Example
Data and Safety Monitoring Plan (DSMP)
Independent Monitoring Committee

NOTE: This sample template is solely for guidance purposes and does not constitute National Center for Complementary and Integrative Health (NCCIH) policy. It is recommended that the text in *italics* and "example" information be deleted from the final DSMP generated for a study.

I. Study Identification Information

A. NIH Study Number—example: "RO1 AT12345-01"

B. Study Title—example: "Treatment of Obesity with Metformin"

C. Name of Principal Investigator (PI)—example: "Josephine Q. Investigator, M.D."

II. Study Overview

A. Brief Description of the Purpose of the Study—example: "The overall goal of this project is to determine whether metformin is an effective treatment for obesity."

B. Adherence Statement—example: "The Data and Safety Monitoring Plan (DSMP) outlined below for RO1 AT12345-01 will adhere to the protocol approved by the _____ GCRC/CTSA Research Review Committee and the _____ IRB."

III. Confidentiality

A. Protection of Subject Privacy

A plan for ensuring subject privacy must be included in the DSMP. For example, "During this study, medical history and physical examination will be performed at baseline and at regular intervals for various metabolic parameters of obesity during the minimal model. DNA will be obtained for genomic analysis. All of the materials collected are for research purposes only, and data will be kept in strict confidence. No information will be given to anyone without permission from the subject. The consent form includes the informed consent statement required by _____ University for studies involving DNA analysis. This statement guarantees confidentiality and identifies the subject as the owner of the information from the DNA analysis. Confidentiality will be ensured by use of identification codes. All data, whether generated in the laboratory or at the bedside, will be identified with a randomly generated identification code unique to the subject."

B. Database Protection

A statement pertaining to protection of the database should be included, such as, "The database will be secured with password protection. The informatics manager will receive only coded information that is entered into the database under those identification numbers. Electronic communication with outside collaborators will involve only

unidentifiable information." *Plans for securing source documents including all paper and electronic records for all enrolled subjects (i.e., case report forms, laboratory reports, subject study binders, etc.) should also be outlined.*

C. Confidentiality During Adverse Event (AE) Reporting

A plan for keeping AE reporting confidential should be included and might say, "AE reports and annual summaries will not include subject- or group-identifiable material. Each report will only include the identification code."

IV. Adverse Event Information

A. Definition

The definition should include the following language: "An adverse event (AE) is any untoward medical occurrence in a subject during participation in the clinical study or with use of the experimental agent being studied. An adverse finding can include a sign, symptom, abnormal assessment (laboratory test value, vital signs, electrocardiogram finding, etc.), or any combination of these."

"A serious adverse event (SAE) is any AE that results in one or more of the following outcomes:

- Death
- A life-threatening event
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant disability/incapacity
- A congenital anomaly or birth defect
- An important medical event based upon appropriate medical judgment"

Note: This U.S. Food and Drug Administration (FDA) definition of an SAE is intended for use in clinical studies. Any deviation from the above definition should be explained.

B. Classification of AE Severity

AEs are most commonly graded by severity (mild, moderate, or severe)— depending on the intensity of the event for the patient. An example of a description of the AE classification plan is: "AEs will be labeled according to severity, which is based on their impact on the patient. An AE will be termed "mild" if it does not have a major impact on the patient, "moderate" if it causes the patient some minor inconvenience, and "severe" if it causes a substantial disruption to the patient's well-being." Please note that a severe AE and an SAE are distinct terms. A subject could experience a severe AE that does not meet the above-listed definition of an SAE; alternatively, a subject could experience a moderate AE that meets the SAE definition.

C. AE Attribution Scale

AEs should also be classified on an assessment of relatedness to the study intervention. An example of a description of the AE attribution scale is: "AEs will be categorized

according to the likelihood that they are related to the study intervention. Specifically, they will be labeled definitely unrelated, definitely related, probably related, or possibly related to the study intervention."

D. Expected Risks

Outline the risks that are expected as part of the subject's participation in the study. An example is: "Expected risks to the subject are as follows:

- Inserting a needle for blood sampling and placing a venous catheter for injection or infusion can be associated with some discomfort and bruising, and very rarely with inflammation and infection of the arm veins.
- Glucose and insulin administration during the minimal model procedure can cause transient hyperglycemia or hypoglycemia.
- Undergoing DXA scan studies is associated with a small degree of radiation exposure."

Address how much impact these risks are likely to have on a given patient. An example of this is: "These risks are considered to be minimal and are addressed in the protocol and consent form."

