



**University of New Mexico
Cancer Trial Office
Data and Safety Monitoring Plan
2007**

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Director and CEO UNM Cancer Research Center

Date

DSMP Version 2/07: The DSMP has been revised to include the following changes in the document;

- PRC - Central Internal Review Board applications require only one (1) medical reviewer with expertise in the study objectives.
- The process of protocol review is focused on investigator-initiated protocols
- A new process and form has been included in the protocol packet; III. CRTc/NMMCA Data and Safety Monitoring Plan Short Form and Study Risk Assignment.

The DSMP for clinical studies conducted by the CTO remains as provided for by this Plan. A new process has been developed and implemented to assure staff and faculty knowledge and understanding of the DSMP as part of the application process. Mandatory education has been included and evidence of completion is required to submit a protocol application. The PRC and MRSC then assign a risk level based on the DSMP criteria and the PI Questionnaire.

- Requirements for review by the PMC for interim review and annual review have been refined to specify review requirements based on cycle.
- Any finding resulting in a protocol deviation based on a PMC reviewer finding requires a correction action item and resolution. A Corrective Action follow-up process has been developed and implemented for the PMC.
- The DSMP covers all clinical trials that have patients receiving treatment. Once the study is closed to accrual or to the IRB and no patient is receiving treatment, the PMC will discontinue monitoring of the study. This process has been developed and included.

These items have been approved by the appropriate management and committee(s).

Summary

The University of New Mexico Cancer Research and Treatment Center (UNM CRTC) places the highest priority on ensuring the safety of patients participating in clinical trials. All clinical trials require monitoring commensurate with the degree of risk involved in participation of studies. Standard Operating Procedures (SOP's) detail functions and processes found in this plan. SOP's are available at <http://hsc.unm.edu/crtc/intranet/ctoforms.asp>.

Data and safety monitoring activities for each study continue until all patients have completed their treatment and all patients are beyond the time point at which study-related adverse events would likely be encountered. The UNM CRTC has implemented a process for routine data monitoring and safety review which takes into account the Essential Elements of the National Cancer Institute (NCI) guidelines:

- 1. Monitoring the progress of trials and the safety of participants**
- 2. Plans for assuring compliance with requirements regarding the reporting of adverse events (AEs)**
- 3. Plans for assuring that any action resulting in a temporary or permanent suspension of an NCI-funded clinical trial is reported to the NCI grant program director responsible for the grant**
- 4. Plans for assuring data accuracy and protocol compliance, including minimization of risks**

The Data Safety and Monitoring Plan takes into account, and complies with, the University of New Mexico Health Sciences Center Human Research Review Committee (HRRC) guidelines for safety and data monitoring (Addendum N, HRRC Guidelines for Safety and Data Monitoring).

Monitoring responsibilities are assumed by the Principal Investigator (PI) and the Clinical Trial Office (CTO) of the UNM CRTC (Addendum A, Resource Organigram), and the specific level of monitoring is determined by the study sponsor and the level of risk associated with the particular study. The Director and CEO of the CRTC holds overall responsibility for overseeing data and safety monitoring, and is assisted by the PMC in its function as the data safety monitoring board for all investigator-initiated trials fielded by the UNM CRTC and the NMCCA. The Medical Director is primarily responsible for the scientific arm of this plan and reports to the Director and CEO of the CRTC. Groups with direct and indirect responsibilities for data and safety monitoring as described in this plan include;

Table 1. Direct and Indirect Data Safety Monitoring Responsibilities

Direct	Indirect
Principal Investigator and Sub-Is	Protocol Review Committee (PRC)
Research nurse/coordinator	CTO Executive Council
Clinical Research Associate(s)	
Quality Assurance Office	
Health Sciences Center Human Research Review Committee (HSC HRRC) or Western IRB	
Protocol Monitoring Committee (PMC)	

All clinical trials are monitored according to the essential elements outlined below. Faculty and staff are required to complete an online DSMP competency course on hire. Documentation is maintained in the Office of Quality Assurance. Faculty are not permitted to submit a protocol application unless the training has been completed. The current DSMP for clinical trials is maintained and available at; <http://hsc.unm.edu/crtc/intranet/ctoforms.asp>.

The DSMP is in keeping with recent recommendations from the NIH and the FDA, as detailed at the following web sites:

- http://grants.nih.gov/grants/peer/hs_review_inst.pdf
- <http://grants.nih.gov/grants/guide/notice-files/not98-084.html>
- <http://www.fda.gov/cber/gdlns/clindatmon.htm>
- <http://www.ncrr.nih.gov/clinical/CRTCpatientsafety20010622.html>

<http://www.nci.nih.gov/clinicaltrials/conducting/dsm-guidelines>

Part I – Overview and Introduction

This document is intended to provide investigators with a Data Safety Monitoring Plan (DSMP) for all phases of cancer clinical trials, in accordance with National Institutes of Health (NIH) and NCI requirements. The NIH/NCI suggests that institutions sponsoring a significant number of clinical trials formulate a DSMP that can be broadly applied to the individual trials in their portfolio. Trials which originate from sponsors outside of UNM and the NMCCA have DSMPs, to which this DSMP defaults. However, this DSMP also specifies the process for monitoring and auditing those studies which are investigator-initiated, for which as DSMP does not already exist. This DSMP is created and maintained by the Medical Director of the CTO, with the assistance and consultation of the CTO Executive Council. This DSMP will be reviewed and revised on an annual basis, and will be forwarded from the CTO Executive Council to be presented at the annual meeting(s) of the PRC and PMC. The CRTC Director will have final review and right of approval.

This document provides the PI and research staff of the CRTC with necessary background information on data and safety monitoring and guidance on NIH required data and safety monitoring. These recommendations have evolved, in part, from a number of incidents in which the presence of greater ongoing oversight of clinical research might have reduced risk to research volunteers.

This DSMP is modeled upon the essential elements as outlined by the NCI. They are as follows:

- ***Monitoring the progress of trials and the safety of participants***
- ***Plans for assuring compliance with requirements regarding the reporting of adverse events (AEs)***
- ***Plans for assuring that any action resulting in a temporary or permanent suspension of an NCI-funded clinical trial is reported to the NCI grant program director responsible for the grant***
- ***Plans for assuring data accuracy and protocol compliance, including minimization of risks***

1. MONITORING THE PROGRESS OF TRIALS AND THE SAFETY OF PARTICIPANTS

Trials are monitored according to the type of sponsor, type of trial and potential risks. Monitoring for clinical trials is a continuous, ongoing review of the conduct of the trial, including adherence to study design and documentation of appropriate reporting of related toxicities. The responsibilities for monitoring are shared amongst the Principal Investigator (PI), all sub-investigators, and the research nurses or data coordinators who are participating in the conduct of the study.

For each protocol and amendment(s) approved, the University of New Mexico Cancer Research and Treatment Center/New Mexico Cancer Care Alliance Medical Review Scientific Review Committee (UNM CRTC/NMCCA PRC) will review protocol applications for scientific merit and feasibility before authorizing the IRB-of-record approval process initiation. Scientific review will be done by the PRC prior to submission to the HRRC or an approved external IRB. The Human Research Review Committee (HRRC), the institutional review board of the University of New Mexico, and the Western Institutional Review Board (WIRB) review the protocols for protection of human subject and other ethical issues. Investigator-initiated, peer-review grant supported, and NCI-Cooperative Group studies are submitted to the UNM Human Research Review Committee (HRRC), while all studies with pharmaceutical company support (including investigator-initiated) are submitted to the Western Institutional Review Board (WIRB). The appropriate committee maintains a copy of all reviews of protocols, which may be requested or reviewed by the NCI.

