The policy states that each institute will have its own system for data and safety monitoring. These institute-specific policies are being developed and issued. Institute data and safety monitoring policies that are known at this time include:

- NCCIH: <https://nccih.nih.gov/research/policies/datasafety>
- NCI: <http://deainfo.nci.nih.gov/grantspolicies/datasafety.pdf>  
<http://www.cancer.gov/research/resources/conducting>
- NEI: <http://www.nei.nih.gov/funding/policy/policy6.asp>
- NHLBI: <http://www.nhlbi.nih.gov/research/funding/human-subjects/data-safety-monitoring-policy>  
<http://www.nhlbi.nih.gov/research/funding/human-subjects/data-safety-monitoring-faq>
- NIA: <https://www.nia.nih.gov/research/dea/implementation-policies-human-intervention-studies-ReqDSMB>
- NIAID: <http://www.niaid.nih.gov/ncn/pdf/clinterm.pdf>
- NIAMS: [http://www.niams.nih.gov/Funding/Clinical\\_Research/data\\_safety\\_monitoring\\_guidelines.asp](http://www.niams.nih.gov/Funding/Clinical_Research/data_safety_monitoring_guidelines.asp)  
[http://www.niams.nih.gov/Funding/Clinical\\_Research/guidelines\\_monitoring\\_plan.asp](http://www.niams.nih.gov/Funding/Clinical_Research/guidelines_monitoring_plan.asp)  
[http://www.niams.nih.gov/Funding/Clinical\\_Research/PI\\_responsibilities\\_related\\_DSMB.pdf](http://www.niams.nih.gov/Funding/Clinical_Research/PI_responsibilities_related_DSMB.pdf)
- NICHD: <https://www.nichd.nih.gov/grants-funding/policies-strategies/policies/Pages/data-safety.aspx>
- NIDA: <http://www.nida.nih.gov/Funding/DSMBSOP.html>

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<sup>13</sup>University of California, San Francisco, Office of Sponsored Research. <http://or.ucsf.edu/cg/6163-DSY.html>  
Accessed August 26, 2013.

- NIDCD: <http://www.nidcd.nih.gov/research/clinicalstudies/Information-for-Researchers-and-Health-Professionals/Pages/NIDCD-Guidelines-for-Data-and-Safety-Monitoring-of-Clinical-Trials.aspx>
- NIDDK: <http://www.niddk.nih.gov/research-funding/process/human-subjects-research/policies-for-clinical-researchers/data-safety-monitoring-plans/Pages/data-and-safety-monitoring-plans.aspx>
- NIDCR: <http://www.nidcr.nih.gov/Research/ToolsforResearchers/Toolkit/DataandSafetyMonitoring.htm>
- NIDDK: <http://www.niddk.nih.gov/research-funding/process/human-subjects-research/policies-for-clinical-researchers/data-safety-monitoring-plans/Pages/data-and-safety-monitoring-plans.aspx>
- NIMH: <http://www.nimh.nih.gov/funding/clinical-research/policy-governing-independent-safety-monitors-and-independent-data-and-safety-monitoring-boards.shtml>  
<http://www.nimh.nih.gov/funding/clinical-research/data-and-safety-monitoring-plan-writing-guidance.shtml>
- NINDS: [http://www.ninds.nih.gov/funding/ninds\\_patient\\_safety\\_guidelines.htm](http://www.ninds.nih.gov/funding/ninds_patient_safety_guidelines.htm)

### *Complete FDA Definitions for Phases of Clinical Trials*

**Phase I Clinical Studies** - Phase I includes the initial introduction of an investigational new drug into humans. These studies are closely monitored and may be conducted in patients but are usually conducted in healthy volunteer study participants. These studies are designed to determine the metabolic and pharmacologic actions of the drug in humans, the side effects associated with increasing doses, and, if possible, to gain early evidence on effectiveness. During Phase I, sufficient information about the drug's pharmacokinetics and pharmacological effects should be obtained to permit the design of well-controlled, scientifically valid, Phase II studies.

