

DEPARTMENT: Yale University Human Investigation Committee
POLICY NUMBER:
SECTION: Data and Safety Monitoring Plan
REVIEW RESPONSIBILITY: IRB Leadership Committee and HIC Policy Review
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Yale University School of Medicine HIC Policy Regarding: Data and Safety Monitoring Plan (DSMP)

I. Purpose: The purpose of this policy is to describe the required elements of a Data and Safety Monitoring Plan (DSMP) in a human subjects research protocol conducted by researchers from the Yale School of Medicine.

II. Background:

A DSMP is a plan, tailored to a particular protocol, that describes who has the responsibility to monitor study data and at which frequency study data must be monitored to ensure the safety of human subjects.

The monitoring of a clinical trial must be commensurate with the risks, and the size and complexity of the trial. For example, in a clinical trial which involves only a small number of human subjects and low risk, close monitoring by the study investigator may be adequate. Other factors that influence the frequency of monitoring may include the potential risks to subjects and the complexity of the trial itself. A multi-site or large clinical trial may require a central monitoring entity.

The essential elements of a DSMP are:

- Monitoring the progress of the trial, the safety of participants, data accuracy and assuring protocol compliance.
- Describing the mechanism and timeframe for appropriate reporting of adverse events, unanticipated problems, and protocol deviations to the IRB and the government agency program official or sponsor representative responsible for the grant or contract.

III. Policy:

All research protocols submitted for review by the HIC must include an explicit plan detailing how the Yale Principal Investigator (PI) will conduct data and safety monitoring for Yale subjects. In addition, for multi-center trials in which the Yale PI serves as the overall PI, the DSMP must include an explicit plan detailing how the PI will conduct data and safety monitoring for those subjects enrolled at other sites.

The HIC is responsible for evaluating the appropriateness of the DSMP when conducting initial and continuing protocol reviews.

The formation and use of a Data Safety Monitoring Board (DSMB) may be required by the HIC when the study poses high risk, or involves a new invention. The HIC may require a DSMB whenever it determines that the protection of subjects is enhanced by board monitoring or when a real or potential interest of a study investigator or the University poses, or may pose, a significant conflict of interest. When a DSMB exists, the DSMP must include plans for submitting DSMB reports to the HIC and other research oversight committees.

IV. Definitions:

DSMP: A plan, tailored to a particular protocol, that describes who has the responsibility to monitor study data and at which frequency study data is monitored to ensure the safety of human subjects.

Risk associated with participating in a study can be categorized as:

- Minimal Risk - Risk commensurate with ordinary daily life or with risks encountered in the performance of routine physical or psychological examinations. Examples may include blood draws of small volumes for research purposes, the collection of biological specimens for research purposes by noninvasive means, the collection of data from medical records, and most research employing surveys, interviews, or focus groups.
- Moderate Risk - Risk that is greater than minimal, but not high and where there is adequate surveillance and protection to minimize risks and discover adverse events promptly. Examples include insulin clamp studies, Phase II and some Phase III trials, and some biopsies.
- High Risk – Risk that in terms of potential harm to a subject is high because of the nature of the study or because there is significant uncertainty about the possible occurrence or nature of the risks. Examples include most Phase I drug trials.

Adverse Event: An undesirable and unintended, although not necessarily unexpected, result of therapy or other intervention.

Unanticipated: Unanticipated events are risks/events which are not cited in the protocol, the consent form or the Investigator's Brochure

Related: An event is "related" if it is possibly, probably, or definitely caused by the research procedures.

Serious Adverse Event - Any adverse event that results in any of the following outcomes: death, a life-threatening experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect, or any other adverse event that, based upon appropriate medical

judgment, may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition.

Unanticipated Problems Involving Risks to Subjects or Others: Any incident, experience or outcome that (a) is unexpected (in terms of nature, severity, or frequency) given the research procedures described in the protocol and the characteristics of the subject population and (b) suggests that the research participation places or has the potential to place subjects at greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized and (c) is related or possibly related to participation in the research.

