University of Wisconsin Comprehensive Cancer Center (UWCCC)

POLICY & PROCEDURES FOR DATA AND SAFETY MONITORING

CRC Review	5/16/01
Submitted to NCI	5/21/01
DOWG Leader Review	6/26/01
Program Manager Review	7/10/01
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I. Data and Safety Monitoring

A. Overview

The Clinical Research Committee (CRC), composed of UWCCC senior leadership, oversees all aspects of clinical research conducted at the UWCCC and makes final decisions on all issues related to clinical trials. The Clinical Affairs Committee (CAC) is responsible for reviewing all new clinical trials and the Clinical Trials Monitoring Committee (CTMC) is responsible for safety, validity of data, appropriate closure of trials, and monitoring of UWCCC Clinical research.

1. Clinical Research Committee

This committee insures that all aspects of the clinical research process at the Cancer Center are conducted according to prescribed standard operating procedures. The Committee:

a) Reviews and approves all UWCCC policies and procedures related to clinical research.

b) Oversees all cancer clinical trials conducted at the UWCCC.

c) Appoints membership and defines responsibility of the Clinical Affairs Committee and the Clinical Trials Monitoring Committee.

d) Serves as review body for the Clinical Affairs Committee and the Clinical Trials Monitoring Committee decisions.

Members of the Clinical Research Committee are key leaders of the UWCCC appointed by the Director. Their term is co-terminous with their leadership role. The committee meets monthly. Interim meetings to address specific issues that require immediate attention are scheduled to insure patient safety. Members are listed in Table 1.

Table 1 Clinical Research Committee Membership	
Name	***Leadership Role***
George Wilding, M.D., Chair	Assoc. Director, Clinical Research Programs
John E. Niederhuber, M.D.	Director, UWCCC
James F. Cleary, M.D.	Chair, CAC
James A. Stewart, M.D.	Chair, CTMC
David L. DeMets, Ph.D.	Chair, Biostatistics & Medical Informatics
KyungMann Kim, Ph.D.	Co-Chair, CAC & CTMC
Paul M. Sondel, M.D., Ph.D.	Section Head, Pediatric Oncology
Minesh Mehta, M.D.	Chairman, Radiation Therapy
Howard H. Bailey, M.D.	Assoc. Director, General Clinical Research Center
Rebecca Marnocha, Pharm. D.	Director, UWHC Pharmaceutical Research Center
Jane Wegenke	Assoc. Director, Administration
Teresa Smith, R.N., M.S.N.	Director, UWHC Oncology Programs
Rhoda Arzoomanian, R.N., B.S.N.	Asst. Director, Clinical Research Programs
Judith D. Schiesel	Manager, Clinical Trials Research Office

2. Clinical Affairs Committee

The Clinical Research Committee delegates the responsibility for the evaluation of data and safety monitoring plans and the determination of potential conflicts of interest for all clinical research performed at the UWCCC to the Clinical Affairs Committee. The Committee:

a) Reviews all new clinical trials for scientific merit.

b) Assesses adequacy of data and safety monitoring plans for each protocol.

c) Identifies potential conflict of interest.

d) Prioritizes new clinical trials to insure adequate patient resources and staff support.

e) Affirms relevance of the proposed clinical trial to the mission of the UWCCC.

f) Reviews quality control and safety reports submitted by the Clinical Trials Monitoring Committee and determines appropriate corrective action.

g) Notifies the Study Chair of the corrective action.

h) Maintains master file of notices provided by Study Chair to IRB, sponsor, and funding agency.

Members are appointed by the UWCCC Director. Membership duration is flexible to maintain required depth and breadth of expertise related to the spectrum of clinical research conducted at the UWCCC. This committee meets every two weeks. Present membership is listed in the Table 2.

Table 2
CAC Membership

Name	***Expertise***
James F. Cleary, M.D., Chair	Medical Oncology
KyungMann Kim, Ph.D., Co Chair	Biostatistics
Paul R. Hutson, Pharm.D, Co-Chair	Pharmacy
Rhoda Z. Arzoomanian, R.N., B.S.N.	Clinical Trials Management
Tara Breslin, M.D.	Surgery
G. Terry Bryan, M.D.	Medical Oncology
Richard Chappell, Ph.D.	Biostatistics
Joseph P. Connor, M.D.	Gynecologic Oncology
Carol Diamond, M.D.	Pediatric Oncology
Kennedy W. Gilchrist, M.D.	Surgical Pathology
Mark B. Juckett, M.D.	Hematology
Brad S. Kahl, M.D.	Hematology
Peter A. Mahler, M.D.	Radiation Oncology
Mark A. Ritter, M.D., Ph.D.	Radiation Oncology
H. Ian Robins, M.D., Ph.D.	Medical Oncology
Sandra E. Ward, R.N., Ph.D.	Nursing
Tracy Weigel, M.D.	Cardiothoracic Surgery

3. Clinical Trials Monitoring Committee

The Clinical Research Committee delegates responsibility for continued review and monitoring of all clinical trials conducted by the UWCCC to the Clinical Trials Monitoring Committee. This committee provides oversight of study progress and safety by review of accrual and adverse events at quarterly meetings. The Committee:

a) Reviews all clinical trials conducted at the UWCCC for progress and safety.

b) Reviews all adverse events requiring expedited reporting as defined in the protocol.

c) Reviews reports generated by the UWCCC data quality control review process (internal audit, quality assurance review, and response review) described in Section II of this document.

d) Submits recommendations for corrective actions to the Clinical Affairs Committee.

e) Notifies the Study Chair of the recommended action.

f) Notifies external sites participating in multiple-institutional clinical trials coordinated by the UWCCC of expedited adverse events and/or committee recommendations.

Members are appointed by the UWCCC Director. Membership duration is flexible to maintain required depth and breadth of expertise related to the spectrum of clinical research conducted at the Cancer Center. Interim meetings are scheduled to address specific issues that require immediate attention to insure patient safety. Present membership is listed in Table 3.

Table 3
CTMC Membership

Name	***Discipline***
James A. Stewart, M.D., Chair	Medical Oncology
KyungMann Kim, Ph.D., Co-Chair	Biostatistics
Patrick L. Remington, M.D., M.P.H.	Cancer Control
Mark A. Ritter, M.D., Ph.D.	Radiation Oncology
Eileen P. Smith, M.D.	Bone Marrow Transplant
Joseph H. Matloub, M.D.	Pediatric Oncology
Judith D. Schiesel	Clinical Trials Management

B. Data and Safety Monitoring Plan

1. Requirements

All clinical trials conducted at the Cancer Center must have a satisfactory data and safety monitoring plan that is described in detail in the protocol. The Clinical Affairs Committee review insures patient safety and that the degree and frequency of data and safety monitoring for individual studies will be commensurate with the size, complexity and risks of the trial.