Phase I studies also evaluate drug metabolism, structure-activity relationships, and the mechanism of action in humans. These studies also determine which investigational drugs are used as research tools to explore biological phenomena or disease processes. The total number of study participants included in Phase I studies varies with the drug but is generally in the range of twenty to eighty.

In Phase I studies, the Center for Drug Evaluation and Research (CDER) can impose a clinical hold (i.e., prohibit the study from proceeding or stop a trial that has started) for reasons of safety, or because of a sponsor's failure to accurately disclose the risk of study to investigators. Although CDER routinely provides advice in such cases, investigators may choose to ignore any advice regarding the design of Phase I studies in areas other than patient safety.

**Phase II Clinical Studies** - Phase II includes the early controlled clinical studies conducted to obtain some preliminary data on the effectiveness of the drug for a particular indication or indications in patients with the disease or condition. This phase of testing also helps determine the common short-term side effects and risks associated with the drug. Phase II studies are typically well-controlled, closely monitored, and conducted in a relatively small number of patients, usually involving several hundred people.

**Phase III Clinical Studies** - Phase 3 studies are expanded controlled and uncontrolled trials. They are performed after preliminary evidence suggesting effectiveness of the drug has been obtained in Phase II and are intended to gather the additional information about effectiveness and safety that is needed to evaluate the overall benefit-risk relationship of the drug. Phase III studies also provide an adequate basis for extrapolating the results to the general population and transmitting that information in the physician labeling. Phase III studies usually include several hundred to several thousand people.

In both Phase II and III, CDER can impose a clinical hold if a study is unsafe (as in Phase I), or if the protocol is clearly deficient in design in meeting its stated objectives. Great care is taken to ensure that this determination is not made in isolation, but reflects current scientific knowledge, agency experience with the design of clinical trials, and experience with the class of drugs under investigation.

**Phase IV Clinical Studies:** Studies involving the safety surveillance (pharmacovigilance) and ongoing technical support of a drug after it receives permission for marketing. The safety surveillance is designed to detect any rare or long-term adverse effects in a much larger patient population and over a longer time period than was possible during the Phase I-III clinical trials. Post marketing surveillance is usually required by FDA and these types of studies can be researched on the FDA site here:

<http://www.accessdata.fda.gov/scripts/cder/pmc/index.cfm>

## Appendix A: Principal Investigator's Responsibilities<sup>14</sup>

### A. General Responsibilities of Principal Investigators

The principal investigator (PI) is responsible for personally conducting or supervising the conduct of human-subjects research and for protecting the rights, safety, and welfare of the subjects enrolled in the research. The PI must ensure that all human-subjects research is conducted in an ethical manner and in accordance with all federal, state, and local laws and regulations, institutional policies, and requirements or determinations of the IRB office.

#### 1. Supervising the conduct of human-subjects research

The PI may delegate study-related tasks but must adequately supervise study personnel to whom tasks are delegated. When supervising the conduct of human-subjects research, the PI must ensure that:

- Study personnel are qualified by training and experience to perform study-related tasks that have been delegated to them;
- Study personnel have an adequate understanding of the research; and
- Study personnel follow the IRB-approved protocol, including the recruitment and consent procedures described in the protocol summary.

The PI should have a plan for supervision and oversight of the research. The intensity of the supervision should take into consideration the study personnel conducting the research, the nature of the research, and the subject population.

#### 2. Protecting the rights, safety, and welfare of research subjects

The PI or other identified qualified individual(s) must be available to provide study subjects with reasonable medical care for any medical problems that arise during participation in the research that are, or could be, related to the research. Additionally, when participation in the research might impact the subject's health and/or medical care, the PI should inform the subject's

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<sup>14</sup> Principal Investigator's Responsibilities. [https://partnershealthcare-public.sharepoint.com/ClinicalResearch/PI\\_Responsibilities.pdf](https://partnershealthcare-public.sharepoint.com/ClinicalResearch/PI_Responsibilities.pdf) Accessed January 22, 2016.

primary care physician about the subject's participation in the research (if the subject has a primary care physician, and if the subject agrees to the primary care physician being informed).