The Medical Director of the CTO will review and approve scientific amendments, except those where there may be a conflict of interest; in that case, the amendments will be reviewed by the Chair of the PRC, or in his or her absence, the Vice-Chair of the PRC. Administrative amendments will be reviewed and approved by the Administrative Director of the CTO or designee.

The PRC will determine the level of safety monitoring required for each protocol on a case by case basis. For protocols that are determined to be of very high risk, the investigator will be required to report on patient safety

after treating a small number of patients before being allowed to accrue more participants. This number will be determined at the time the protocol is approved, but in general will be approximately 3-5 patients.

For some time now, NCI policy has required that a Data Safety Monitoring Board (DSMB) be in place for all Phase III randomized clinical trials (<http://deainfo.nci.nih.gov/grantspolicies/datasafety.htm>). This policy has been recently modified, in that there is no longer a blanket requirement for DSMB in the cases of low-risk behavioral and nutritional trials. All such trials should include a DSMP, but this may or may not include a DSMB, depending chiefly on the anticipated level of risk to participants. Nor does NIH or NCI policy require that formal DSMB's be constituted for clinical trials other than Phase III, however for investigator-initiated non-Phase III trials the Protocol Monitoring Committee (PMC) will act as or designate a Data Safety Monitoring Board for all investigator-initiated phase I-III studies initiated at UNM CRTC or the NMCCA. The PMC may designate a field expert to convene a protocol specific Data Safety Monitoring Board.

All studies opened at the CRTC or NMCCA are assigned a risk level after PRC review and approval. Most studies at the CRTC and NMCCA are high risk.

CTO Risk Definition Table

Level of Risk	Explanation	Examples
Low Risk	Study poses no more risk than expected in daily life	Behavioral Studies Nutrition/food supplement Studies Observation Studies MRI Studies Survey/Questionnaire Studies Biological sample acquisition
High Risk	Phase I, II, III, IV therapeutic, palliative or prevention trials that are sponsored by national cooperative groups or NCI/NIH that already include independent appropriate/approved data and safety monitoring plans *Phase I, II, or III therapeutic, palliative or prevention trials sponsored by industry that include appropriate/approved monitoring plans Investigator initiated Phase I, II or III single institution studies that utilize FDA approved agents or agents that have already been the subject of two publications of a clinical trial All recombinant protein vaccine studies	Most cancer treatment studies
Very High Risk	All Phase III investigator initiated multi center trials Phase I studies with agents that have never been used in humans; gene therapies that are not FDA approved for commercial distribution High dose studies All viral, bacterial, or cellular based vaccine studies, regardless of whether or not the vaccine is "live" or "killed"	Implantation of device with an IDE never used before Involves the use of a new chemical or drug for which there is less than 20 patients or no toxicology data in humans A gene therapy study or research involving recombinant DNA molecules (gene transfer) A Principal Investigator initiated multi-center trial Investigator initiated phase III clinical trial Involves the manufacturing of agents on campus Bone marrow support needed after chemotherapy

All protocols will have an annual report which will be drafted and forwarded to the IRB of record for protocol renewal.

Items to be Monitored

In general, these will be specified by the individual protocol. However, most studies will evaluate the following patient-specific data:

- Patient's Birth Date
- Patient's Gender
- Patient's Ethnicity
- Date of Patient Entry
- Eligibility Status
- Baseline Performance Status
- Prior therapy
- Baseline, on-therapy, and follow-up labs and radiographic studies
- Agent(s) and dose(s)
- Dose modification
- Cycle or course number
- Concomitant medications
- Adverse event reporting
 - Type
 - Grade
 - Attribution
 - Resolution
- Response to therapy
- Off Treatment Reason
- Date of Last Treatment
- Off Study Reason
- Off Study Date

Monitoring Determined by Type of Protocol Sponsor

Sponsor: National Institutes of Health

The following types of NCI-sponsored cooperative group trials are currently conducted by UNM CRTC/NMCCA: American College of Surgeons Oncology Group (ACOSOG), Cancer and Leukemia Group B (CALGB), Gynecologic Oncology Group (GOG), Radiation Therapy Oncology Group (RTOG), Southwest Oncology Group (SWOG), Children's Oncology Group (COG), North Central Cancer Treatment Group (NCCTG), National Surgical Adjuvant Breast and Bowel Project (NSABP), and Eastern Cooperative Oncology Group (ECOG). Phase I, II and III clinical trials that are sponsored by the NCI Cooperative Groups are monitored by mandated, long-standing and established data and safety monitoring committees at the cooperative group level. These cooperative group studies are not monitored by the PMC, but they are included in the annual internal audits conducted by the Quality Assurance Office of the CTO.

National Institutes of Health R01, R02, and Quicktrial/R21 grant mechanisms provide funding for small pilot, phase I or phase II clinical trials of agents. These grants supporting clinical trials are required to provide specific data and safety monitoring plans to receipt of funding. Studies monitored under a Phase I contract will use the NCI-specified reporting mechanisms. These trials will be monitored by the PMC every three to six months, depending upon their level of risk, and they are included in the internal audits conducted by the CTO.

Sponsor: Local, Investigator-Initiated Clinical Trials, Limited Institution Trials

For local, investigator-initiated Phase I and Phase II clinical trial protocols, the principal investigator is required to continuously monitor Phase I trials and Phase II trials. In order to avoid potential conflicts of interest, investigator-initiated trials will be subjected to monitoring by a Clinical Research Associate (or equivalent position) who will generate a report that will be submitted to the PMC, with a copy to the PI and a copy to the CTO Executive Council. For Phase I clinical trials, quarterly safety and data monitoring reports are submitted to the PMC by the PI, and they are included in the internal audits conducted by the CTO. For Phase II clinical

trials, safety and data monitoring reports are submitted by the PI to the PMC every six months, and they are included in the internal audits conducted by the CTO.

Therapeutic clinical trials, initiated by an investigator at another institution, to be carried out at a limited number of institutions including UNM CRTC/NMCCA are monitored by the local PI, with reports submitted on a quarterly or semi-annual basis to the PMC, depending upon the level of risk, and they are included in the internal audits conducted by the CTO, as above.

Sponsor: NIH or Pharmaceutical Company; Local, Investigator-Initiated Phase III Clinical Trials

Local, investigator-initiated randomized phase III clinical trials sponsored by either the NIH or the pharmaceutical industry must be monitored by protocol-specific data safety and monitoring boards (DSMBs). As required by the NIH, these DSMBs will consist of clinical investigators, biostatisticians, clinical trial experts, and patient advocates independent of investigators involved in the design and conduct of the trial. Data and safety monitoring plans must be specified in the protocol, and these plans must be approved by the IRB of record (the UNM HRRC or WIRB). These trials will be monitored every three to six months, depending upon the degree of risk involved.

Multi-center, limited-institution randomized phase III trials sponsored by either the NIH or the pharmaceutical industry will be held to the same standards as local, investigator-initiated phase III trials and be required to submit formal safety and data monitoring plans that have been reviewed and approved by the IRB. However, the PMC will not monitor these trials.