2. Elements of a Data and Safety Monitoring Plan

a) Delineation of oversight responsibilities (either external DSMB or UWCCC Clinical Trials Monitoring Committee).

b) Description of data and safety review process.

c) Time table for submission of data, safety, and progress information to the DSMB or UWCCC Clinical Trials Monitoring Committee, the IRB, and the sponsor.

d) Process to implement closure of studies when significant risks or benefits are identified.

e) Description of adverse event reporting procedures.

A template that can be used by investigators to describe an internal data and safety monitoring plan for their protocol is presented in Appendix I. Guidelines for establishing and operating an external DSMB are presented in Appendix II.

C. Guidelines for Data and Safety Monitoring Implementation

1. Monitoring and Reporting Requirements

UWCCC monitoring requirements for trials without an acceptable external DSMB are as follows:

a) Phase I Trials

Investigators will conduct continuous review of data and patient safety at their weekly Phase I/Disease Group meetings where the results of each patient's treatment are discussed and the discussion is documented in the minutes. The discussion will include for each dose level: the number of patients, significant toxicities as described in the protocol, dose adjustments, and responses observed. Quarterly summaries will be submitted to the Clinical Trials Monitoring Committee for review.

b) Phase I/II and Phase II Trials

Data related to these trials are discussed at regularly scheduled Disease Oriented Working Group meetings where the results of each patient's treatment are discussed and the discussion is documented in the minutes. The discussion will include for each treatment arm/dose level: the number of patients, significant toxicities as described in the protocol, dose adjustments, and responses observed. Twice yearly, summaries will be submitted to the Clinical Trials Monitoring Committee for review.

c) Phase III Trials and Trials Enrolling >300 Patients

All phase III trials and trials enrolling >300 patients will have an external Data and Safety Monitoring Board (DSMB) whose composition and review procedures are approved by the UWCCC Clinical Affairs Committee.

d) Phase I – III Behavioral and Nutritional Trials

These trials must have a data and safety monitoring plan commensurate with the level of risk to the participants and approved by the Clinical Affairs Committee.

e) Training Grant Trials

Studies developed by an investigator in training who is supported on a training grant or mentored by a UWCCC investigator will be subject to the guidelines described above.

2. Review and Oversight Requirements

a) Adverse Event – Reported By Phone Within 24 Hours

Adverse events requiring expedited reporting by phone within 24 hours (as described in the protocol) will also be reported by phone to the Clinical Trials Monitoring Committee administrator within one business day. Confirmation that all appropriate parties were notified will be done at this time. Hardcopies or electronic versions of NCI ADEERS form (#3500) and/or any other documentation available at that time will also be reviewed by the Committee Chair who will determine if immediate action is required. Within 10 working days all subsequent SAE documentation that is available will be submitted with a completed UWCCC SAE Evaluation Checklist to the Committee Chair who will determine if further action is required. All information will be tracked in the UWCCC database.

If the AE occurs on a multiple-institutional clinical trial coordinated by the UWCCC, the Safety Coordinator will insure that all participating sites are notified of the event and resulting action within one working day of the determination.

b) Adverse Event – Reported within 10 Days

Adverse events requiring expedited AE reports in writing within 10 working days (as described in the protocol) will be sent to the UWCCC Safety Coordinator. Hardcopies or electronic versions of NCI ADEERS form (#3500) or other required forms will be submitted along with a copy of the SAE Evaluation Checklist. The Committee Chair will review these forms and determine if further action is required. This information will be tracked in the UWCCC database.

If the AE occurs on a multiple-institutional clinical trial coordinated by the UWCCC, the Safety Coordinator will insure that all participating sites are notified of the event and resulting action within one working day of the determination.

c) Study Progress – Quarterly Review

Study progress assessment to determine whether accrual projections are being met and to determine if the trial should be continued based upon the likelihood of timely completion are reviewed at quarterly Clinical Trials Monitoring Committee meetings. Cumulative reports of adverse events requiring expedited reporting and any new adverse event requiring expedited reporting are also reviewed at the committee's quarterly meetings.

An overall assessment of accrual, toxicities as described in the protocol, and responses will enable the committee members to assess whether significant benefits or risks are occurring that would warrant study closure. This information is provided by Disease Group meeting minutes, internal audit and/or response review reports. The committee may request external DSMB reports or further information from the Disease Groups, or Study Chair.

The Clinical Trials Monitoring Committee recommendations for modifications to the trial are forwarded to the Clinical Affairs Committee. The Study Chair is notified of this recommendation in order that he/she may alert all investigators, at the UWCCC and at external sites involved in the trial, about the potential action. At this time the Study Chair may submit to the Clinical Affairs Committee additional information that could affect the Committee's decision. The Clinical Affairs Committee will notify the Study Chair if they concur with the Clinical Trials Monitoring Committee recommendations, including suspension or closure. The Study Chair will notify all investigators involved with the study at the UWCCC and external sites, the IRB, the sponsor and the funding agency and provide written documentation of these notifications to the Clinical Affairs Committee.

The UWCCC Clinical Research Committee (CRC), composed of Cancer Center senior leaders oversees these activities.

d) Review of Adverse Event Rates

Once a month, adverse event rates will be monitored utilizing the UWCCC Clinical Trials database. If any study has had two or more of the same AE reported in a month or more than six of the same AE in six months, the CTMC Chair will review the summary of SAEs, discuss events with Study Chair, and conduct a more detailed review with the Study Chair or the external DSMB if warranted. The Committee Chair will determine if further action is required.

If this occurs on a multiple-institutional clinical trial coordinated by the UWCCC, the Safety Coordinator will insure that all participating sites are notified of the resulting action.

II. Data Quality Control

Three types of procedures insure that UWCCC protocol/patient data are of the highest quality. These are auditing, response review, and quality assurance review. Reports of these quality control activities are submitted and discussed at the quarterly Clinical Trials Monitoring Committee meeting and then submitted with recommendations for follow-up or corrective action to the Clinical Affairs Committee. The Clinical Affairs Committee reviews the reports, implements corrective action, and notifies the Clinical Research Committee of these actions. This review process is detailed in UWCCC quality control standard operating procedures.

A. Internal Audit

The audit procedure is a formal, comprehensive, source document review of any institutional study not otherwise audited by an external agency. Twice a year, two trials from this group are selected for audit. Ten percent of the cases from these trials are randomly selected for review. Typically two members of the clinical research staff and one clinical investigator, who is not a principal in the study, serve as auditors. The following elements are reviewed:

1. Source document verification of eligibility, response, and toxicity.
2. Regulatory review of IRB compliance and external reporting requirements.
3. Drug accountability and handling.
4. Completeness and quality of data.