When protecting the rights, safety, and welfare of research subjects, the PI must ensure that:

- S/he or other identified, qualified individual(s) provides study subjects with reasonable medical care for any adverse events, including clinically significant laboratory values, related to the research;
- S/he or another specific qualified individual is available to study subjects to answer questions or provide care during the conduct of the research; and
- S/he and all research staff conducting the study adhere closely to the research plan, such as inclusion/exclusion criteria, safety assessments, safety monitoring and reporting of unanticipated problems, and procedures to protect privacy of subjects and confidentiality of identifiable data, in order to minimize risks to subjects.

The PI should not commence the research without adequate resources to protect subjects participating in the research and should stop the research if the resources necessary to protect subjects become unavailable. These resources might include research personnel, space, equipment, time, and availability of medical or psychological care for problems that arise during participation in the research.

## **B. More Specific Responsibilities of Principal Investigators**

The PI must ensure that:

- IRB office approval is obtained prior to initiation of the research;
- The research is conducted in accordance with the IRB office-approved protocol, including, when applicable, the approved recruitment and consent procedures;
- When informed consent is required, informed consent is obtained prior to the initiation of any study-related procedures;
- When written informed consent is required, informed consent is obtained and documented using the current IRB office-approved research consent form;

- When drugs, biological products, and devices are being investigated or used, they are managed and controlled as required by institutional policy and, when applicable, FDA regulations [21 CFR 312](#) and [21 CFR 812](#);
- Changes to the IRB office-approved protocol and/or the research consent form are not initiated without prospective IRB office approval unless necessary to eliminate apparent immediate hazards to the subject;
- Unanticipated problems involving risks to subjects or others (including adverse events and protocol deviations, if applicable) are reported promptly to the IRB office in accordance with appropriate IRB Policy.
- When applicable, Data and Safety Monitoring Board or other monitoring group reports are submitted promptly to the IRB office for review;
- Continuing review is conducted prior to expiration of IRB office approval in accordance with IRB office policy;
- Should IRB office approval lapse, research procedures such as recruitment and enrollment of subjects, study procedures on currently enrolled subjects, review of health/medical records, collection of tissue or other samples, or analysis of data are not conducted until the IRB office re-approves the research, or until special permission is obtained from the IRB office to continue previously enrolled subjects because it is in their best interests to do so;
- When the research has been completed or is being closed out prior to completion, a final continuing review report is submitted to the IRB office;
- Adequate and accurate research records are kept and retained as required by the IRB office and, when applicable, by the sponsor or FDA; and
- Research records are made available to the IRB office, the QA/QI Program, the sponsor, and when applicable, the Office for Human Research Protections (OHRP), and the Food and Drug Administration (FDA) upon request for monitoring and oversight of the research.

Guidance based on U.S. Dept. of Health and Human Services, Food and Drug Administration, et al. [Guidance for Industry: Protecting the Rights, Safety, and Welfare of Study Subjects](#). Guidance October 2009

## Appendix B: Independent Monitors/Monitoring Group<sup>15</sup>

A qualified and objective individual or group not directly involved with the design and conduct of the study (e.g., safety officer, designated Medical Monitor or Monitoring Group) could perform this function. These individuals may or may not be employees of the institution or the study sponsor. However, conflict of interest is an important consideration when employees of the study sponsor have the primary responsibility for monitoring data from the standpoint of scientific integrity and participant safety.

This type of plan is often appropriate to monitor data and safety for clinical trials that involve:

- Endpoints that are not serious irreversible events;
- An intervention (for example, to relieve symptoms) that is not high-risk and the effects of which would not generally be so compelling as to ethically warrant early termination for effectiveness;
- Short term treatments where effects are evaluated over periods of a few days to a few months; and
- A smaller number of subjects, where the study is completed quickly and the risk can be adequately assessed through simple comparisons.