Include the measures that will be taken to minimize study risk. For example, it might be stated that "Because glucose and insulin administration during the minimal model procedure can cause transient hyperglycemia or hypoglycemia, blood sugars will be monitored at frequent intervals during this part of the study and patients will be followed for a sufficient period of time after the procedure to ensure stabilization of blood sugars. Metformin is commonly associated with gastrointestinal upset and less commonly with other short- and long-term side effects, so patients will be monitored at frequent intervals for expected and unexpected AEs related to metformin administration."

E. AE Reporting and Followup

Provide a plan for collecting, reporting, and followup of all AEs, including abnormal lab values. Please refer to Tables 4, 5, and 6 in Appendix A for suggested formats for data collection and reporting.

F. SAE Reporting

Unexpected, serious, and intervention-related SAEs must be reported to the Independent Monitor(s), IRB, GCRC/CTSA, NCCIH, and other oversight organizations as appropriate.

If the study is conducted under an IND/IDE from the FDA, the SAE reporting plan might read as follows:

"SAEs that are unanticipated, serious, and possibly related to the study intervention will be reported to the Independent Monitors(s), IRB, GCRC/CTSA (if applicable), FDA, and NCCIH in accordance with requirements. For the IND/IDE:

- 7-day IND Safety Report (unexpected fatal or life-threatening AEs related to the intervention); a copy of the report sent to the FDA will be submitted to the NCCIH Program Officer within 24 hours of FDA notification.
- 15-day IND Safety Report (any other serious and unexpected AE related to the intervention); a copy of the report submitted to the FDA will be submitted to the NCCIH Program Officer within 24 hours of FDA notification.
- Other AEs documented during the course of the trial will be included in the annual IND report. In the annual AE summary, the Independent Monitor(s) Report will state that they have reviewed all AE reports."

If the study is not conducted under and IND/IDE from the FDA, the SAE reporting plan might read as follows:

"SAEs that are unanticipated, serious, and possibly related to the study intervention will be reported to the Independent Monitor(s), IRB, GCRC/CTSA (if applicable), and NCCIH in accordance with requirements.

- Unexpected fatal or life-threatening AEs related to the intervention will be reported to the NCCIH Program Officer within 7 days. Other serious and unexpected AEs related to the intervention will be reported to the NCCIH Program Official within 15 days.
- Anticipated or unrelated SAEs will be handled in a less urgent manner but will be reported to the Independent Monitor(s), IRB, GCRC/CTSA, NCCIH, and other oversight organizations in accordance with their requirements. In the annual AE summary, the Independent Monitor(s) Report will state that they have reviewed all AE reports."

V. Data Quality and Safety Review Plan and Monitoring

A. Data Quality and Management

1. **Description of Plan for Data Quality and Management—*example:*** "The PI or study staff will review all data collection forms on an ongoing basis for data completeness and accuracy as well as protocol compliance." *The procedures by which collected data will be verified should be provided (i.e., list procedures for verification of all primary and secondary endpoint data against original source documents). It is anticipated that data verification will be performed by someone other than the individual originally collecting the data, or by double-data entry. A statement reflecting the results of the ongoing data review will be incorporated into the Annual Report for the Independent Monitor(s).*

2. **Frequency of Data Review for this Study—**This will vary according to the particular study. The PI should specify who will review the data at the specified intervals. Example: "The frequency of data review for this study differs according to the type of data and can be summarized in the following Sample Table:"

SAMPLE TABLE

Data type	Frequency of review	Reviewer
Subject accrual (including compliance with protocol enrollment criteria)	Quarterly	PI, Independent Monitor(s)
Status of all enrolled subjects, as of date of reporting	Quarterly	PI, Independent Monitor(s)
Adherence data regarding study visits and intervention	Quarterly	PI, Independent Monitor(s)
AEs and rates (including out-of-range lab values)	Quarterly	PI, Independent Monitor(s)
SAEs	Per occurrence	PI, Independent Monitor(s), NCCIH, FDA (if applicable)

B. Subject Accrual and Compliance

1. **Measurement and Reporting of Subject Accrual, Compliance With Inclusion/Exclusion Criteria—*example*:** "Review of the rate of subject accrual and compliance with inclusion/exclusion criteria will occur monthly during the 4-month recruitment phase and then every 3 months to ensure that a sufficient number of participants are being enrolled and that they meet eligibility criteria and the targeted ethnic diversity goals outlined in the grant proposal (Targeted/Planned Enrollment Table)." *Please see Tables 1 and 2 in Appendix A for suggested formats for data collection.*