Data and Safety Monitoring Board (DSMB), Data Monitoring Committee or other Monitoring Committees (DSMC): The use of protocol-specific monitoring committees, such as Data and Safety Monitoring Boards (DSMBs) or Data Monitoring Committees (DMCs), provides a broader context for safety monitoring. The sponsor, investigator, or steering committee of a study charges the DSMB/DMC with protecting subject safety by examining the accruing data for indications of benefit or harm. The DSMB/DMC makes a judgment as to whether the trial should continue. The DSMB/DMC usually looks at global data, as investigators forward all adverse event reports to a data coordinating center, which compiles the data for the DSMB/DMC to review at predefined intervals. Data presented to the DSMB/DMC is either completely unblinded, or categorized by treatment arm. As such, the DSMB/DMC is able to determine whether a clear effect exists in one arm of the study versus the other(s).

V. Guidance:

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

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

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

The DSMP must be listed in the section of the HIC protocol application entitled:
Protection of Research Subjects

Plans should include the following elements:

All plans must include an explicit statement of risk. Overall risk assessment associated with the protocol may be assessed by the investigator as minimal, moderate or high.

The DSMP for **minimal** risk studies must include:

1. Identification of the individual(s) who will be responsible for monitoring the data, assuring protocol compliance, conducting the safety reviews, and the required frequency of the reviews
2. Explicit statement of risk(s) (minimal)
3. A statement that adverse events are not anticipated
4. Plan for reporting to the HIC serious unanticipated adverse events and unanticipated problems involving risks to subjects or others at Yale or other sites, when applicable for multi-center trials.

The DSMP for **moderate** or **high** risk studies must, at a minimum, include:

1. Identification of the individual(s) who will be responsible for monitoring the data, assuring protocol compliance, reporting protocol non-compliance, conducting the safety reviews, and the specified frequency of the reviews.
2. Explicit statement of risk (moderate or high)
3. Plan for attribution of adverse events
4. Plan for grading adverse events
5. Plan for reporting serious unanticipated adverse events, anticipated adverse events occurring at a greater frequency than expected, and unanticipated problems involving risks to subjects or others at Yale or other sites, when applicable for multi-center trials to the HIC.
6. Plan for reporting adverse events and unanticipated problems to co-investigators on the study, and, as appropriate, to the protocol's research monitor(s), e.g., industrial sponsor, Yale Cancer Center monitors, the Yale Center for Clinical Investigation (YCCI) Research Subject Advocates (RSAs), Cancer Center's Quality Assurance, Compliance and Safety Committee (QUACS), DSMBs, study sponsors, funding and regulatory agencies, and regulatory and decision-making bodies.

Below is a more detailed explanation of the required elements.

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

Identify who is responsible for monitoring the study.

Example: The principal investigator or designee, e.g., co-investigator, will monitor the data and conduct safety reviews, at a specified frequency appropriate to the level of risk. The PI should specify the frequency of reviews in the DSMP. During the review process the principal investigator will evaluate whether the study should continue unchanged, require modification/amendment, or close to enrollment.

Define the parameters whereby the individual will analyze the monitoring and safety review data, (e.g., by time or per subject basis or any other specific and predetermined parameter or outcome). The focus of the analysis is to determine whether enrollment should continue or be closed, whether the trial should continue as originally designed or require modification/amendment.

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

B. Explicit Statement of Risk:

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

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

C. Plan for Attribution of Adverse Events:

The principal investigator is responsible for determining the likelihood that an adverse event is related to the study and must describe the plan for assessing relatedness. This is called attribution of adverse events. A sample scale is provided below.

Example: Attribution of adverse events:

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

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

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

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

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

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

D. Plan for Grading Adverse Events:

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

Example: Grades of Adverse Events:

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

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

Serious Adverse Events:

In addition to grading the adverse event, the PI must determine whether the adverse event meets the criteria for a Serious Adverse Event (SAE). An adverse event is considered serious if it:

1. is life-threatening, or
2. results in in-patient hospitalization or prolongation of existing hospitalization, or
3. results in persistent or significant disability or incapacity, or
4. results in a congenital anomaly or birth defect, or
5. results in death, or
6. based upon appropriate medical judgment, may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition, or
7. adversely affects the risk/benefit ratio of the study

An adverse event may be graded as severe but still not meet the criteria for a Serious Adverse Event. Similarly, an adverse event may be graded as moderate but still meet the criteria for an SAE. It is important for the PI to consider the grade of the event as well as its "seriousness" when determining whether reporting to the HIC is necessary.