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<sup>15</sup> Partners Healthcare Human Research Affairs Data and Safety Monitoring Plans in Human-Subjects Research [http://navigator.partners.org/ClinicalResearch/DSMP\\_in\\_Human\\_Subjects\\_Research.pdf](http://navigator.partners.org/ClinicalResearch/DSMP_in_Human_Subjects_Research.pdf)

## Appendix C: DSMP Template

*General DSMP for Low Risk Study<sup>16</sup>*

**<Insert Study Title Here>**

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<sup>16</sup> [https://www.iths.org/wp-content/uploads/DSMP\\_low\\_risk\\_template.docx](https://www.iths.org/wp-content/uploads/DSMP_low_risk_template.docx)

## BRIEF STUDY OVERVIEW

<<Insert a brief description/abstract of the study here.>>

## OVERSIGHT RESPONSIBILITIES

Oversight of the trial is provided by the Principal Investigator (PI), Dr. <<insert PI last name>> and <<insert names of additional investigators who will be actively involved in the conduct of the study>> (“co-investigators” throughout).

## MONITORING PROCEDURES

Dr. <<insert PI last name>> assures that informed consent is obtained prior to performing any research procedures, that all subjects meet eligibility criteria, and that the study is conducted according to the IRB-approved research plan.

Study data are accessible at all times for the PI <<insert if applicable: and co-investigators>> to review. The PI <<insert if applicable: and co-investigators>> review(s) study conduct (<<specify what will be reviewed: accrual, drop-outs, protocol deviations>>) on a <<provide time interval, for example: weekly, monthly, quarterly, semi-annual, annual>> basis. The PI <<insert if applicable: and co-investigators>> review(s) AEs individually real-time and in aggregate on a <<provide time interval, for example: weekly, monthly, quarterly, semi-annual, annual>> basis. The PI <<insert if applicable: and co-investigators>> review(s) serious adverse events (SAEs), <<if applicable: dose-limiting toxicities>>, and <<list other specific intervention complications>> in real-time. <<If applicable, add any other additional reviews the PI/co-investigators will do.>> The PI ensures all protocol deviations, AEs, and SAEs are reported to the <<if applicable: sponsor>> and IRB according to the applicable regulatory requirements.

## COLLECTION AND REPORTING OF SAEs AND AEs

For this study, the following standard AE definitions are used:

**Adverse event:** Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medical treatment or procedure, regardless of whether it is considered related to the medical treatment or procedure.

**Serious Adverse Event:** Any AE that results in any of the following outcomes:

- Death
- Life-threatening
- Event requiring inpatient hospitalization or prolongation of existing hospitalization
- Persistent or significant disability/incapacity

AEs are graded according to the following scale <<use scale below or whatever scale is proposed for the study>>:

**Mild:** An experience that is transient and requires no special treatment or intervention. The experience does not generally interfere with usual daily activities. This includes transient laboratory test alterations.

**Moderate:** An experience that is alleviated with simple therapeutic treatments. The experience impacts usual daily activities. Includes laboratory test alterations indicating injury, but without long-term risk.

**Severe:** An experience that requires therapeutic intervention. The experience interrupts usual daily activities. If hospitalization (or prolongation of hospitalization) is required for treatment it becomes an SAE.

The study uses the following AE attribution scale *<<use scale below or whatever scale is proposed for the study>>*:

**Not related:** The AE is clearly not related to the study procedures (i.e., another cause of the event is most plausible, and/or a clinically plausible temporal sequence is inconsistent with the onset of the event).

**Possibly related:** An event that follows a reasonable temporal sequence from the initiation of study procedures, but that could readily have been produced by a number of other factors.

**Related:** The AE is clearly related to the study procedures.

AEs are identified *<<describe how AEs will be captured, for example: during hospital admission when potential AEs are assessed through a review of the hospital chart on a daily basis and a physical examination of the subject. After discharge, AEs are assessed at time of study follow-up visits.>>*

SAEs and specific procedure-associated AEs are reported to the *<<insert monitoring body listed above>>* within 24 hours. In addition, all AEs are reported according to the *<<insert name of IRB overseeing the study>>* AE reporting guidelines.