Sponsor: Pharmaceutical Company

Protocols sponsored by a pharmaceutical company are monitored by the company holding the IND; specific arrangements for monitoring are included in the institutional agreement with the sponsoring company and outlined in the DSMP described in the protocol.

For non-therapeutic trials and those trials without significant health or safety risks:

For trials based upon survey research, questionnaires, blood or tissue sampling, observational studies, or limited interventional studies typically addressing research in cancer prevention and control, monitoring is primarily through the principal investigator and research nurse or data coordinator. The CTO monitors all central elements on an annual basis. The conduct of the study and any observed toxicities (including AE and SAE events) are reported in annual documentation to the IRB of record.

Discontinuing Protocol Monitoring Process: If a study is closed to accrual or closed to the IRB and no patients are receiving treatment or follow-up evaluations, a notice for discontinuing the monitoring process is required to be submitted from the PI to the IRB of record, with a copy submitted to the Chair of the PMC. Documentation of the discontinuation is kept in the Office of Quality Assurance and the CTO.

Protocol and Site Auditing

Integral to assuring both the safety of all subjects participating in any clinical trial, as well as the quality of all data generated, are the related processes of monitoring and auditing. While similar, they are not identical. Monitoring entails verification of all protocol-required data which is generated by all participants, while auditing is assuring that the appropriate processes are in place to maximize safety and data integrity, and that there is close adherence to the processes. Monitoring focuses upon the study subjects and their outcomes, while auditing focuses upon the behaviors of the site and investigative team.

In line with the NCI's quality assurance requirements, and in accordance with UNM-CRTC SOPs, when a new site or center is added to either the UNM-CRTC (a satellite site) or joins the NMCCA, that site will be audited after entering their first subject in a cancer treatment trial, regardless of sponsor. Subsequent audits will be performed on a schedule which is determined by the outcome of the initial audit. Pharmaceutical trials are audited by the protocol sponsor, but cooperative group and investigator-initiated trials will be audited at least annually.

Auditors review three main categories of information: 1) conformance to Institutional Review Board and informed consent requirements, 2) shipping, storage, and use of drugs and other agents, and 3) individual patient cases.

The site prepares for the audit by gathering all source documentation pertaining to the selected case (or cases for subsequent audits). For each selected case, the following records should be available:

- Informed consent documents
- Protocol flow sheets
- Hospital charts
- Physician and research notes
- Outpatient and clinic records
- Correspondence
- X-rays
- Scans
- Other pertinent studies

All records regarding the disposition of investigational drugs, specifically copies of drug orders, return receipts, transfer forms, and the NCI Drug Accountability Records, must be available. The Pharmacy should be alerted that the auditors will conduct an on-site inspection of investigational agent storage facilities, procedures, and records.

The Principal Investigator or designee for the site, and his/her research staff, should be available throughout the audit to answer any questions and help the auditors locate necessary information in the source documents. The audit team members will sign the site audit log. The audit team will use the source documents to verify specific data related to the clinical research trial. The Regulatory Binder and all source documents need to be available to the auditor. An appointment with the Pharmacist should be scheduled if a pharmacy audit is planned or the visit is a site close-out visit.

The following three components of the audit are the focus of an audit:

- Regulatory Compliance
- Accountability of Investigational Agents and Pharmacy Operations
- Individual Patient Case Records

The auditor will verify:

- The informed consent is signed, dated, and on file for the patient.
- The appropriate version of the consent is signed.
- Documentation that confirms patient met the eligibility criteria.
- Data collected (as provided by the Cooperative Group sponsoring the trial) is in compliance with the protocol and is consistent with source documentation. The auditor will identify variation, determine accuracy of endpoint, and compliance to adverse event reporting.

In addition, the auditor will confirm that the following regulatory documents are on file:

- IRB approval letters
- IRB letters of annual approval
- IRB approved consent forms
- Copy of IRB assurance
- FDA 1572 Form and curriculum vitae for each investigator
- Site registration approval letters and e-mails
- Laboratory certification when applicable
- Safety reports and memos with appropriate IRB correspondence
- Additional documents as deemed per case

In line with NCI terminology, the following ratings will be used to communicate findings of the audit both to the site, as well as the administrative structure of the UNM-CRTC and NMCCA:

- Acceptable
- Acceptable Needs Follow up
- Unacceptable

The three components of the audit are independently assigned a rating based on findings at the time of the audit.

Major deficiency is defined as a variance from protocol-specified procedures that makes the resulting data questionable. The following are examples of major deficiencies:

- Protocol never approved by IRB
- Expired IRB reapproval
- Informed consent document does not have the elements required by the Code of Federal Regulations
- Patient did not meet all eligibility criteria specified in the protocol
- Pre-entry and entry clinical or laboratory assessments that are missed or obtained outside the protocol specifications
- Reporting errors that affect patient stratification
- Patient's signed consent form missing
- Consent form used was not current IRB approved version at the time of patient registration
- Reportable adverse event not reported to IRB
- Toxicity that would require filling an Expedited Adverse Event Report (AER) was not reported
- Grades, types, or dates/duration of serious toxicities inaccurately recorded
- Incorrect agent/treatment used
- Concomitant medication that is prohibited by the protocol was administered
- Dose deviations (error outside the range of +/- 10%)
- Receipt, use, and disposition of supplied investigational agents cannot be tracked
- NCI Drug Accountability Forms (DARFs) are not maintained
- Tumor measurements/evaluation of status or diseases not performed according to protocol parameters
- Errors were made in reporting endpoints as specified in the protocol
- Recurrent missing documentation
- Numerous transcription errors, without reasonable explanation and corrective action
- Delinquent data submission

A lesser deficiency is one that is judged to not have a significant impact on the outcome or interpretation of the study and is not described as a major deficiency. An unacceptable frequency of a lesser deficiency is treated as a major deficiency in determining the final rating of a component.

If the site is found to have deficiencies in any of the three categories (Regulatory Compliance, Pharmacy Accountability, and/or Individual Patient Case Records), the site will be required to submit a written response and/or corrective action plan to the UNM-CRTC.

Any component designated as "unacceptable" will have a mandatory re-audit within a fixed period of time, usually within three months.

A copy of the audit report will be sent to the site to document audit findings, and copies of the audit will be sent to the Cancer Center Director, the Executive Director of the CRTC Clinical Trials Office, the Executive Director of the NMCCA, the Medical Director of the CRTC Clinical Trials Office, the Medical Director of the NMCCA, and the Chair of the Protocol Monitoring Committee, and the HRRC or WIRB, depending upon the protocol(s) reviewed.

2. PLANS FOR ASSURING COMPLIANCE WITH REQUIREMENTS REGARDING THE REPORTING OF ADVERSE EVENTS

Adverse Events (AEs) are events occurring to patients while on study. Further, as defined by the NIH and NCI, an AE is any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medical treatment or procedure that may or may not be considered related to the medical treatment or procedure. AE documentation is the responsibility of the PI, and any sub-PIs and research nurses who may be participating in the care of the patients, and a report is prepared by the PI with the research nurse or data coordinator.

An AE is a term that is a unique representation of a specific event used for medical documentation and scientific analyses. Each AE is graded on the NCI CTCAE scale from 1 to 5 and are defined by three sets of terms, expected/unexpected, serious/non-serious, or unlikely/possibly/probably/definitely attributed to the protocol. Expected AE are those listed as such in the protocol.