B. Response Review

Response Review is performed prior to quarterly Clinical Trials Monitoring Committee meetings on all cases exhibiting a partial response or complete response on any therapeutic clinical trial conducted at the UWCCC. An independent investigator who is not a principal involved in the study, reviews and confirms measurements and source documentation.

C. Quality Assurance Review

Quality Assurance Review is performed on all therapeutic clinical trials conducted at the UWCCC. The statistician randomly selects five cases for Quality Assurance Review every quarter from all studies at risk for review in this group. Typically two members of the clinical research staff, not involved in the conduct of the study, serve as reviewers. The Quality Assurance Review concentrates on data management and system procedures, quality of data collection and protocol adherence. The following elements are reviewed.

1. Eligibility and treatment compliance.
2. Assessment of disease status.
3. Completeness and quality of data.
4. Compliance with reporting procedures (including adverse events requiring expedited reporting).
5. Research chart organization.

III. Conflict of Interest

The Clinical Affairs Committee is responsible for identifying, during their scientific review, potential conflicts of interest involved in any UWCCC clinical trial. Investigators must indicate on the protocol submission form any potential conflict of interest resulting from their involvement in the trial. If a potential conflict is identified by the Committee, the investigator must work with his/her department chair and the UW Conflict of Interest Committee to create a plan to eliminate or manage the conflict of interest. The University of Wisconsin Policies and Procedures for Conflict of Interest govern this process.

APPENDIX I

PROTOCOL TEMPLATES FOR A DATA & SAFETY MONITORING PLAN FOR CLINICAL TRIALS THAT DO *NOT* HAVE AN EXTERNAL DATA AND SAFETY MONITORING BOARD

Investigator: Insert selected information into protocol document.

Oversight And Monitoring Plan

(Investigator: Insert entire section into your protocol)

The UWCCC Clinical Trials Monitoring Committee (CTMC) is responsible for monitoring data quality and patient safety for all UWCCC clinical studies. A summary of CTMC activities follows:

- Review of all clinical trials conducted at the UWCCC for progress and safety
- Review of all adverse events requiring expedited reporting as defined in the protocol
- Review of reports generated by the UWCCC data quality control review process
- Submit recommendations for corrective action to the Clinical Affairs Committee (CAC)
- Notify the Study Chair of the CTMC recommendation to the CAC
- Notify external sites participating in multiple-institutional clinical trials coordinated by the UWCCC of adverse events requiring expedited reporting and subsequent committee recommendations for study modifications.

Monitoring And Reporting Guidelines

(Investigator: Insert the appropriate section that applies to your clinical trial into your document and delete all others)

Phase I Trials

Investigators will conduct continuous review of data and patient safety at their weekly Phase I/Disease Group meetings where the results of each patient's treatment are discussed and the discussion is documented in the minutes. The discussion will include for each dose level: the number of patients, significant toxicities as described in the protocol, doses adjustments, and responses observed. Quarterly summaries will be submitted to the Clinical Trials Monitoring Committee for review.

Phase I/II and Phase II Trials

Data related to these trials are discussed at regularly scheduled Disease Oriented Working Group meetings where the result of each patient's treatment is discussed and the discussion is documented in the minutes. The discussion will include for each treatment arm/dose level, the number of patients, significant toxicities as described in the protocol, dose adjustments, and responses observed. Twice yearly, summaries will be submitted to the Clinical Trials Monitoring Committee for review.

Phase I – III Behavioral and Nutritional Trials

These trials must have a data and safety monitoring plan commensurate with the level of risk to the participants and approved by the Clinical Affairs Committee.

REVIEW AND OVERSIGHT REQUIREMENTS

(Investigator: Insert entire section into your protocol)

a) Adverse Event – Reported By Phone Within 24 Hours

Adverse events requiring expedited reporting by phone within 24 hours (as described in the protocol) will also be reported by phone to the Clinical Trials Monitoring Committee administrator within one working day. Confirmation that all appropriate parties were notified will be done at this time. Hardcopies or electronic versions of NCI ADEERS form (#3500) and/or any other documentation available at that time will also be reviewed by the Committee Chair who will determine if immediate action is required. Within ten working days all subsequent SAE documentation that is available will be submitted with a completed UWCCC SAE Evaluation Checklist to the Committee Chair who will determine if further action is required. All information will be tracked in the UWCCC database.

If the AE occurs on a multiple-institutional clinical trial coordinated by the UWCCC, the Safety Coordinator will insure that all participating sites are notified of the event and resulting action within one working day of the determination.

b) Adverse Event – Reported within 10 Days

Adverse events requiring expedited AE reports in writing within 10 working days (as described in the protocol) will be sent to the UWCCC Safety Coordinator. Hardcopies or electronic versions of NCI ADEERS form (#3500) or other required forms will be submitted along with a copy of the SAE Evaluation Checklist. The Committee Chair will review these forms and determine if further action is required. This information will be tracked in the UWCCC database.

If the AE occurs on a multiple-institutional clinical trial coordinated by the UWCCC, the Safety Coordinator will insure that all participating sites are notified of the event and resulting action within one working day of the determination.

c) Study Progress – Quarterly Review

Study progress assessment to determine whether accrual projections are being met and to determine if the trial should be continued based upon the likelihood of timely completion are reviewed at quarterly Clinical Trials Monitoring Committee meetings. Cumulative reports of adverse events requiring expedited reporting and any new adverse event requiring expedited reporting are also reviewed at the committee's quarterly meetings.

An overall assessment of accrual, toxicities as described in the protocol, and responses will enable the committee members to assess whether significant benefits or risks are occurring that would warrant study closure. This information is provided by Disease Group meeting minutes, internal audit and/or response review reports. The committee may request external DSMB reports or further information from the Disease Groups, or Study Chair.

The Clinical Trials Monitoring Committee recommendations for modifications to the trial are forwarded to the Clinical Affairs Committee. The Study Chair is notified of this recommendation in order that he/she may alert all investigators, at the UWCCC and at external sites involved in the trial, about the potential action. At this time the Study Chair may submit to the Clinical Affairs Committee additional information that could affect the Committee's decision. The Clinical Affairs Committee will notify the Study Chair if they concur with the Clinical Trials Monitoring Committee recommendations, including suspension or closure. The Study Chair will notify all investigators involved with the study at UWCCC and external sites, the IRB, the sponsor and the funding agency and provide written documentation of these notifications to the Clinical Affairs Committee.