## MANAGEMENT OF RISKS TO SUBJECTS

### Expected AEs

Expected AEs associated with the *<<insert: drugs being used in the study and study procedures>>* include:

- *<<List expected toxicities of the study drugs/procedures>>*

### AE Management

*<< If applicable, insert description of any specific management plans for expected AEs.>>*

## Dose Escalation and Dose-Limiting Toxicities

*<<If applicable, insert description of plan for dose escalation and what will be considered dose-limiting toxicities.>>*

### **DATA ANALYSIS PLANS**

*<<Describe the planned interim analysis for efficacy, safety, or both. Specify the safety parameters that will be reviewed (for example: expected AEs in aggregate, all SAEs, and dose-limiting toxicities). Describe study stopping rules, if applicable.>>*

### **PLAN FOR DATA MANAGEMENT**

Compliance of regulatory documents and study data accuracy and completeness will be maintained through an internal study team quality assurance process.

Confidentiality throughout the trial is maintained by *<<insert description of study-specific confidentiality procedures>>*.

## Appendix D: DSMB Template

**Multi-Center Clinical Trial**

**<Insert Study Title Here>**

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## 1 Study Performance Review Process

*Describe review process and roles of the following in relation to content, format, and process of review. Specify what reports will be generated, to whom they will be sent, and what procedures the recipients should follow for review.*

### 1.1 Data Management Center

The Data Management Center (DMC) will produce administrative reports on a <insert frequency> basis that describe study progress including:

- Accrual by site
- Demographics in aggregate and by site
- Study subject status in aggregate and by site
- Outstanding study forms
- Error rate pertaining to adherence to inclusion/exclusion criteria and the study protocol in aggregate and by site

These reports will be reviewed internally by the DMC for ongoing quality control and will be presented to the Data Safety Monitoring Board (DSMB) and <<insert applicable institute>>.

### 1.2 Study Statistician

*If the study statistician is involved in study performance review or report generation, describe their role. Otherwise, delete this section.*

### 1.3 Data Safety Monitoring Board

Reports produced by the DMC (listed above) will be reviewed at scheduled meetings.

## 2 Safety Reports

### 2.1 Data Management Center

The DMC will produce safety reports that list adverse events, serious adverse events, deaths, and disease or treatment specific events by institution <<insert frequency of report generation>> and in aggregate for DSMB meetings.

*State if a medical monitor will review adverse events or treatment descriptions to ensure appropriate clinical care and to quickly identify any potential trends. If so, state if the medical monitor is independent (outside of the study team) or is one of the project investigators. State which events will be reviewed, the process and frequency of review, and how findings will be communicated and to whom.*

## **2.2 Study Statistician**

*State if the statistician will review data routinely and, if so, specify the frequency of review and that they will alert the institute and the DSMB if event rates are of statistical concern, occur in a disproportionate number in one of the treatment groups, or fall out of specific boundaries which should be defined. State if the study statistician will distribute interim safety reports to the DSMB between meetings to allow members to call special sessions when appropriate and, if so, specify the frequency.*

## **2.3 Data Safety Monitoring Board**

*State if the DSMB will review safety reports and, if so, whether in an aggregate fashion, by blinded treatment group, or both, or if unblinded data will be reviewed. If blinded data is used, state that if there are a significant number of adverse events, the DSMB may request that the treatment groups be unblinded to ensure there are not problematic side effects. Specify how data are to be presented. If blinded data is used, specify triggers for presenting safety data in an unblinded manner.*

## **2.4 Safety Report Coordination**

*Describe the process for reporting safety concerns among the groups listed below.*

### **The Institutional Review Board**

All problems having to do with subject safety will be reported by the Principal Investigator to the IRB within ten working days. Specifically, the following will be reported, in writing: 1) all serious adverse events associated with the study procedures, and/or 2) any incidents or problems involving the conduct of the study or patient participation, including problems with the recruitment and/or consent processes. The Principal Investigator will provide a discussion of any side effects or problems noticed during each year in the course of the study to your institution's committee on human research on an annual basis.

Summaries of safety information from reports generated to or by the DSMB will provided to the IRB.