Serious AE (SAEs) include toxicities which cause death, are life-threatening, result in new hospitalization, or a prolongation of an existing hospitalization, cause a persistent disability, congenital anomaly, or psychiatric disorder.

Attribution of the AE will be made by the protocol PI in the case of serious or unexpected AE, and by the assigned research nurse in other cases.

AE reporting procedures are specified in detail in each individual protocol, depending on the type of study, the type and severity of the AE, the trial sponsor, and existence of an IND.

All events that fall under the definition of serious or unexpected AE including the ones occurring within 30 days following the last treatment date, must be reported to the sponsor within the specified time frame in the protocol and within 24 hours of learning of the event.

For all trials with an external sponsor, internal AE's from UNM CRTC or other NMCCA sites are to be reported to both the protocol sponsor and the IRB of record according to the HRRC policy found at http://hsc.unm.edu/som/research/hrrc/hrrc_Guidelines.htm. For investigator-initiated trials, all unexpected Grade 3 and 4 AEs documented for that reporting period (either every 3 or six months) are submitted to the PMC for review, who then passes this report to the HRRC with the appropriate recommendations to either continue the protocol as is, amend the protocol, or terminate the protocol, for safety reasons. For multicenter trials which are coordinated by the UNM CRTC, the Regulatory Office also submits copies of all documentation to the Principle Investigators at the participating sites, as well as any feedback documentation generated by the PMC, the HRRC, and subsequent responses by the UNM CRTC PI. It will be the responsibility of the PIs at the various sites to submit this information on to their respective IRBs.

For trials of an investigational agent for which NCI is *not* the IND holder: The controlling regulations are those of the Food and Drug Administration (21 CFR, Part 312.32: Expedited Safety Reporting Requirements for Human Drug and Biological Products) and are available at <http://www.fda.gov/cder/aers/fr07oc97.htm>. They describe the responsibilities of the investigator and the IND holder. Additional sponsor or institutional requirements may be appropriate for specific agents and included in the pertinent protocol sections.

For trials involving commercially available agents only (no INDs involved): Serious adverse events that occur with commercially available agents/devices are reported through Food and Drug Administration Medwatch (<http://www.fda.gov/medwatch/index.html>).

For trials involving recombinant DNA molecules (gene transfer): In addition to the reporting requirements for investigational agents, investigators should adhere to NIH Guidelines for Research Involving Recombinant DNA Molecules (Gene Transfer). (<http://grants.nih.gov/grants/guide/notice-files/NOT-OD-02-052.html>)

Food and Drug Administration reporting requirements of serious adverse events for post-marketing trials of vaccines: Serious adverse events must be reported according to applicable FDA regulations (<http://www.fda.gov/cber/vaers/vaers.htm>).

For trials involving behavioral or nutritional interventions that do not use an investigational agent: Since there are no standard grading scales for adverse events, defining suitable grades for adverse events is the responsibility of individual investigators for each protocol. Adverse events of a psychological nature can occur with behavioral trials and should be specified for the particular intervention in question.

Adverse Event Reporting

EXPECTED EVENT ¹	UNEXPECTED EVENT ²
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Grades 1 - 3	Grades 4 and 5 Regardless of Attribution ¹	Grades 1– 2 Attribution of Possible, Probable or Definite	Grades 3 - 5 Regardless of Attribution
Adverse Event Expedited Reporting NOT required.	<p>Report by phone or email to PMC and HRRC within 24 hrs of learning of the event. Expedited report to follow within 5 working days.</p> <p>This includes all deaths up to 30 days after the last dose of treatment with an investigational agent regardless of attribution.</p> <p>Any late death attributed to the agent (possible, probable, or definite) should be reported within 5 working days.</p>	Adverse Event Expedited Reporting NOT required.	<p>Report by phone or email to PMC and HRRC within 24 hrs of learning of the event. Expedited report to follow within 5 working days.</p> <p>This includes all deaths up to 30 days after the last dose of treatment with an investigational agent regardless of attribution.</p> <p>Any late death attributed to the agent (possible, probable, or definite) should be reported within 5 working days.</p>

¹The exception to this is expected grade 4 myelosuppression or other grade 4, as specified in each protocol.

²These toxicities should always be submitted as part of the study results.

3. Plans for assuring that any action resulting in a temporary or permanent suspension of an NCI-funded clinical trial is reported to the NCI grant program director responsible for the grant. This applies only to NCI sponsored trials.

Any NCI sponsored trial suspended temporarily or permanently will be reported by the PI to the NCI grant program director responsible for the grant within 5 working days. The name and address of the NCI grant program director responsible for the grant must appear on the CRTC PROTOCOL ABSTRACT form. If CTEP drugs are used in the study, the suspension will also be reported immediately to CTEP. If the suspension is temporary, the NCI and CTEP will also be notified in a timely manner by the PI regarding the resolution of the issues that caused the suspension, and the date that the suspension was lifted. A note to file must document that the NCI (and CTEP, if applicable) has been notified. Any action taken by the HRRC will follow HRRC policy, and be reported to the NCI.

4. Plans for assuring data accuracy and protocol compliance, including minimization of risks.

It is the responsibility of the PI to lead their specific clinical research team according to Good Clinical Practice guidelines. All research project personnel who work with research subjects, data or samples must complete the HRRC Web-Based Training Program, which can be accessed at <http://hscapp.unm.edu/hrcc/index.html>.

HIPAA training is also required and can be accessed at: <http://hsc.unm.edu/som/research/HRRC/>. All study personnel must answer a UNM conflict of interest form. UNM Conflict of Interest matters are deliberated by the UNM Conflict of Interest Committee. A “yes” response to the Conflict of Interest questionnaire will require management by this committee and may result in delay in the initiation of the research project. Information about the Conflict of Interest Committee policies and procedures can be accessed at: <http://research.unm.edu/coi>, and http://www.unm.edu/~ors/pdf_files/unm_forms/COI_Policy.pdf

Additionally, all of the following conditions must be met:

- 4.1 All protocol participants must be registered in the CTO database.
- 4.2 If any answer indicates the participant does not completely meet eligibility, a note with the rationale for inclusion must be included in the patient chart by the PI. For NCI sponsored studies, the system does not allow registration of participants with less than complete eligibility.

- 4.3 The date in the current informed consent document is displayed to ensure only the most current IRB-approved version is used.
- 4.4 A case report form must be filled to collect data required by the protocol to meet protocol objectives. Consent date, registration date, off study date, and eligibility data are required for all registrants. The current electronic data capture system of the CRTC must be used for all investigator initiated trials. An accession log will be maintained allowing patient identification by study personnel only. All case report forms to be reviewed by outside personnel will be anonymous. For pharmaceutical trials, the company case report form will be used, as needed. For cooperative group trials, the case reporting system of the cooperative group will be used. HIPPA rules are implemented per UNM regulations.
- 4.5 The Quality Assurance Office will retrospectively audit high and very high risk investigator initiated trials and cooperative group studies. A random selection of charts will be chosen for studies prioritized by the PMC. Internal audits may occur at higher frequencies as required by the CRTC Clinical Director, the CTO Medical Director, PRC, and PMC.
- 4.6 Protocol deviations for investigator-initiated trials will be reviewed quarterly or every six months, depending upon the level of risk of the trial. If any trend becomes apparent, a corrective action plan will need to be drawn up and submitted to the IRB of record by the PI.