The UWCCC Clinical Research Committee (CRC), composed of Cancer Center senior leaders oversees these activities.

d) Review of Adverse Event Rates

Once a month, adverse event rates will be monitored utilizing the UWCCC Clinical Trials database. If any study has had two or more of the same AE reported in a month or more than six of the same AE in six months, the CTMC Chair will review the summary of SAEs, discuss events with Study Chair, and conduct a more detailed review with the Study Chair or the external DSMB if warranted. The Committee Chair will determine if further action is required.

If this occurs on a multiple-institutional clinical trial coordinated by the UWCCC, the Safety Coordinator will insure that all participating sites are notified of the resulting action.

EXPEDITED REPORTING OF ADVERSE EVENTS

(Investigator: Insert entire section into your protocol)

Depending on the nature, severity, and attribution of the event an ADR report will be phoned in, submitted in writing, or both according to Tables A-D below. Telephoned Adverse Events must also be reported by phone to the UWCCC Clinical Trials Monitoring Committee within one working day of the event. All adverse events must also be reported to the UW IRB, and any sponsor/funding agency not already included in the list.

Telephone reports to:

(Investigator: Insert names and phone numbers for required notifications)

- UWCCC Clinical Trials Monitoring Committee Administrator 608-263-0169 within one working day of the event

Written reports to:

(Investigator: Insert names, fax numbers, and addresses for required notifications)

UWCC Clinical Trials Monitoring Committee Administrator –
FAX 608-263-8613 or deliver to K4/642
UW IRB – Copy of final written report to Sponsor.

EXPEDITED REPORTING TABLE

(Investigator: Choose the appropriate Reporting Summary from the following tables and insert into your protocol document)

Category	***Applicable Table***
NCI Holds IND	Tables A-I – A-III
Other Holds IND	Tables B-I – B-II
No IND	Table C
Cancer Vaccine Trials	Table D

TABLE A-I-1

Summary Of Reporting Requirements For Adverse Events On Trials Supported By Grant Or Contract Where NCI Holds IND (See Table A-II for DNA Molecules – Gene Transfer)

EXPEDITED REPORTING FOR PHASE I STUDIES

Unexpected Event		**Expected Event**	
GRADES 2 – 3 Attribution of Possible, Probable, or Definite	**GRADES 4 and 5 Regardless of Attribution**	**GRADES 1 - 3**	**GRADES 4 and 5 Regardless of Attribution**
Grade 2 - Expedited report within 10 working days to IDB. *Grade 3* - Report by phone to IDB within 24 hrs. Expedited report to follow within 10 working days. (*Grade 1* - Adverse Event Expedited Reporting NOT required.)	Report by phone to IDB within 24 hrs. Expedited report to follow within 10 working days. This includes all deaths within 30 days of the last dose of treatment with an investigational agent regardless of attribution. Any late death attributed to the agent (possible, probable, or definite) should be reported within 10 working days.	Adverse Event Expedited Reporting NOT required.	Report by phone to IDB within 24 hrs. Expedited report to follow within 10 working days. This includes all deaths within 30 days of the last dose of treatment with an investigational agent regardless of attribution. Any late death attributed to the agent (possible, probable, or definite) should be reported within 10 working days.

For Hospitalization Only – Any medical event equivalent to the CTC Grade 3,4,5 which precipitated hospitalization (or prolongation of existing hospitalization) must be reported regardless of requirements for phase of study, expected or unexpected and attribution.

Expedited reporting may not be appropriate for specific expected adverse events for certain later phase 2 and phase 3 protocols. In those situations the adverse events that will not have expedited reporting must be specified in the text of the approved protocol. An expected Grade 3 event that is using the generic reporting criteria, for instance. In a trial of investigational agents where grade 3 diarrhea requiring hospitalization is expected, only diarrhea requiring ICU care (Grade 4) might be designated for expedited reporting.

TABLE A-I-2

Summary Of Reporting Requirements For Adverse Events On Trials Supported By Grant Or Contract Where NCI Holds IND (See Table A-II for DNA Molecules – Gene Transfer)

EXPEDITED REPORTING FOR PHASE 2 AND PHASE 3 STUDIES

Unexpected Event		**Expected Event**	
GRADES 2 - 3 Attribution of Possible, Probable, or Definite	**GRADES 4 and 5 Regardless of Attribution**	**GRADES 1 - 3**	**GRADES 4 and 5, Regardless of Attribution**
Expedited report within 10 working days to IDB. (Grade 1 - Adverse Event Expedited Reporting NOT required.)	Report by phone to IDB within 24 hrs. Expedited report to follow within 10 working days. This includes all deaths within 30 days of the last dose of treatment with an investigational agent regardless of attribution. Any late death attributed to the agent (possible, probable, or definite) should be reported within 10 working days.	Adverse Event Expedited Reporting NOT required.	Report by phone to IDB within 24 hrs. Expedited report to follow within 10 working days. This includes all deaths within 30 days of the last dose of treatment with an investigational agent regardless of attribution. Any late death attributed to the agent (possible, probable, or definite) should be reported within 10 working days. Grade 4 Myelosuppression or other Grade 4 events that do not require expedited reporting will be specified in the protocol.

IDB = Investigational Drug Branch

For Hospitalization Only – Any medical event equivalent to the CTC Grade 3,4,5 which precipitated hospitalization (or prolongation of existing hospitalization) must be reported regardless of requirements for phase of study, expected or unexpected and attribution.

Expedited reporting may not be appropriate for specific expected adverse events for certain later phase 2 and phase 3 protocols. In those situations the adverse events that will not have expedited reporting must be specified in the text of the approved protocol. An expected Grade 3 event that is using the generic reporting criteria, for instance. In a trial of investigational agents where grade 3 diarrhea requiring hospitalization is expected, only diarrhea requiring ICU care (Grade 4) might be designated for expedited reporting.

TABLE A-II-1

Summary Of Reporting Requirements For Adverse Events On Trials Involving DNA Molecules Or Gene Transfer Supported By Grant Or Contract Where NCI Holds IND

EXPEDITED REPORTING FOR PHASE I STUDIES

Unexpected Event		**Expected Event**	
GRADES 2 - 3 Attribution of Possible, Probable, or Definite	**GRADES 4 and 5 Regardless of Attribution**	**GRADES 1 - 3**	**GRADES 4 and 5, Regardless of Attribution**
Grade 2 - Expedited report within 10 working days to IDB/OBA. Grade 3 - Report by phone to IDB/OBA within 24 hrs. Expedited report to follow within 10 working days. (Grade 1 - Adverse Event Expedited Reporting NOT required.)	Report by phone to IDB/OBA within 24 hrs. Expedited report to follow within 10 working days. This includes all deaths within 30 days of the last dose of treatment with an investigational agent regardless of attribution. Any late death attributed to the agent (possible, probable, or definite) should be reported within 10 working days.	Adverse Event Expedited Reporting NOT required.	Report by phone to IDB/OBA within 24 hrs. Expedited report to follow within 10 working days. This includes all deaths within 30 days of the last dose of treatment with an investigational agent regardless of attribution. Any late death attributed to the agent (possible, probable, or definite) should be reported within 10 working days.