2. **Measurement and Reporting of Participant Adherence to Treatment Protocol**

   Example 1: "Data on adherence to the treatment protocol will be collected twice weekly by research staff and reviewed quarterly by the PI, the study statistician, and the safety officer. Adherence of participants will be evaluated by performing pill counts and by monitoring the appropriate metabolic measures at each visit. Available data on the use of metformin suggests an overall compliance rate of 75%. If adherence falls below the suggested rate of 75%, which might inhibit the ability of the study to test its primary hypotheses, the safety officer will suggest a conference call for study investigators to discuss methods for improving adherence."

   Example 2: "Data on adherence to the treatment protocol will be collected twice weekly by research staff and reviewed quarterly by the PI, the study statistician, and the safety officer. Adherence of participants will be evaluated for each strength training exercise at each session on the following scale: 0 = absence; 1 = failed to

increase weight according to training protocol on any set; 2 = followed protocol on 1 set and either didn't complete additional sets or didn't follow protocol on additional sets; 3 = followed protocol on 2 or more sets. A summary adherence score for all 8 exercises will be established for each participant for each session. This summary score will be entered and used in these safety monitoring reports. The protocol for increasing weight on each exercise is as follows: After 2 sessions during which a participant lifted the same weight 10 times during each set completed, the weight will be increased by the smallest possible increment. If the higher weight is lifted at least 8 times on the 1st set, and 6 times on the 2nd set, additional set(s) will be attempted with the higher weight. Otherwise, the weight will revert to the amount lifted in the previous session. If the safety officer has concerns about whether adherence has reached a level that might inhibit the ability of the study to test its primary hypotheses, he/she will suggest a conference call for study investigators to discuss methods for improving adherence."

C. Justification of Sample Size

Justify the number of subjects being exposed to the intervention. For example, "The goal of the study is to determine if metformin is an effective weight loss therapy in obese individuals compared to placebo. The primary analysis will compare the difference in percentage of subjects exhibiting a weight loss of at least 25% from baseline between the two groups at 12 months. If we assume that 5% of subjects in the control group will achieve a weight loss of 25% or greater and we want to demonstrate at least a 20% improvement in the number of metformin-treated subjects achieving a 25% or greater weight loss over the control, then 44 subjects per arm would be sufficient to detect a difference between groups for a two-sided, 0.05 test of proportions with 80% power. If it is expected that the loss to followup rate will be 20%, the sample size should be increased to 55 subjects per arm."

D. Stopping Rules

Example: "This study will be stopped prior to its completion if: (1) the intervention is associated with adverse effects that call into question the safety of the intervention; (2) difficulty in study recruitment or retention will significantly impact the ability to evaluate the study endpoints; (3) any new information becomes available during the trial that necessitates stopping the trial; or (4) other situations occur that might warrant stopping the trial." *If stopping rules do not apply, please justify. Stopping rules might be used to explain the process the PI will use for deciding if difficulties in recruitment, retention, measurement, or other issues make it futile to continue. For example,* "The PI will include an assessment of futility in the annual progress report to NIH (using statistical means such as predictive probability, if appropriate) and will consult with the study monitors to assess the impact of significant data loss due to problems in recruitment, retention, or data collection."

E. Designation of a Monitoring Committee

The PI will designate an Independent Monitoring Committee (IMC) to perform an independent review of ongoing study progress and safety. An example might read, "The Monitoring Committee for this study is comprised of Drs. X, Y. and Z. Drs. X, Y, and Z

are not associated with this research project and thus work independently of the PI, Dr. Josephine Q. Investigator. They are not part of the key personnel involved in this grant. They are qualified to review the patient safety data generated by this study because of their unique expertise in the area of the genetics of obesity. The CVs of all members of the IMC are attached."

Please note that the GCRC/CTSA Independent Monitors can serve as members of the study IMC if the study is using a GCRC/CTSA. It is acceptable for the Committee members to receive a small amount of compensation for their services.