Part II – Responsibilities/Processes

Investigator

The PI of each study is ultimately responsible for every aspect of the design, conduct, and final analysis of their protocol. The Principal Investigator is responsible to ensure that:

- Protocol includes the data and safety monitoring plan and procedures for its implementation.
- All studies have a structured adverse event determination, monitoring and reporting system.
- Protocols describe procedures for protection of human subjects.
- All masked studies describe a randomization scheme, and specific criteria and procedures for unmasking. If a DSMB is not proposed, the application should also designate individuals with access to unmasked data.
- In specific cases where an outside agency is the sponsor of the test agent, i.e., holder of the Investigational New Drug (IND) application, the Principal Investigator submits individual adverse event reports to the funding agency (ies) (sponsor) in accordance with agency and FDA regulations.
- Regularly submits reports as designated and required by this plan.
- Protocol amendments are submitted per this plan for review prior to HRRC.
- Protocol serious adverse events, adverse events and protocol deviations are submitted to the IRB of Record and the Sponsor of the trial.

Clinical Trial Office (CTO)

The CTO encompasses the administrative/regulatory and scientific aspects of clinical protocol implementation and management at the UNM CRTC. All UNM CRTC related trials involving human subjects or samples are implemented and managed through this office.

The Director and CEO of the CRTC is responsible for the CTO, and delegates the day to day operations to the CTO Executive and Medical Directors.

The CTO is organized in two (2) components: A regulatory component called *Clinical Protocol Data Management and Informatics* (CPDM & I) and a scientific component called *Protocol Review and Monitoring System* (PRMS). The CTO supports all essential services necessary to perform clinical research in compliance with all regulations of Good Clinical Practice (GCP).

The ***CPDM & I administrative and regulatory activities*** related to data and safety monitoring are as follows;

- ❖ Clinical Research Nurse Office
 - Implements and manages the Data Safety Monitoring Plan
 - Hires and supports clinical staff responsible for coordinating and implementing studies
 - Reviews proposed protocols for procedural nursing issues
 - Coordinates clinical research activities in compliance with sponsor and regulatory requirements
 - Screens patients for clinical studies
 - Assists with consenting patients to clinical trials
 - Reviews eligibility criteria and implementation of study criteria
 - Assesses patient safety
 - Coordinates study treatment administration
 - Tracks all protocol deviations
 - Conducts patient follow-ups
 - Collects research data
 - Resolves monitoring queries
 - Assists with external and internal audits
 - Tallies patient demographics and outcomes
 - Prepares study initiation meetings

- ❖ Regulatory Office
 - Assembles all documents needed to open a study
 - Initiates confidentiality and Disclosure Agreements
 - Coordinates IRB applications and correspondence
 - Processes adverse events
 - Tracks study contract
 - Coordinates protocol annual review and reports
 - Coordinates protocol amendments
 - Implements study terminations
 - Retains training logs, CLIA's and curriculum vitae
 - Retains document storage, conflict of interest records and communication with all UNM, NMCCA, Affiliates, cooperative groups, NCI, sponsors, and FDA regulatory committees or spokesperson
 - Arranges site initiation meetings

- ❖ Informatics Support Office
 - Manages hardware and software to support regulatory and scientific components
 - Provides continuous training and support for staff
 - Provides data management support
 - Manages CRTC CTO internet and intranet website

- ❖ Investigational Pharmacy
 - Reviews protocol for study drug concerns
 - Receives investigational and/or study drugs
 - Maintains drug accountability
 - Verifies ordering physician is on the 1572
 - Stores, prepares and dispenses study drugs

- ❖ Quality Assurance Office
 - Conducts ongoing retrospective and focused audits on selected protocols

- Coordinates internal and external audits
- Receives and reviews results of external audits
- Prepares or coordinates formal external triennial audit responses with cooperative groups
- Provides education based on audit results
- Provides quarterly report of auditing activity to the CRTC Director, CTO and NMCCA Executive Director and Medical Director, HRRC, WIRB, and the Chairs of the PRC and PMC
- Reports to the Director and CEO of the CRTC

❖ Internal Audit System

Auditing is a post facto review that regularly assesses major aspects of a trial, including compliance with the study design, documentation required for primary study objectives, toxicity reporting and data integrity. Internal auditing is conducted by the UNM CRTC CTO under the supervision of the Director and CEO, to avoid conflict of interest.

The University of New Mexico Cancer Research and Treatment Center Clinical Trial Office conducts audits on all cooperative group and investigator initiated studies.

All high or very high risk studies with an open active status within the past three years are eligible for audit based on the essential elements guideline Section I. Each study is audited once annually and a minimum of 10% of the patients enrolled in a study are randomly selected for review. A minimum of one record is reviewed per site. The annual audit plan sample (Addendum B, 2007 Audit Plan) is attached to this plan. Prior to each scheduled audit, a current patient list will be reviewed. If the enrollment has increased by $\geq 10\%$ or more patients, the sample will be adjusted for the audit.

The purpose of the CTO Internal Audit System (see above) is to assess and enforce compliance in the following areas:

- Appropriateness of informed consent process
- Patient competency to grant informed consent
- Patient eligibility for study
- Completion of pre-study tests and procedures
- Adherence to treatment requirements, including drug dosages and appropriate treatment delays and dose reductions
- Accuracy, completeness, and timeliness of data collection and submission
- Appropriate and timely reporting of adverse events (AEs) and serious adverse events (SAEs) to appropriate internal and external agencies
- Adherence to patient follow-up requirements
- Consistency of data in research record with data in medical record source documents
- Maintenance of drug accountability records

Following intensive review of the research and medical records, a formal written report of the audit findings is sent to the Principal Investigator for a response, and a corrective action plan is required. The PI's response and audit report is submitted to the PMC for review and final approval.

At the request of the CTO Medical Director or the PMC for investigator initiated trials, focuses audits may be carried out when there is specific concern regarding patient safety or data integrity.

The PRMS scientific activities (Addendum B, Protocol Process) specifically related to data and safety monitoring are as follows;

❖ UNM CRTC/NMCCA Protocol Review Committee (PRC)

Appointments: The PRC is an interdisciplinary committee of approximately 20 physicians from medical oncology, surgical oncology, radiation oncology, and pediatric oncology. It functions as the Protocol Review Committee (PRC) for both the cancer center, as well as the NMCCA as a whole. Additional representatives from the New Mexico Tumor Registry, and oncology pharmacy will also contribute to the PRC. Physician members will be chosen from the Alliance membership with approximately 50% coming from the UNM faculty and 50% from the community. A Chairperson and Vice-Chairperson will be chosen from the committee membership by the Alliance Board of Directors. The Chairperson may request any additional ad hoc members.

Authority: The PRC will have the authority of initiating protocols, assigning a risk level, approving amendments to open protocols, and recommending amendments to, or termination of, a protocol for accrual or scientific reasons (such as the development of therapy which is superior to that proposed in the protocol, or a change in the standard of care which is no longer reflected in the protocol).

Scope: Clinical trials will be considered by the PRC, and hence the NMCCA, if they are Phase I, II or Phase III NCI cooperative group trials, pharmaceutical company (Industry) sponsored research or institutional (UNM) or other investigator-initiated clinical trials focusing on cancer prevention, cancer control or cancer treatment that have been approved by the Tumor-Specific Working Groups. It always remains the discretion of the sponsor whether or not a particular site (practice organization) will be allowed to participate in any one study.