IND = Investigational Drug Branch OBA = Office of Biotechnology Activities

For Hospitalization Only – Any medical event equivalent to the CTC Grade 3,4,5 which precipitated hospitalization (or prolongation of existing hospitalization) must be reported regardless of requirements for phase of study, expected or unexpected and attribution.

Expedited reporting may not be appropriate for specific expected adverse events for certain later phase 2 and phase 3 protocols. In those situations the adverse events that will not have expedited reporting must be specified in the text of the approved protocol. An expected Grade 3 event that is using the generic reporting criteria, for instance. In a trial of investigational agents where grade 3 diarrhea requiring hospitalization is expected, only diarrhea requiring ICU care (Grade 4) might be designated for expedited reporting.

TABLE A-II-2

Summary Of Reporting Requirements For Adverse Events On Trials Involving DNA Molecules Or Gene Transfer Supported By Grant Or Contract Where NCI Holds IND

EXPEDITED REPORTING FOR PHASE 2 AND PHASE 3 STUDIES

Unexpected Event		**Expected Event**	
GRADES 2 - 3 Attribution of Possible, Probable, or Definite	**GRADES 4 and 5 Regardless of Attribution**	**GRADES 1 - 3**	**GRADES 4 and 5, Regardless of Attribution**
Expedited report within 10 working days to IDB/OBA. (Grade 1 - Adverse Event Expedited Reporting NOT required.)	Report by phone to IDB/OBA within 24 hrs. Expedited report to follow within 10 working days. This includes all deaths within 30 days of the last dose of treatment with an investigational agent regardless of attribution. Any late death attributed to the agent (possible, probable, or definite) should be reported within 10 working days.	Adverse Event Expedited Reporting NOT required.	Report by phone to IDB/OBA within 24 hrs. Expedited report to follow within 10 working days. This includes all deaths within 30 days of the last dose of treatment with an investigational agent regardless of attribution. Any late death attributed to the agent (possible, probable, or definite) should be reported within 10 working days. Grade 4 Myelosuppression or other Grade 4 events that do not require expedited reporting will be specified in the protocol.

IDB = Investigational Drug Branch OBA = Office of Biotechnology Activities

For Hospitalization Only – Any medical event equivalent to the CTC Grade 3,4,5 which precipitated hospitalization (or prolongation of existing hospitalization) must be reported regardless of requirements for phase of study, expected or unexpected and attribution.

Expedited reporting may not be appropriate for specific expected adverse events for certain later phase 2 and phase 3 protocols. In those situations the adverse events that will not have expedited reporting must be specified in the text of the approved protocol. An expected Grade 3 event that is using the generic reporting criteria, for instance. In a trial of investigational agents where grade 3 diarrhea requiring hospitalization is expected, only diarrhea requiring ICU care (Grade 4) might be designated for expedited reporting.

TABLE A-III-1

Summary Of Reporting Requirements For Adverse Events
On Cooperative Group Trials Where NCI Holds IND

EXPEDITED REPORTING FOR PHASE I STUDIES

Unexpected Event		**Expected Event**	
GRADES 2 - 3 Attribution of Possible, Probable, or Definite	**GRADES 4 and 5 Regardless of Attribution**	**GRADES 1 - 3**	**GRADES 4 and 5, Regardless of Attribution**
Grade 2 - Expedited report within 10 working days to IDB/CG. Grade 3 - Report by phone to IDB/CG within 24 hrs. Expedited report to follow within 10 working days. (Grade 1 - Adverse Event Expedited Reporting NOT required.)	Report by phone to IDB/CG within 24 hrs. Expedited report to follow within 10 working days. This includes all deaths within 30 days of the last dose of treatment with an investigational agent regardless of attribution. Any late death attributed to the agent (possible, probable, or definite) should be reported within 10 working days.	Adverse Event Expedited Reporting NOT required.	Report by phone to IDB/CG within 24 hrs. Expedited report to follow within 10 working days. This includes all deaths within 30 days of the last dose of treatment with an investigational agent regardless of attribution. Any late death attributed to the agent (possible, probable, or definite) should be reported within 10 working days.

IDB = Investigational Drug Branch CG= Cooperative Group

For Hospitalization Only – Any medical event equivalent to the CTC Grade 3,4,5 which precipitated hospitalization (or prolongation of existing hospitalization) must be reported regardless of requirements for phase of study, expected or unexpected and attribution.

Expedited reporting may not be appropriate for specific expected adverse events for certain later phase 2 and phase 3 protocols. In those situations the adverse events that will not have expedited reporting must be specified in the text of the approved protocol. An expected Grade 3 event that is using the generic reporting criteria, for instance. In a trial of investigational agents where grade 3 diarrhea requiring hospitalization is expected, only diarrhea requiring ICU care (Grade 4) might be designated for expedited reporting.

TABLE A-III-2

Summary Of Reporting Requirements For Adverse Events
On Cooperative Group Trials Where NCI Holds IND

EXPEDITED REPORTING FOR PHASE 2 AND PHASE 3 STUDIES

Unexpected Event		**Expected Event**	
GRADES 2 - 3 Attribution of Possible, Probe, or Definite	**GRADES 4 and 5 Regardless of Attribution**	**GRADES 1 - 3**	**GRADES 4 and 5, Regardless of Attribution**
Expedited report within 10 working days to IDB/CG. (Grade 1 - Adverse Event Expedited Reporting NOT required.)	Report by phone to IDB/CG within 24 hrs. Expedited report to follow within 10 working days. This includes all deaths within 30 days of the last dose of treatment with an investigational agent regardless of attribution. Any late death attributed to the agent (possible, probable, or definite) should be reported within 10 working days.	Adverse Event Expedited Reporting NOT required.	Report by phone to IDB/CG within 24 hrs. Expedited report to follow within 10 working days. This includes all deaths within 30 days of the last dose of treatment with an investigational agent regardless of attribution. Any late death attributed to the agent (possible, probable, or definite) should be reported within 10 working days. Grade 4 Myelosuppression or other Grade 4 events that do not require expedited reporting will be specified in the protocol.

IDB = Investigational Drug Branch CG = Cooperative Group

For Hospitalization Only – Any medical event equivalent to the CTC Grade 3,4,5 which precipitated hospitalization (or prolongation of existing hospitalization) must be reported regardless of requirements for phase of study, expected or unexpected and attribution.