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

The HIC requires reporting only for serious AND unanticipated AND possibly, probably or definitely related events and anticipated adverse events occurring with a greater frequency than expected. The HIC also requires reporting for all unanticipated problems involving risks to subjects or others that is unexpected AND suggests that research participation places the subject or others at greater risk of harm than was previously known or recognized AND is related or possibly related to the subjects participation.

Reports must be in writing and made in a timely manner (within 48 hours) using the HIC form, which requires the investigator to assess the need for change to the protocol, the procedures or the consent document(s).

For more information on the reporting of adverse events and unanticipated problems involving risks to subjects or others see the HIC policy at:

<http://info.med.yale.edu/hic/policy/AdverseEventPolicy.doc>

http://www.info.med.yale.edu/hic/policy/UPIRSO_Policy_5.17.07_Final.pdf

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

Define plans for reporting and reviewing adverse events to fellow investigators and key study personnel, sponsors, research monitors and other oversight bodies.

For Multicenter trials when Yale is the coordinating site, the Yale PI is responsible for reviewing safety reports forwarded by sponsors or cooperative groups. As the PI assesses these reports, they should be categorized as serious or non-serious, and unanticipated or anticipated. Reporting of such to the HIC should be based upon HIC policy.

Define plans for reviewing and reporting **non-serious, unanticipated and anticipated** adverse events to fellow investigators, key study personnel and appropriate research monitors. Investigators must review ALL adverse events. However, non-serious or anticipated adverse events should not be reported to the HIC.

When is a DSMB/DSMC Required?

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

A DSMB/DSMC may be appropriate:

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

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

DSMB Attributes

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

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

DSMP Examples:

- **Minimal Risk**
- **Moderate Risk**
- **High Risk**

Please note: the following templates should be modified to reflect the unique attributes of each study.

To download, see the DSMP Template at
<http://info.med.yale.edu/hic/templates/dsmp.doc>

Example: Minimal Risk DSMP

The principal investigator is responsible for monitoring the data, assuring protocol compliance, and conducting the safety reviews at the specified frequency [*e.g., monthly, quarterly, etc.*]. During the review process the principal investigator will evaluate whether the study should continue unchanged, require modification/amendment, continue or close to enrollment.

Either the principal investigator, the Human Investigation Committee (HIC) or [*enter the names of other oversight bodies that have this authority, e.g., QUACS*] have the authority to stop or suspend the study or require modifications.

This protocol presents minimal risks to the subjects and adverse events or other problems are not anticipated. In the unlikely event that such events occur, serious and unanticipated and related adverse events or unanticipated problems involving risks to subjects or others will be reported in writing within 48 hours to the HIC (using the appropriate HIC forms from the website) and any appropriate funding and regulatory agencies. The investigator will apprise fellow investigators and study personnel of all adverse events that occur during the conduct of this research project [*describe how the investigator will meet with obligation, e.g., through regular study meetings, via email as they are reviewed by the principal investigator.*] [*Where appropriate, modify the following sentence to apply to the specific research protocol.*] The protocol's research monitor(s), e.g., industrial sponsor, Yale Cancer Center monitors, the Yale Center for Clinical Investigation (YCCI) Research Subject Advocates (RSAs), Cancer Center Protocol Review Committee (PRC), Quality Assurance and Compliance and Safety Committee (QUACS), DSMBs, study sponsors, funding and regulatory agencies, and regulatory and decision-making bodies will be informed of [*specify types of adverse events that require reporting to these oversight bodies*] adverse events within 5 days [*enter other appropriate duration*] of the event becoming known to the principal investigator.

Moderate Risk DSMP

1. Personnel responsible for the safety review and its frequency:

The principal investigator will be responsible for monitoring the data, assuring protocol compliance, and conducting the safety reviews at the specified frequency which must be conducted at a minimum of every 6 months (including when reapproval of the protocol is sought). During the review process, the principal investigator (monitor) will evaluate whether the study should continue unchanged, require modification/amendment, continue or close to enrollment. Either the principal investigator, the HIC or [*enter the names of*

other oversight bodies that have this authority, e.g., QUACSI have the authority to stop or suspend the study or require modifications.