The committee will meet annually to review processes and receive training as needed. The Chairperson may call an ad-hoc committee meeting at any time to solve on-going problems.

Conflict of Interest: Abstention from protocol/amendment review or voting by committee members will be accepted only if the committee member has a conflict of interest and/or a lack of expertise in the scientific subject of the protocol. A committee member who is a Principal Investigator on a study submitted to the PRC will be asked to recuse him/herself from the review process.

Protocol Review Process (Figure 1):

Protocols which have been submitted to the UNM CRTC or the NMCCA from outside sponsors (cooperative groups, pharmaceutical industry, or other institutional sponsors), or are investigator initiated from either the UNM CRTC or NMCCA will be referred to the appropriate Tumor-Specific Working Group for evaluation. Currently, the following working groups are functional and capable of protocol review: Breast Cancer, Gastrointestinal Cancers, Genitourinary Cancers, Gynecologic Cancers, Hematologic Neoplasms, Lung Cancers, and Pediatric Neoplasms. The Tumor Specific Working Group will review each protocol to determine if it is scientifically sound, is of interest and will help forward the academic goals of the specific working group, if the working group has a sufficient patient population to support participation in the protocol, and if the rate of accrual is reasonable for the patient population. Exceptions will be made for certain protocols which will be available for rare neoplasms. If a protocol addresses a neoplasm, or a supportive care scenario, which does not specifically fall under a specific Tumor Specific Working Group, then the protocol will be reviewed by the Medical Director, or in his or her absence, or if there is a potential conflict of interest, the PRC Chair. The staff will determine the process for review based on the type of study (intervention studies require full review and non-intervention studies may be expedited) as defined in the Cancer Center Support Grant guidelines of September 2004 (http://www3.cancer.gov/cancercenters/summaries12_04.pdf). Reviews will be done twice monthly unless determined otherwise by the Chairperson of the committee.

Protocols: Protocols are to be evaluated by assigned reviewers. All investigator-initiated and pharmaceutical-company-sponsored trials must undergo a full review, where two (2) medical reviewers, a committee member from oncology pharmacy, and the statistician of the Protocol Review Committee will review all protocols. Within the Tumor Specific Working Groups, a Research Nurse or Data Coordinator will also evaluate each protocol for the working group to determine the

logistics of each study, and if sufficient resources are currently available to conduct the study safely and efficiently.

If a protocol is derived from a national cooperative group and it has Central IRB approval, or CIRB approval is pending, an expedited review will be performed by the Medical Director of the CTO (or in his or her absence, or if there is a potential conflict of interest issue, by the Chair or Vice Chair of the PRC), after the Tumor Specific Working Group has completed its review. The results of the review will be presented at the next PRC meeting. Prior to initiation of the protocol, CIRB approval must be documented, and such documentation must be maintained in the study file. Protocol Evaluation forms are required from the Tumor Specific Working Group and one additional medical reviewer (including the expedited review) before the committee can approve the protocol. If evaluations from the non-medical reviewers have not been returned, the protocol can still be discussed and voted upon. PI's are to abstain from voting and may be asked to leave the room for discussion of the trial, though they should be available for discussion of key questions. An approval of 51% is necessary for a clinical trial to become approved by the PRC. Requests for any changes will have to be addressed by the principal investigator but once corrections are made the trial will come to the Chairperson of the Committee for approval before going to the HRRC and will not have to go back to committee. Committee members will receive an addendum to the minutes stating the corrections or changes that have been made to the satisfaction of the Committee Chairperson. If a trial is rejected by the PRC, the PI has the right to appeal the decision, provided each point of concern raised by the review process is addressed in the appeal.

Criteria for Review: The reviewers will be given the protocol, the protocol abstract and a review form. The review form collecting all the following elements is to be used by all reviewers. This form will include date, protocol title, phase of study, sponsor information, protocol number, principal investigator name, all reviewer names. The abstract will list the major review criteria, which are the scientific rationale for the study, study design, study population, statistics, and innovation. The reviewer will list all major points for which he/she has a scientific critique. The protocols can be rejected outright for major criteria flaws, requiring re-submission, unless the PI answers satisfactorily to these critiques. The reviewer will list all minor points for which he/she has a critique. The minor review criteria are accrual feasibility, eligibility criteria soundness, competing protocols, procedures and clinical assessment practicality, adequacy of appendices for reporting results, drug accountability, and typos. Protocols with minor criteria flaws can be approved pending corrections as needed; the PI should make all revisions within a month prior to advancing the finished protocol to the IRB of record, or explain why an extension of time is required.

Prioritization: The responsibility for protocol prioritization rests with the Tumor Specific Working Groups. If two or more protocols compete for patients or institutional support, protocol approval will be based on priorities. Criteria for prioritization are, in order of decreasing priorities: 1) studies that are investigator-initiated from bench to bedside, 2) investigator initiated protocols with currently available drugs and containing translational components, 3) investigator-initiated with current available drugs without translation, 4) cooperative group studies originating from a CRCC member, 5) cooperative group studies, 6) industry fully sponsored phase I and pharmacologic studies, 7) industry fully sponsored phase III randomized pivotal studies, and 8) industry fully sponsored phase II studies. If two or more protocols are opened by a Tumor Specific Working Group, but for logistical reasons cannot (or will not) be opened and available to all NMCCA sites, this must be stated clearly, along with the reasons for differential availability, to the PRC in writing from the Tumor Specific Working Group.

Risk: The Chairperson of the PRC determines the risk of the study. Risk level is documented in the CRCC/NMCCA Protocol Packet. The assigned level of risk designates the level of review of the study by the CRCC Protocol Monitoring Committee (PMC) and CRCC Quality Assurance Office.

Amendment Review: The PRC reviews scientific amendments and designates approval based on the following guidelines. All review dispositions (Addendum F- PRC Amendment/Change Disposition) are forwarded to the HRRC with the HRRC amendment form (Table 4).

Table 3. Study Risk Profile and Monitoring Requirements

	Low	High	Very High
Reports and Monitoring Frequency	HRRC Annual Progress Report (Addendum M).	6 month report and HRRC Annual Progress Report*	3 month reports and HRRC Annual Progress Report
Subject Recruitment & Retention	Required	Required	Required including drop out analysis
Cumulative Adverse Events		Grades 4-5 expected, and 3-5 unexpected AEs	Grades 4-5 expected, and 3-5 unexpected AEs
Study specific DSMB			As required #
Internal Audit	As required	Required	Required
Analysis of 1 st and 2 nd efficacy parameters, outcomes, if applicable	As required	As required	As required

* Phase I, II, or III therapeutic, palliative or prevention trials sponsored by cooperative groups or are investigator-initiated will be monitored quarterly or every six months, and those of the cooperative groups will be monitored by the specific group at least every three years; all protocols will be audited annually, or more often if major deviations are found.

The study-specific DSMB Charter supersedes the requirements of this table

Amendment Review: The PRC will delegate review of administrative and scientific amendments based on the following guidelines. The CPDM & I will review all amendments and forward amendments requiring scientific review to the UNM CRTC CTO and NMMCCA Medical Director or the PRC Chairperson.