Expedited reporting may not be appropriate for specific expected adverse events for certain later phase 2 and phase 3 protocols. In those situations the adverse events that will not have expedited reporting must be specified in the text of the approved protocol. An expected Grade 3 event that is using the generic reporting criteria, for instance. In a trial of investigational agents where grade 3 diarrhea requiring hospitalization is expected, only diarrhea requiring ICU care (Grade 4) might be designated for expedited reporting.

TABLE B-I-1

Summary Of Reporting Requirements For Adverse Events On Industry Trials Where A Corporate Sponsor Holds IND

EXPEDITED REPORTING FOR PHASE I STUDIES

Unexpected Event		**Expected Event**	
GRADES 2 - 3 Attribution of Possible, Probable, or Definite	**GRADES 4 and 5 Regardless of Attribution**	**GRADES 1 - 3**	**GRADES 4 and 5, Regardless of Attribution**
Grade 2 - Expedited report within 10 working days to CS. Grade 3 - Report by phone to CS within 24 hrs. Expedited report to follow within 10 working days. (Grade 1 - Adverse Event Expedited Reporting NOT required.)	Report by phone to CS within 24 hrs. Expedited report to follow within 10 working days. This includes all deaths within 30 days of the last dose of treatment with an investigational agent regardless of attribution. Any late death attributed to the agent (possible, probable, or definite) should be reported within 10 working days.	Adverse Event Expedited Reporting NOT required.	Report by phone to CS within 24 hrs. Expedited report to follow within 10 working days. This includes all deaths within 30 days of the last dose of treatment with an investigational agent regardless of attribution. Any late death attributed to the agent (possible, probable, or definite) should be reported within 10 working days.

CS = Corporate Sponsor

For Hospitalization Only – Any medical event equivalent to the CTC Grade 3,4,5 which precipitated hospitalization (or prolongation of existing hospitalization) must be reported regardless of requirements for phase of study, expected or unexpected and attribution.

Expedited reporting may not be appropriate for specific expected adverse events for certain later phase 2 and phase 3 protocols. In those situations the adverse events that will not have expedited reporting must be specified in the text of the approved protocol. An expected Grade 3 event that is using the generic reporting criteria, for instance. In a trial of investigational agents where grade 3 diarrhea requiring hospitalization is expected, only diarrhea requiring ICU care (Grade 4) might be designated for expedited reporting.

TABLE B-I-2

Summary Of Reporting Requirements For Adverse Events On Industry Trials Where A Corporate Sponsor Holds IND

EXPEDITED REPORTING FOR PHASE 2 AND PHASE 3 STUDIES

Unexpected Event		**Expected Event**	
GRADES 2 - 3 Attribution of Possible, Probable, or Definite	**GRADES 4 and 5 Regardless of Attribution**	**GRADES 1 - 3**	**GRADES 4 and 5, Regardless of Attribution**
Expedited report within 10 working days to CS. (Grade 1 - Adverse Event Expedited Reporting NOT required.)	Report by phone to CS within 24 hrs. Expedited report to follow within 10 working days. This includes all deaths within 30 days of the last dose of treatment with an investigational agent regardless of attribution. Any late death attributed to the agent (possible, probable, or definite) should be reported within 10 working days.	Adverse Event Expedited Reporting NOT required.	Report by phone to CS within 24 hrs. Expedited report to follow within 10 working days. This includes all deaths within 30 days of the last dose of treatment with an investigational agent regardless of attribution. Any late death attributed to the agent (possible, probable, or definite) should be reported within 10 working days. Grade 4 Myelosuppression or other Grade 4 events that do not require expedited reporting will be specified in the protocol.

CS = Corporate Sponsor

For Hospitalization Only – Any medical event equivalent to the CTC Grade 3,4,5 which precipitated hospitalization (or prolongation of existing hospitalization) must be reported regardless of requirements for phase of study, expected or unexpected and attribution.

Expedited reporting may not be appropriate for specific expected adverse events for certain later phase 2 and phase 3 protocols. In those situations the adverse events that will not have expedited reporting must be specified in the text of the approved protocol. An expected Grade 3 event that is using the generic reporting criteria, for instance. In a trial of investigational agents where grade 3 diarrhea requiring hospitalization is expected, only diarrhea requiring ICU care (Grade 4) might be designated for expedited reporting.

TABLE B-II-1

Summary Of Reporting Requirements For Adverse Events On Trials Where The Investigator Holds IND

EXPEDITED REPORTING FOR PHASE I STUDIES

Unexpected Event		**Expected Event**	
GRADES 2 - 3 Attribution of Possible, Probable, or Definite	**GRADES 4 and 5 Regardless of Attribution**	**GRADES 1 - 3**	**GRADES 4 and 5, Regardless of Attribution**
Grade 2 - Expedited report within 15 working days to FDA. Grade 3 - Report by phone to FDA within 24 hrs. Expedited report to follow within 15 working days. (Grade 1 - Adverse Event Expedited Reporting NOT required.)	Report by phone to FDA within 24 hrs. Expedited report to follow within 15 working days. This includes all deaths within 30 days of the last dose of treatment with an investigational agent regardless of attribution. Any late death attributed to the agent (possible, probable, or definite) should be reported within 15 working days.	Adverse Event Expedited Reporting NOT required.	Report by phone to FDA within 24 hrs. Expedited report to follow within 15 working days. This includes all deaths within 30 days of the last dose of treatment with an investigational agent regardless of attribution. Any late death attributed to the agent (possible, probable, or definite) should be reported within 15 working days.

For Hospitalization Only – Any medical event equivalent to the CTC Grade 3,4,5 which precipitated hospitalization (or prolongation of existing hospitalization) must be reported regardless of requirements for phase of study, expected or unexpected and attribution.

Expedited reporting may not be appropriate for specific expected adverse events for certain later phase 2 and phase 3 protocols. In those situations the adverse events that will not have expedited reporting must be specified in the text of the approved protocol. An expected Grade 3 event that is using the generic reporting criteria, for instance. In a trial of investigational agents where grade 3 diarrhea requiring hospitalization is expected, only diarrhea requiring ICU care (Grade 4) might be designated for expedited reporting.