### **2.4.2 Data Safety Monitoring Board**

*Specify which safety events will be forwarded to the DSMB and the timeframe for reporting.*

On a scheduled basis (as agreed upon by the DSMB) blinded safety data will be communicated to all DSMB members or to the one member who serves as the designated safety officer. Any concerns noted should be brought to the attention of the chair or designated safety officer who will take appropriate action.

### **2.4.3 <<insert institute name>>**

*If applicable, specify institute-specific events requiring safety reports and the associated timeframe. If there are no institute-specific reporting requirements, delete this section.*

## 3 Interim Analysis

### 3.1 *Preparing the data for analyses*

*Enter information as applicable.*

### 3.2 *Procedures for freezing the data sets*

*Enter information as applicable.*

### 3.3 *Interim analysis schedule*

*Enter information as applicable.*

## 4 Steps Following Data Review

The review of data may result in early termination of the study (see stopping guidelines section below), amendment to the protocol, or changes to the data collection plan or study forms. Should the protocol be amended as a result of data review, the <insert your institution's name> committee on human research will be notified and the amendment approved prior to study amendment implementation unless the protocol amendment must be implemented to protect the immediate safety of the study subjects. In such a case, the protocol amendment will be immediately implemented and the <insert your institution's name> committee on human research will be notified directly after protocol amendment implementation.

*Specify procedures for notifying the institute. Specify procedures for notifying the DSMB.*

If the review of study data causes changes to the data collection plan or study forms, *specify procedures for documenting and implementing any changes.*

## 5 Statistical Considerations

*Address "multiple testing," spending the study "alpha," and powering the study for "multiple looks," as applicable.*

## 6 Stopping Guidelines

*Specify the guidelines for stopping the study.*

## 7 DSMB Charter

The investigators are conducting a clinical trial of <<insert description of intervention>>. This Data Safety and Monitoring Board (DSMB) will act in an advisory capacity to <<insert institute name>> to monitor patient safety and evaluate the efficacy of the intervention that is described in the research plan.

The DSMB will approve the initiation of the trial. After this approval, and at periodic intervals during the course of the trial, the DSMB responsibilities are to:

- review the research protocol, informed consent documents and plans for data safety and monitoring;
- evaluate the progress of intervention trial(s), including periodic assessments of data quality and timeliness, participant recruitment, accrual and retention, participant risk versus benefit, performance of the trial site, and other factors that can affect study outcome;
- consider factors external to the study when relevant information, such as scientific or therapeutic developments that may have an impact on the safety of the participants or the ethics of the trial;
- review clinical center performance, make recommendations and assist in the resolution of problems
- protect the safety of the study participants;
- report on the safety and scientific progress of the trial;
- 
- make recommendations to the Institutional Officials and the principal investigator concerning continuation, termination or other modifications of the trial based on the observed beneficial or adverse effects of the treatment under study;
- if appropriate, conduct interim analysis of efficacy in accordance with stopping guidelines which are clearly defined in advance of data analysis and have the approval of the DSMB;
- ensure the confidentiality of the trial data and the results of monitoring; and,
- assist <<insert institute>> by commenting on any problems with study conduct, enrollment, sample size and/or data collection.

### 7.1 Membership

The Data Safety Monitoring Board will consist of three voting members. Two members will constitute a quorum. The members are experts in <<insert indication>>, clinical studies and statistics. The <insert institute> will approve the composition of the DSMB and appoint the members. Membership will consist of persons completely independent of the investigators who have no financial, scientific, or other conflict of interest with the trial. Collaborators, <<define what constitutes as collaborator for the purpose of this plan>>, at the same institutions as the Principal Investigator(s) are not eligible to serve in the DSMB. Written documentation attesting to absence of conflict of interest is required. Disciplines represented on the DSMB should include experts in or representatives of the fields of:

- relevant clinical expertise,
- clinical trial methodology, and
- biostatistics.

Additional DSMB membership consideration may be given to medical ethics, and a public ombudsman.

A chairperson will be selected by <<insert institute>> in consultation with the PI prior to or at the first meeting, this person will be responsible for overseeing the meetings, developing the agenda and summarizing the meeting. The chair is the contact person for the DSMB. The <<insert institute>> official(s) will serve as an ex-officio member of the DSMB. The logistical management and support of the board shall be provided by the <<insert your institution's name>> study center.