F. Safety Review Plan

The PI should review the safety and progress of this study on an ongoing basis and should specify how frequently summaries of subject recruitment, retention, and AEs will be provided to the Independent Monitor(s). An example might be: "Study progress and safety will be reviewed monthly (and more frequently if needed). Progress reports, including patient recruitment, retention/attrition, and AEs will be provided to the Independent Monitor(s) following each of the monthly reviews. An Annual Report will be compiled and will include a list and summary of AEs. In addition, the Annual Report will address (1) whether AE rates are consistent with pre-study assumptions; (2) reason for dropouts from the study; (3) whether all participants met entry criteria; (4) whether continuation of the study is justified on the basis that additional data are needed to accomplish the stated aims of the study; and (5) conditions whereby the study might be terminated prematurely. The Annual Report will be sent to the Independent Monitor(s) and will be forwarded to the IRB and NCCIH and, if applicable, the GCRC/CTSA, FDA, and sponsoring industry collaborator. The IRB and other applicable recipients will review progress of this study on an annual basis." The PI will also send copies of signed recommendations and comments from the Independent Monitor(s) or Chair of the IMC to the NCCIH Program Officer within 1 month of each monitoring review.

G. Study Report Outline for the Independent Monitors(s) (Interim or Annual Reports)

The study team should develop a plan for generating regular Study Reports for the Independent Monitor(s), in order to provide relevant information in a standardized format—See Appendix B, Sample Study Report Outline. It should be noted that Study Reports for the Independent Monitor(s) should not provide data on primary or secondary endpoints, unless there is a pre-existing approved interim analysis plan for the study.

"The study team will generate Study Reports for the Independent Monitor and will provide information on the following study parameters: . . ."

"Study Report tables will be generated only from aggregate (not by group assignment) baseline and aggregate safety data for the study population. A separate Closed Safety Report, with masked group baseline and safety data, will be generated for the Independent Monitor(s) by a designated unmasked member of the team but will not be reviewed by the study team."

VI. Informed Consent

An example of the description of the informed consent process being used during the study might be: "Written informed consent will be obtained from each subject at entry into the study. Informed consent is obtained by the following process:

1. The subject (If applicable, parent/guardian) will be asked to review the study consent form.
2. The PI or Co-Investigator (Co-I) will meet with the subject to review the form, to confirm the subject's understanding of the study, and to answer any questions that the subject might have.
3. Once the subject demonstrates understanding of the study and agrees to participate in the study, the consent will be signed in the presence of the PI (or Co-I) and a witness."

VII. Reporting Changes in Study Status

Any action resulting in a temporary or permanent suspension of an NCCIH-funded clinical study must be reported to the NCCIH Program Official responsible for the grant. These actions include any actions by the FDA, an IRB, a commercial sponsor, or one of the study investigators.

An example of the plan for reporting changes in study status might be:

"During the funding of this study, any action by the FDA (if applicable), an IRB, the commercial sponsor (list commercial sponsor name), or one of the study investigators that results in a temporary or permanent suspension of the study will be reported to the NCCIH Program Official within 1 business day of notification."

NOTE: This is an example DSMP for a clinical study. Not all elements listed in the template are relevant to all clinical studies. Some information in this example refers to a GCRC/CTSA and will not be applicable for studies that do not use a GCRC/CTSA.

Data and Safety Monitoring Plan

Appendix A

The tables below are EXAMPLE TABLES that can be used or modified to report study progress and patient safety data to oversight groups including the IRB, Independent Monitor(s), NCCIH, and the FDA.

Table 1. Enrollment by Month of Study

Month	# Expected	# Screened	# Enrolled or Randomized	# Withdrawn	# Actual (# Enrolled - # Withdrawn)	# Cumulative (Sum of # Actual by Month)
2	6	4	3	0	3	3
4	8	6	5	1	4	7

*Enrollment can also be displayed graphically in a Figure, with cumulative subject accrual plotted over time.

Table 2. Demographics

Characteristics	**N**	**N%**
Gender		
Female		
Male		
Ethnicity		
Hispanic or Latino		
Not Hispanic or Latino		
Unknown		
Age		
Mean (SE)		
Median (min, max)		
Race		
AIAN		
Asian		
Nat Hawaiian/Other Pac Islander		
Black or African American		
White		
Other		
More than one race		
Unknown		

Table 3. Subject Status

Pt Identifier	Date Enrolled	Date Completed Study	Study Status	Reason for Withdrawal	% Adherence to Intervention	Intervention Duration (Weeks)
Subj001	08/02/2010	N/A	A			
Subj002	07/26/2010	9/20/2010	C		87%	8 weeks
Subj003	08/04/2010	N/A	W	Injury unrelated to intervention		