TABLE B-II-2

Summary Of Reporting Requirements For Adverse Events On Trials Where The Investigator Holds IND

EXPEDITED REPORTING FOR PHASE 2 AND PHASE 3 STUDIES

Unexpected Event		Expected Event	
GRADES 2 - 3 Attribution of Possible, Probable, or Definite	**GRADES 4 and 5 Regardless of Attribution**	**GRADES 1 - 3**	**GRADES 4 and 5, Regardless of Attribution**
Expedited report within 15 working days to FDA. (Grade 1 - Adverse Event Expedited Reporting NOT required.)	Report by phone to FDA within 24 hrs. Expedited report to follow within 15 working days. This includes all deaths within 30 days of the last dose of treatment with an investigational agent regardless of attribution. Any late death attributed to the agent (possible, probable, or definite) should be reported within 15 working days.	Adverse Event Expedited Reporting NOT required.	Report by phone to FDA within 24 hrs. Expedited report to follow within 15 working days. This includes all deaths within 30 days of the last dose of treatment with an investigational agent regardless of attribution. Any late death attributed to the agent (possible, probable, or definite) should be reported within 15 working days. Grade 4 Myelosuppression or other Grade 4 events that do not require expedited reporting will be specified in the protocol.

For Hospitalization Only – Any medical event equivalent to the CTC Grade 3,4,5 which precipitated hospitalization (or prolongation of existing hospitalization) must be reported regardless of requirements for phase of study, expected or unexpected and attribution.

Expedited reporting may not be appropriate for specific expected adverse events for certain later phase 2 and phase 3 protocols. In those situations the adverse events that will not have expedited reporting must be specified in the text of the approved protocol. An expected Grade 3 event that is using the generic reporting criteria, for instance. In a trial of investigational agents where grade 3 diarrhea requiring hospitalization is expected, only diarrhea requiring ICU care (Grade 4) might be designated for expedited reporting.

TABLE C-1

Summary Of Reporting Requirements For Adverse Events On Trials Involving Commercial Agents With No IND Is Voluntary (Med Watch Form)

EXPEDITED REPORTING FOR PHASE I STUDIES

Unexpected Event		**Expected Event**	
GRADES 2 - 3 Attribution of Possible, Probable, or Definite	**GRADES 4 and 5 Regardless of Attribution**	**GRADES 1 - 3**	**GRADES 4 and 5, Regardless of Attribution**
Grade 2 - Expedited report within 15 working days to FDA. Grade 3 - Report by phone to FDA within 24 hrs. Expedited report to follow within 15 working days. (Grade 1 - Adverse Event Expedited Reporting NOT required.)	Report by phone to FDA within 24 hrs. Expedited report to follow within 15 working days. This includes all deaths within 30 days of the last dose of treatment with an investigational agent regardless of attribution. Any late death attributed to the agent (possible, probable, or definite) should be reported within 15 working days.	Adverse Event Expedited Reporting NOT required.	Report by phone to FDA within 24 hrs. Expedited report to follow within 15 working days. This includes all deaths within 30 days of the last dose of treatment with an investigational agent regardless of attribution. Any late death attributed to the agent (possible, probable, or definite) should be reported within 15 working days.

NOTE: Use Med Watch Form

For Hospitalization Only – Any medical event equivalent to the CTC Grade 3,4,5 which precipitated hospitalization (or prolongation of existing hospitalization) must be reported regardless of requirements for phase of study, expected or unexpected and attribution.

Expedited reporting may not be appropriate for specific expected adverse events for certain later phase 2 and phase 3 protocols. In those situations the adverse events that will not have expedited reporting must be specified in the text of the approved protocol. An expected Grade 3 event that is using the generic reporting criteria, for instance. In a trial of investigational agents where grade 3 diarrhea requiring hospitalization is expected, only diarrhea requiring ICU care (Grade 4) might be designated for expedited reporting.

TABLE C-2

Summary Of Reporting Requirements For Adverse Events On Trials Involving Commercial Agents With No IND Is Voluntary (Med Watch Form)

EXPEDITED REPORTING FOR PHASE 2 AND PHASE 3 STUDIES

Unexpected Event		**Expected Event**	
GRADES 2 - 3 Attribution of Possible, Probable, or Definite	**GRADES 4 and 5 Regardless of Attribution**	**GRADES 1 - 3**	**GRADES 4 and 5, Regardless of Attribution**
Expedited report within 15 working days to FDA. (Grade 1 - Adverse Event Expedited Reporting NOT required.)	Report by phone to FDA within 24 hrs. Expedited report to follow within 15 working days. This includes all deaths within 30 days of the last dose of treatment with an investigational agent regardless of attribution. Any late death attributed to the agent (possible, probable, or definite) should be reported within 15 working days.	Adverse Event Expedited Reporting NOT required.	Report by phone to FDA within 24 hrs. Expedited report to follow within 15 working days. This includes all deaths within 30 days of the last dose of treatment with an investigational agent regardless of attribution. Any late death attributed to the agent (possible, probable, or definite) should be reported within 15 working days. Grade 4 Myelosuppression or other Grade 4 events that do not require expedited reporting will be specified in the protocol.

Note: Use Med Watch Form

For Hospitalization Only – Any medical event equivalent to the CTC Grade 3,4,5 which precipitated hospitalization (or prolongation of existing hospitalization) must be reported regardless of requirements for phase of study, expected or unexpected and attribution.

Expedited reporting may not be appropriate for specific expected adverse events for certain later phase 2 and phase 3 protocols. In those situations the adverse events that will not have expedited reporting must be specified in the text of the approved protocol. An expected Grade 3 event that is using the generic reporting criteria, for instance. In a trial of investigational agents where grade 3 diarrhea requiring hospitalization is expected, only diarrhea requiring ICU care (Grade 4) might be designated for expedited reporting.

TABLE D-1

Summary Of Reporting Requirements For Adverse Events On Cancer Vaccine Trials

NOTE: *Until further guidelines are established, any AE occurring subsequent to administration of a cancer vaccine will be reported to the FDA using the VADERS system according to the tables below.*

EXPEDITED REPORTING FOR PHASE I STUDIES

Unexpected Event		**Expected Event**	
GRADES 2 - 3 Attribution of Possible, Probable, or Definite	**GRADES 4 and 5 Regardless of Attribution**	**GRADES 1 - 3**	**GRADES 4 and 5, Regardless of Attribution**
Grade 2 - Expedited report within 15 working days to FDA. Grade 3 - Report by phone to FDA within 24 hrs. Expedited report to follow within 15 working days. (Grade 1 - Adverse Event Expedited Reporting NOT required.)	Report by phone to FDA within 24 hrs. Expedited report to follow within 15 working days. This includes all deaths within 30 days of the last dose of treatment with an investigational agent regardless of attribution. Any late death attributed to the agent (possible, probable, or definite) should be reported within 15 working days.	Adverse Event Expedited Reporting NOT required.	Report by phone to FDA within 24 hrs. Expedited report to follow within 15 working days. This includes all deaths within 30 days of the last dose of treatment with an investigational agent regardless of attribution. Any late death attributed to the agent (possible, probable, or definite) should be reported within 15 working days.

For Hospitalization Only – Any medical event equivalent to the CTC Grade 3,4,5 which precipitated hospitalization (or prolongation of existing hospitalization) must be reported regardless of requirements for phase of study, expected or unexpected and attribution.