## **7.2 Board Process**

The first meeting will take place face-to-face after the initiation of the trial, to discuss the protocol and to establish guidelines to monitor the study. The chair, if appointed prior to the meeting, and investigators will prepare the agenda to address the commencement of the trial, specifically stopping guidelines, interim analysis plan, etc.

Meetings of the DSMB shall be held approximately <<insert timeframe>> times a year at the call of the chair.

Meetings shall be closed to the public because discussions may address confidential, patient data. Meetings are attended, when appropriate, by the study investigators. Meetings may be convened as conference calls as well as in person. An emergency meeting of the Board may be called at any time by the chairperson or by any member of the board should questions of patient safety arise.

## **7.3 Meeting Format**

The DSMB meetings will consist of an open and a closed session. The open sessions may be attended by the investigators, institution staff, etc. Issues discussed at open sessions usually include conduct and progress of the study, including patient accrual, compliance with protocol, and problems encountered. Patient-specific data and treatment group data may not be presented in the open session.

The closed session will be attended only by voting DSMB members, and by the unblinded representatives of the <<insert your institution's name>> study center. The discussion at the closed session is completely confidential.

Should the board decide to issue a termination recommendation, full vote of the board will be required. In the event of a split vote, majority vote will rule and a minority report should be appended.

## **7.4 Closed Sessions/Access to Unblinded Grouped Data**

In addition to the DSMB members, the following individuals may be present at the closed sessions of the DSMB:

<<insert your institution's name>> Staff:

*Specify the staff that will attend closed DSMB sessions.*

The individual treatment codes will be available only to the study statistician. They will be stored and maintained off-site from the data coordinating center.

*Specify any other relevant details regarding treatment code security.*

## **7.5 Reports**

### **7.5.1 Interim Reports**

Interim reports are generally prepared by the study statistician(s) and distributed to the DSMB, preferably at least ten days prior to a scheduled meeting. The contents of the report are determined by the DSMB. Additions and other modifications to these reports may be directed by the DSMB on a one-time or continuing basis. Interim data reports generally consist of two parts. Part 1 (Open Session Report) provides information on study aspects such as accrual, baseline characteristics, and other general information on study status. Part 2 (Closed Session Report) may contain data on study outcomes, including safety data and, depending on the study, perhaps efficacy data. The Closed Session Report is considered confidential. Copies distributed prior to and during a meeting are collected by the study statistician(s) following the meeting. Data files to be used for interim analyses should have undergone established editing procedures to the greatest extent possible. Interim analyses of efficacy data are performed only if they are specified and approved in advance and criteria for possible stopping are clearly defined.

### **7.5.2 Reports from the DSMB**

Each report should conclude with a recommendation to continue or to terminate the study. This recommendation should be made by formal majority vote. A recommendation to terminate the study should be transmitted to the Primary Investigator and relevant Institutional Officials as rapidly as possible, by immediate telephone and fax if sufficiently urgent. In the event of a split vote in favor of continuation, a minority report should be contained within the regular DSMB report. The report will not include unblinded data, discussion of the unblinded data, etc. A separate set of minutes summarizing the unblinded session will also be created by the DSMB chair. Copies of the blinded DSMB report will be sent to the local IRB of each site involved in the study.

## **7.6 Mailings to the DSMB**

On a scheduled basis (as agreed upon by the DSMB) blinded safety data will be communicated to all DSMB members or to the one member who serves as the designated safety officer. Any concerns noted should be brought to the attention of the chair or designated safety officer who will take appropriate action.

## **7.7 Access to Interim Data**

Access to the accumulating endpoint data will be limited to as small a group as possible. Limiting the access to interim data to the DSMB relieves the investigators of the burden of deciding whether it is ethical to continue to randomize patients and helps protect the study from bias in patient entry and/or evaluation.

## **7.8 Confidentiality**

All materials, discussions, and proceedings of the DSMB are completely confidential. Members and other participants in DSMB meetings are expected to maintain confidentiality.