2. The risks associated with the current study are deemed moderate for the following reasons: (choose those that apply)

1. We do not view the risks associated with the _____ as minimal.
2. We do not view the risks associated with the combined use of _____ and _____ as minimal.
3. Given the now established safety and validity of the current _____ in our prior work, we do not view the proposed studies as high risk.
4. Given our experience with the combined co-administration _____, we do not view the proposed studies as high risk.

Although we have assessed the proposed study as one of moderate risk, the potential exists for anticipated and/or unanticipated adverse events, serious or otherwise, to occur since it is not possible to predict with certainty the absolute risk in any given individual or in advance of first-hand experience with the proposed study methods. Therefore, we provide a plan for monitoring the data and safety of the proposed study as follows:

3. Attribution of Adverse Events:

Adverse events will be monitored for each subject participating in the study and attributed to the study procedures / design by the principal investigator (*Insert Investigator Name*) according to the following categories:

- a.) Definite: Adverse event is clearly related to investigational procedures(s)/agent(s).
- b.) Probable: Adverse event is likely related to investigational procedures(s)/agent(s).
- c.) Possible: Adverse event may be related to investigational procedures(s)/agent(s).
- d.) Unlikely: Adverse event is likely not to be related to the investigational procedures(s)/agent(s).
- e.) Unrelated: Adverse event is clearly not related to investigational procedures(s)/agent(s).

4. Plan for Grading Adverse Events:

The following scale will be used in grading the severity of adverse events noted during the study:

1. Mild adverse event
2. Moderate adverse event
3. Severe

5. Plan for Determining Seriousness of Adverse Events:

Serious Adverse Events:

In addition to grading the adverse event, the PI will determine whether the adverse event meets the criteria for a Serious Adverse Event (SAE). An adverse event is considered serious if it:

1. is life-threatening
2. results in in-patient hospitalization or prolongation of existing hospitalization
3. results in persistent or significant disability or incapacity
4. results in a congenital anomaly or birth defect OR
5. results in death
6. based upon appropriate medical judgment, may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition, or
7. adversely affects the risk/benefit ratio of the study

An adverse event may be graded as severe but still not meet the criteria for a Serious Adverse Event. Similarly, an adverse event may be graded as moderate but still meet the criteria for an SAE. It is important for the PI to consider the grade of the event as well as its "seriousness" when determining whether reporting to the HIC is necessary.

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

The investigator will report the following types of adverse events to the HIC; a) serious AND unanticipated AND possibly, probably or definitely related events; b) anticipated adverse events occurring with a greater frequency than expected; and c) other unanticipated problems involving risks to subjects or others.

These adverse events or unanticipated problems involving risks to subjects or others will be reported to the HIC within 48 hours of it becoming known to the investigator, using the appropriate HIC forms found on the website.

7. Plan for reporting adverse events to co-investigators on the study, as appropriate the protocol's research monitor(s), e.g., industrial sponsor, Yale Center for Clinical Investigation Research Subject Advocates (RSAs), Cancer Center's Quality Assurance, Compliance and Safety Committee (QUACS) Protocol Review Committee (PRC), DSMBs, study sponsors, funding and regulatory agencies, and regulatory and decision-making bodies.

For the current study, the following individuals, funding, and/or regulatory agencies will be notified: (choose those that apply)

- i. All Co-Investigators listed on the protocol.
- ii. **Yale Center for Clinical Investigation Research Subject Advocates (RSAs)**
- iii. Quality Assurance and Compliance and Safety Committee (QUACS)

- iv. National Institutes of Health
- v. Food and Drug Administration (Physician-Sponsored IND # _____)
- vi. _____ Medical Research Foundation (Grant _____)

The principal investigator (*Insert Investigator Name*) will conduct a review of all adverse events upon completion of every study subject. The principal investigator will evaluate the frequency and severity of the adverse events and determine if modifications to the protocol or consent form are required.

High Risk DSMP

(Please note: in addition to a DSMP, a DSMB will likely be required)

1. Personnel responsible for the safety review and its frequency:

The principal investigator will be responsible for monitoring the data, assuring protocol compliance, and conducting the safety reviews at the specified frequency which must be conducted at a minimum of every 6 months (including when reapproval of the protocol is sought). During the review process, the principal investigator (monitor) will evaluate whether the study should continue unchanged, require modification/amendment, continue or close to enrollment. Either the principal investigator, the HIC or [*enter the names of other oversight bodies that have this authority, e.g., QUACS*] have the authority to stop or suspend the study or require modifications.