Table 3, Amendment Review

Administrative - completed by the CPDM&I Manager	Process for Review
All Low Risk Trials Nominal changes Grammatical changes	Designate a determination and sign the Amendment Review Disposition Form (Addendum E, Amendment/change Disposition). Forward completed document to regulatory coordinator. Forward copy of the review disposition form with the amendment paperwork to the IRB.
Scientific – completed by the Medical Director	Process for Review
Research objectives Treatment Response	Designate a determination and sign the Amendment Review Disposition Form (Addendum E, Amendment/change Disposition). Forward completed document to the CPDM&I Manager.

Accrual Criteria for review

Accrual	Recommendation
0-49% of projected accrual	Study may be required to be amended or considered for termination. The PRC regards a situation of zero accrual as a Potentially flawed study after two years.
50% - 74% of projected accrual	Extenuating circumstances are considered first. The Principal Investigator is then asked to justify continuing the study. Constructive suggestions to improve accrual will be considered such as altering the design or eligibility criteria, seeking extramural funding, activating the study at affiliate centers or through the outreach network, etc.
75%-100% of projected accrual	No Recommendation. Acceptable.
> 25% of projected accrual	Recommendation by the committee in accordance with the level of over accrual.

Each study should be reviewed for accrual at least quarterly. A study that meets $\leq 74\%$ accrual target will require a review of screening data as part of the annual review. This will include an analysis of total number of screens, number of patients who failed screening and the reason for failure.

❖ Protocol Monitoring Committee (PMC)

Appointments: The Chairperson of the PMC will be appointed for a three year term, renewable once, by the CRTC Director and CEO. Committee members include a Committee Chairperson, four members who are active investigators appointed for a two year term renewable twice, and six (6) permanent members: the Medical Director of the NMCCA and UNM CRTC CTO, UNM CRTC CTO Nurse Manager, the Executive Director of the Clinical Trial Office, the Chairperson of the PRC, the Human Protection Specialist, and the CPDM & I Manager. One of these members will act as Vice-Chairperson and serve three years. Any additional members may be requested by the Chairperson, as needed.

Authority: The PMC will act as or designate the Data Safety Monitoring Board for studies approved by the PRC unless otherwise specified by this plan or the IRB of record. The PMC will review and monitor all study progress for investigator-initiated trials, or those designated by the PRC. If appropriate, the PMC will designate and monitor corrective action(s) based on review outcome. The PMC will have the responsibility of recommending amending and/or terminating protocols based upon issues of safety or accrual, though only the PI or the IRB of record may terminate a trial because of safety concerns. The Chairperson may call an ad-hoc committee meeting at any time to solve on-going problems.

The PI is responsible for following all protocol-specific early stopping rules. As the DSMB for UNM CRTC and the NMCCA, the PMC will insure that the following early stopping rules will be implemented for intervention protocols based on the guidelines below:

Phase I	Phase II	Phase III
The design is an early stopping rule in itself. No action needed	The two step design will permit reevaluation after completion of the first step. Unless otherwise specified in the protocol, the PMC will consider closure of the study for unexpected >50% Grade 4 hematologic toxicity	These studies have an independent data safety monitoring board. The charter of this board must specify the early stopping rules.

	and >20% grade 3/4 non hematologic toxicity when patients are treated at the lowest dose level	
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Confidentiality: All PMC members must abide by the Confidentiality Agreement they signed upon hire by the University of New Mexico or consistent with their participation agreement with the New Mexico Cancer Care Alliance.

Conflict of Interest: Abstention from monitoring review or voting by committee members will be accepted only if the committee member has a conflict of interest and/or a lack of expertise in the scientific subject of the protocol. A committee member who is an investigator on a study will be asked to rescues him/herself from the review process.

Monitoring Review Process: The PMC will conduct monitoring reviews per the schedule below for investigator-initiated trials. This includes trials which are monitored internally, and by a CRO, as well. Staff will determine the level of review and implement the review process. The PMC will review reports regarding study status and progress as designated by the risk assignment and level of review. These reports will include gender, ethnicity, race, protocol deviations, patient accruals and analysis of adverse events at a minimum per the following guide.

Monitoring Review Components and Schedule

	Gender, Race, Ethnicity	Adverse Event Analysis	HRRC Event Form	Previous PMC Review	Endpoints
Quarterly Monitoring Review		✓		✓	If appropriate – institutional studies only
Bi Annual Monitoring Review		✓		✓	
Annual Progress Report	✓	✓		✓	
Serious Adverse Event		✓	✓	✓	
Protocol Deviation		✓	✓	✓	

Annual Monitoring Review Process: The PMC will have an option of two levels of review; expedited and full based on the following guide;

Full Review: This will be performs for all investigator-initiated High Risk and Very High Risk trials. Staff compiles the study review forms (Addendum G, PMC Interim Review and Report Form) and forwards to two (2) members of the committee for review. One reviewer must be a physician. If a committee member cannot review the protocol report within three (3) working days, the committee member must notify the appropriate staff within one (1) working day. If a committee member does not respond to 80% of the request for reviews, that member can be removed from the PMC and his/her department Chairperson will be notified of the decision. Abstention from reviewing or voting by committee members will be accepted only if the committee member has a conflict of interest and/or a lack of expertise in the scientific subject of the protocol.

Staff will compile the results of the member reviews and forward to the Chairperson of the committee.

The Chairperson reviews the committee decisions and if there are no outstanding issues signs the report. The staff forwards the report to the PI, Research Nurse, and Regulatory Coordinator.

Expedited Review: This will be performed for all Low Risk investigator initiated Low Risk trials. Staff will compile the studies eligible for expedited review on a monthly basis. for review by the Chairperson. If no issues are found, the Chairperson will sign the Disposition Letter, approving the study and return it to the staff. The Chairperson has the right to request a full review, call a committee meeting or request other action if the Chairperson finds the expedited review insufficient.

Review Outcome: The PMC will make the following recommendation;

- **Approved** – Enrollment may continue
- **Close to accrual** – Close enrollment
- **Close study** – No patients on active treatment or follow up
- **Temporarily Close to Accrual** – delinquent progress report

The PMC may make requests or recommendation(s) for additional information to be provided to the committee, an internal audit of patient record(s) and regulatory information, or protocol amendment(s).

Additional requested items may be;

- Exceptions in eligibility or treatment
- Best response to treatment for each patient, for Phase II and III studies
- Treatment arm for each patient, for Phase III studies
- Study and survival status of each patient
- Results of any interim analyses required by the protocol
- Copies of abstracts or papers written using study data

The PI will be required to provide any additional information within a specific time frame as determined by the committee. Staff will follow up and provide the Chairperson with the required information. The Chairperson will review the information and uphold the review outcome or make further recommendations.

All PMC decisions are conveyed in writing to the Investigator (Addendum H, PMC Disposition Letter). PMC will state specific reason(s) for the decision. Principal Investigators may appeal PMC decisions in writing (Addendum I, PMC Appeal) to the PMC Chairperson within five (5) working days. The Principal Investigator must respond to each reason(s) in the decision.

Appeals will be electronically distributed to two (2) members of the PMC which were not involved with the original review. Reviewers will have five (5) working days to complete their review and return comments to the PMC Chairperson. The PMC Chairperson will convey the results in writing to the Principal Investigator. All appeal decisions will be final.

Temporary or permanent suspension of any NCI-sponsored clinical trial by either the PMC or the HRRC will be reported immediately to the NCI project manager for that trial. If CTEP drugs are used in the study, the suspension will also be reported immediately to CTEP. If the suspension is temporary, the NCI and CTEP will also be notified in a timely manner regarding the resolution of the issues that caused the suspension, and the date that the suspension was lifted.