Status:
A = Active
C = Completed
W = Withdrew
L = Lost to followup

% Compliance to Intervention:
(# tablets taken/total # per protocol)*100
or
(# classes taken/total # of sessions should have attended per protocol)*100

Table 4. Adverse Events

Pt Identifier	AE Onset	AE End	AE Code (MedRA, CTCAE)	Severity	SAE? (Y/N)	Relatedness	Action Taken	Outcome	Comments
Subj001	08/02/2010			1		2	1	4	Subj felt Achilles tendon pain during yoga class; history of tendonitis; will not attend class next week
Subj002	07/26/2010			2		2	1	1	
Subj003	08/04/2010			3		0	4	4	Subj broke leg while skiing; withdrew from study

Severity of AE:
1 = Mild
2 = Moderate
3 = Severe
4 = Life threatening or disabling

Relatedness to Intervention:
0 = Definitely unrelated
1 = Unlikely
2 = Possibly related
3 = Probably related
4 = Definitely related

Action Taken:
0 = None
1 = Dose modification
2 = Medical intervention (specify in comments)
3 = Hospitalization
4 = Intervention discontinued
5 = Other

Outcome:
1 = Resolved
2 = Recovered with minor sequelae
3 = Recovered with major sequelae
4 = Continuing treatment
5 = Condition worsening
6 = Patient death**

**Provide further details regarding all reported serious AEs and deaths in the SAE and Subject Deaths tables listed at the end of this section.

Table 5. Frequency of Specific Symptoms

Symptoms	AE Code (MedRA, CTCAE)	N%
Fatigue		
Malaise		
Nausea		
Dizziness		
Muscle Aches		

Table 6. Out-of-Range Laboratory Values

Pt ID	Visit #	HCT	WBC	PLT	Protein	Urine RBC	Creatinine	ALT	AST	Cholesterol	Amylase	BUN	CPK	Related to Intervention
Subj001														
Subj002														
Subj003														

*If the study is collecting data on patient-reported outcomes or other assessments, which should be regularly assessed with safety data during the study, a similar table listing out-of-range values or scores can be generated for the Report.

Table 7. Serious Adverse Events

Pt Identifier	Age	Treatment Date	SAE	SAE Date	Related to Intervention	Description of Actions and Outcomes (e.g., hospitalization, withdrawn from study)
Subj001						
Subj002						
Subj003						

Table 8. Subject Deaths

Pt Identifier	DOB	Date Enrolled	Treatment Date	Cause of Death	Date of Death	Comments
Subj001		08/02/2010				
Subj002		07/26/2010				
Subj003		08/04/2010				

DSMP Sample Study Report Outline for the Independent Monitor(s)

Appendix B

The study's Data Management team usually prepares a study safety report, which begins with a brief introduction section describing the study status, issues, and procedures that produced the report (e.g., data obtained by specific date). A study description with a current timetable and study schedule should be included. Data are presented that describe the administrative status of the study, including recruitment and forms handling. Study data reports describe demographic and baseline clinical characteristics and provide a safety assessment. Study Report tables should be generated only from aggregate (not by study group assignment) baseline and aggregate safety data for the study population. A separate Closed Study Report, with masked group baseline and safety data, can be generated for the monitor(s) by a designated unmasked member of the team, but this data/report should not be reviewed by the study team.

Study Report Outline

I. Table of Contents
II. Introduction
    A. Summary of Study Status and Issues or Problems
    B. Report Preparation Procedures
III. Study Description
    A. Project Organization Chart, Personnel
    B. Brief Statement of Purpose of Trial
    C. Projected Timetable and Schedule
    D. List of Any Resource Centers
IV. Study Administration
    A. Recruitment Status
        i. Enrollment by Year/Month
        ii. Comparison of Targeted to Actual Enrollment
    B. Retention Status
        i. Overall Subject Status
        ii. Individual Subject Status
V. Study Data Reports/Tables or Figures
    A. General Information
        i. Enrollment (see Appendix A, Table 1)
        ii. Demographic/Baseline Data (see Appendix A, Table 2)
        iii. Subject Status (see Appendix A, Table 3)
    B. Safety Assessment
        i. Treatment Duration for All Subjects (see Appendix A, Table 3)
        ii. AE Data
            a. Overall Listing (see Appendix A, Table 4)
            b. Specific Symptom Listing (see Appendix A, Table 5)
            c. Out-of-Range Laboratory Values (see Appendix A, Table 6)
            d. SAE Listing (see Appendix A, Table 7)
            e. Subject Deaths (see Appendix A, Table 8)