2. The risks associated with the current study are deemed high for the following reasons: (choose those that apply)

- 1. We do not view the risks associated with the _____ as minimal/moderate.
- 2. We do not view the risks associated with the combined use of _____ and _____ as minimal/moderate.
- 3. Given the now established safety and validity of the current _____ in our prior work, we do not view the proposed studies as minimal/moderate.
- 4. Given our experience with the combined co-administration _____, we do not view the proposed studies as minimal/moderate.

Since it is not possible to predict with certainty the absolute risk in any given individual or in advance of first-hand experience with the proposed study methods, we provide a plan for monitoring the data and safety of the proposed study as follows:

3. Attribution of Adverse Events:

Adverse events will be monitored for every subject participating in the study and attributed to the study procedures / design by the principal investigator (*Insert Investigator Name*) according to the following categories:

- a.) Definite: Adverse event is clearly related to investigational procedures(s)/agent(s).
- b.) Probable: Adverse event is likely related to investigational procedures(s)/agent(s).
- c.) Possible: Adverse event may be related to investigational procedures(s)/agent(s).
- d.) Unlikely: Adverse event is likely not to be related to investigational procedures(s)/agent(s).
- f.) Unrelated: Adverse event is clearly not related to investigational procedures(s)/agent(s).

4. Plan for Grading Adverse Events:

The following scale will be used in grading the severity of adverse events noted during the study:

- 1 Mild adverse event
- 2 Moderate adverse event
- 3 Severe adverse event

5. Plan for Determining Seriousness of Adverse Events:

Serious Adverse Events:

In addition to grading the adverse event, the PI will determine whether the adverse event meets the criteria for a Serious Adverse Event (SAE). An adverse event is considered serious if it:

- 1. is life-threatening
- 2. results in in-patient hospitalization or prolongation of existing hospitalization
- 3. results in persistent or significant disability or incapacity
- 4. results in a congenital anomaly or birth defect OR
- 5. results in death
- 6. based upon appropriate medical judgment, may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition, or
- 7. adversely affects the risk/benefit ratio of the study

An adverse event may be graded as severe but still not meet the criteria for a Serious Adverse Event. Similarly, an adverse event may be graded as moderate but still meet the criteria for an SAE. It is important for the PI to consider the grade of the event as well as its "seriousness" when determining whether reporting to the HIC is necessary.

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

The investigator will report the following types of adverse events to the HIC; a) serious AND unanticipated AND possibly, probably or definitely related events; b) anticipated

adverse events occurring with a greater frequency than expected; and c) other unanticipated problems involving risks to subjects or others.

These adverse events and unanticipated problems involving risks to subjects or others will be reported to the HIC within 48 hours of it becoming known to the investigator, using the appropriate HIC forms found on the website.

7. Plan for reporting adverse events to co-investigators on the study, as appropriate the protocol's research monitor(s), e.g., industrial sponsor, Yale Center for Clinical Investigation Research Subject Advocates (RSAs), Cancer Center's Quality Assurance, Compliance and Safety Committee (QUACS) DSMBs, study sponsors, funding and regulatory agencies, and regulatory and decision-making bodies.

For the current study, the following individuals, funding, and/or regulatory agencies will be notified:

- i. All Co-Investigators listed on the protocol.
- ii. **Yale Center for Clinical Investigation Research Subject Advocates (RSAs)**
- iii. Quality Assurance and Compliance and Safety Committee (QUACS)
- iv. National Institutes of Health
- v. Food and Drug Administration (Physician-Sponsored IND # _____)
- vi. Medical Research Foundation (Grant _____)

The principal investigator (*Insert Investigator Name*) will conduct a review of all adverse events upon completion of every study subject. The principal investigator will evaluate the frequency and severity of the adverse events and determine if modifications to the protocol or consent form are required.

For more guidance on Adverse Event reporting and DSMP see http://oscar.med.yale.edu/hsp/module_6/4_guidance.asp