Expedited reporting may not be appropriate for specific expected adverse events for certain later phase 2 and phase 3 protocols. In those situations the adverse events that will not have expedited reporting must be specified in the text of the approved protocol. An expected Grade 3 event that is using the generic reporting criteria, for instance. In a trial of investigational agents where grade 3 diarrhea requiring hospitalization is expected, only diarrhea requiring ICU care (Grade 4) might be designated for expedited reporting.

TABLE D-2

Summary Of Reporting Requirements For Adverse Events On Cancer Vaccine Trials

NOTE: *Until further guidelines are established, any AE occurring subsequent to administration of a cancer vaccine will be reported to the FDA using the VADERS system according to the tables below.*

EXPEDITED REPORTING FOR PHASE 2 AND PHASE 3 STUDIES

Unexpected Event		**Expected Event**	
GRADES 2 - 3 Attribution of Possible, Probable, or Definite	**GRADES 4 and 5 Regardless of Attribution**	**GRADES 1 - 3**	**GRADES 4 and 5, Regardless of Attribution**
Expedited report within 15 working days to FDA. (Grade 1 - Adverse Event Expedited Reporting NOT required.)	Report by phone to FDA within 24 hrs. Expedited report to follow within 15 working days. This includes all deaths within 30 days of the last dose of treatment with an investigational agent regardless of attribution. Any late death attributed to the agent (possible, probable, or definite) should be reported within 15 working days.	Adverse Event Expedited Reporting NOT required.	Report by phone to FDA within 24 hrs. Expedited report to follow within 15 working days. This includes all deaths within 30 days of the last dose of treatment with an investigational agent regardless of attribution. Any late death attributed to the agent (possible, probable, or definite) should be reported within 15 working days. Grade 4 Myelosuppression or other Grade 4 events that do not require expedited reporting will be specified in the protocol.

For Hospitalization Only – Any medical event equivalent to the CTC Grade 3,4,5 which precipitated hospitalization (or prolongation of existing hospitalization) must be reported regardless of requirements for phase of study, expected or unexpected and attribution.

Expedited reporting may not be appropriate for specific expected adverse events for certain later phase 2 and phase 3 protocols. In those situations the adverse events that will not have expedited reporting must be specified in the text of the approved protocol. An expected Grade 3 event that is using the generic reporting criteria, for instance. In a trial of investigational agents where grade 3 diarrhea requiring hospitalization is expected, only diarrhea requiring ICU care (Grade 4) might be designated for expedited reporting.

APPENDIX II

GUIDELINES FOR ESTABLISHING AND OPERATING AN EXTERNAL DSMB

1. Membership

a) Monitoring activities should be conducted by experts in all scientific disciplines needed to interpret the data and insure patient safety. Clinical trial experts, biostatisticians, bioethicists, and clinicians knowledgeable about the disease and treatment under study should be part of the monitoring group or be available if warranted.

b) Voting members may be from within or outside the institution, but the majority should not be affiliated with the institution. Members should view themselves as representing the interest of patients and not that of the institutions. Investigators directly involved with the conceptual design or analysis of the particular trial are not eligible to serve on the DSMB.

2. Meeting Procedures

a) Frequency

(1) DSMB meetings will be held at least annually and more often depending on the nature and progress of the trial being monitored.

b) Elements for Review

(1) A written summary of status, toxicity and outcome of the clinical trial will be prepared by the clinical trial statistician. The summary will be submitted to DSMB members allowing sufficient review time prior to meeting.

(2) This summary will also address specific toxicity concerns as well as concerns about the conduct of the trial. It may contain recommendations for consideration by the DSMB concerning whether to close the trial, report the results, or continue accrual or follow-up.

c) Meeting Structure DSMB

Meetings will be divided into three sessions as follows:

(1) **Open Session** – members of the clinical trial team present review of the trial conduct and answer questions from DSMB members. Focus is on accrual, protocol compliance, and general toxicity.

(2) **Closed Session** – Includes DSMB members and the clinical trial statistician(s). The statistician presents and discusses outcome results with DSMB.

(3) **Executive Session** – DSMB members only discuss the general conduct of trial, all outcome results including toxicities as described in the protocol, all adverse events and develop recommendations.

3. Recommendations

a) It is the responsibility of the Study Chair, the clinical trial statistician(s), and individual DSMB members to insure that the DSMB is kept appraised of non-confidential results from other related studies that became available, and any programmatic concerns related to the clinical trial being monitored. It is the responsibility of the DSMB to determine the extent to which this information is relevant to its decisions related to the specific trial.

b) DSMB recommendations will be given to the Study Chair and the sponsor. The DSMB must provide an adequate rationale for recommendation made to change the trial for other than safety or efficacy reasons or for slow accrual.

c) The Study Chair is responsible to implement the change recommended by the DSMB as expeditiously as possible.

d) The sponsor must be informed of the reason for disagreement in the unlikely situation that the Study Chair does not agree with the DSMB recommendation.

e) The sponsor, DSMB Chair, and Study Chair will be responsible for reaching a mutually acceptable decision about the study.

4. Release of Outcome Data

a) In general, outcome data should not be made available to individuals outside of the DSMB until accrual has been completed and all patients have completed their treatment.

b) The DSMB may approve the release of outcome data on confidential basis to the Study Chair for planning the preparation of manuscripts and/or to a small number of others for future trial planning purposes.

c) Any release of outcome data prior to the DSMB recommendation for general dissemination of results must be reviewed and approved by the DSMB

5. Confidentiality

a) No communication, either written or verbal, of the deliberations or recommendations of the DSMB will be made outside of the DSMB.

b) Outcome results are strictly confidential and must not be divulged to any non-member, except as indicated above in Recommendations, until the recommendation to release the results are accepted and implemented.

c) Each member of the DSMB, including non-voting members, must sign a statement of confidentiality.

6. Conflict of Interest

a) DSMB members are subject to the UW policies regarding standards of conduct.

b) Individuals invited to serve on the DSMB (voting or non-voting) will disclose any potential conflicts of interest, whether real or perceived, to the Study Chair and the appropriate institutional officials, in accordance with the UW Conflict of Interest Policies. Conflict of interest can include professional interest, proprietary interest, and miscellaneous interest as described in the NIH Grants Policy Statement, Page II-12, and 45 CFR Part 94.

c) Decision concerning whether individuals with potential conflicts of interest or the appearance of conflicts of interest may participate in the DSMB will be made in accordance with the UW Conflict of Interest Policies.

d) Potential conflicts, which develop during a member's tenure on a DSMB, must also be disclosed and addressed in accordance with the UW Conflict of Interest Policies.