The committee will review the CRO monitoring results as they are generated, or at least quarterly. All documentation and correspondence must be kept in the Quality Assurance Office.

The committee will meet at least annually to review processes and receive training as needed

Corrective Action Item(s) Request and Disposition: Corrective action item(s) may be requested based on review findings. Any review finding that results in a protocol deviation requires correction action. The reviewer provides a recommendation for corrective action on the PMC Reviewer Form. The PMC Coordinator compiles the reviewer findings for the Chairperson. The Chairperson reviews and approves requested corrective action. The key members of the Research Team receive a copy of the PMC disposition with the required corrective action.

Corrective action items are classified as Administrative or Scientific based on the following criteria:

Corrective Action Criteria for Investigator-Initiated Trials	
Administrative – issues reflecting;	Scientific – items reflecting;
All Low Risk trials	Research Objectives
Nominal changes to protocols	Consent/Eligibility
Data Quality	Treatment/Response
Accrual Targets	Adverse Events
PMC Chairperson	Full PMC

Corrective action items are followed by the PMC Coordinator. A follow up disposition is completed when a corrective action item(s) is completed or delinquent and reviewed by the appropriate individual per the above criteria. The disposition is forwarded to the key members of the Research Team and the HRRC. Documentation is maintained in the Office of Quality Assurance and the study regulatory manual in the CTO.

Internal Audit Report Review: The PMC will review internal audit reports. The PMC will have an option of two levels of review; expedited and full based on the following guide;

Table Audit Ratings

Expedited Review	Full Review
Acceptable	Acceptable with follow up >2 major deviations
Acceptable with follow up 1-2 major deviations	Unacceptable

Full Review: Staff compiles the audit review form (Addendum F, Audit Review Form) and forwards to two (2) members of the committee for review. One reviewer must be a physician. If a committee member cannot review the protocol report within three (3) working days, the committee member must notify the PMC Coordinator within one (1) working day. If a committee member does not respond to 80% of the request for reviews, that member can be removed from the PMC and his/her department Chairperson will be notified of the decision. Abstention from reviewing or voting by committee members will be accepted only if the committee member has a conflict of interest and/or a lack of expertise in the scientific subject of the protocol.

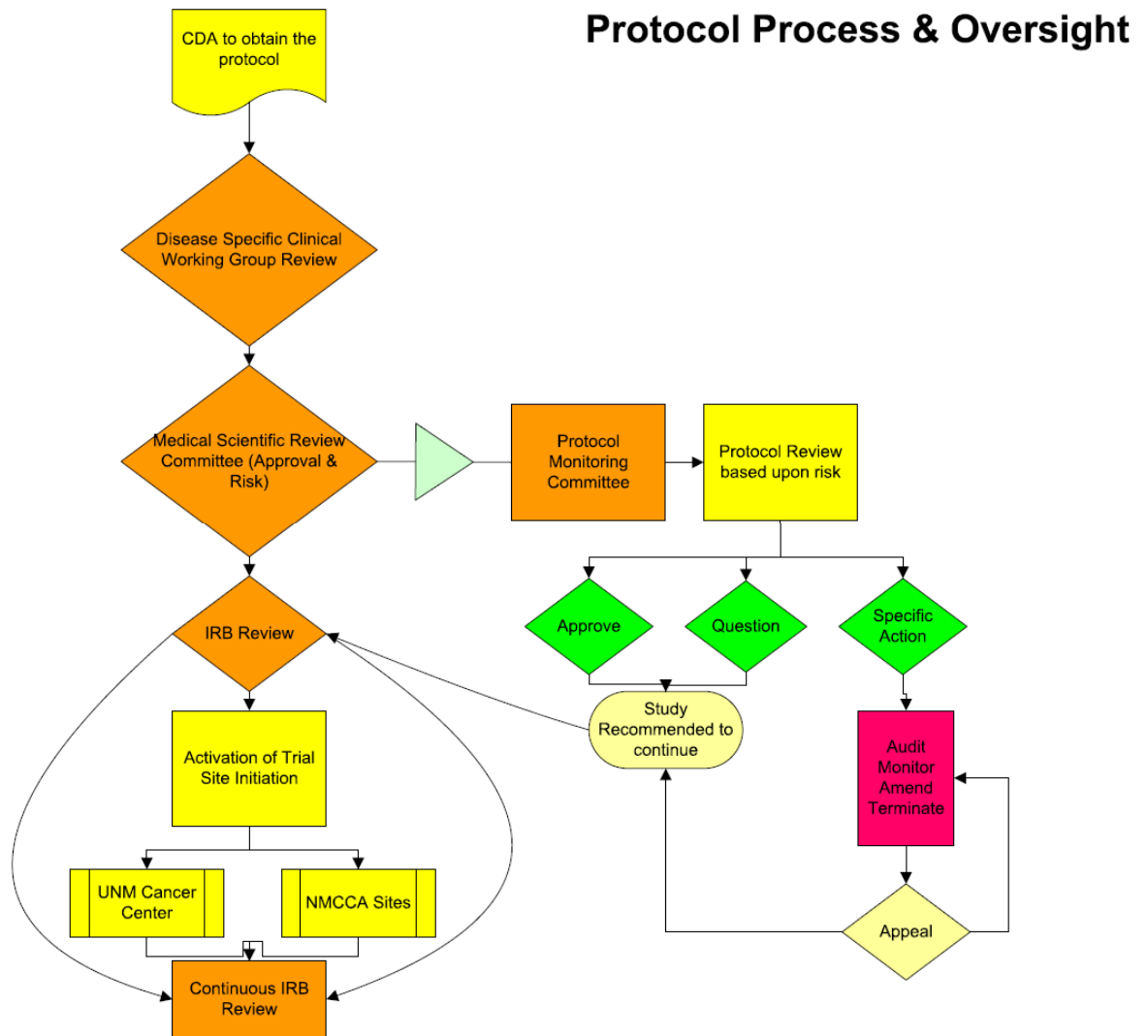
Staff will compile the results of the member reviews and forward to the Chairperson of the committee.

The Chairperson reviews the committee decisions and if there are no outstanding issues signs the report.

Expedited Review: Staff will compile the study monitor or audit reports eligible for expedited review for review by the Chairperson. If no issues are found, the Chairperson will sign the disposition letter, approving the report and return it to the staff. The Chairperson has the right to request a full review, call a committee meeting or request other action if the Chairperson finds the expedited review insufficient.

Documentation of the review and outcome is maintained in the Office of Quality Assurance and the study regulatory binder. The review disposition is forwarded to the Primary Investigator, Human Protection Specialist, Nurse Manager, CPDM Manager, Research Nurse.

Figure 1.



Training Grants

Certain types of NCI career and training awards may support clinical trials, directly or indirectly. NCI's DSM policy covers those career and training awards in which the trainee has direct responsibility for conduct of the clinical trial or in which award funds directly support the trial. Responsibility for compliance with NCI's DSM policies rests with the grant recipient; this may be either the trainee or the training program director, depending

on the award (individual versus institutional). Trainees in a mentored career program should consult with their mentors about adapting or designing suitable DSM plans for their clinical trials. In most cases the trainees will be in a mentored stage of their career and will lack the experience needed to provide appropriate oversight of the trial. The DSM plan must therefore clearly identify the senior individual responsible for monitoring the trial and the function of the trainee in this process.

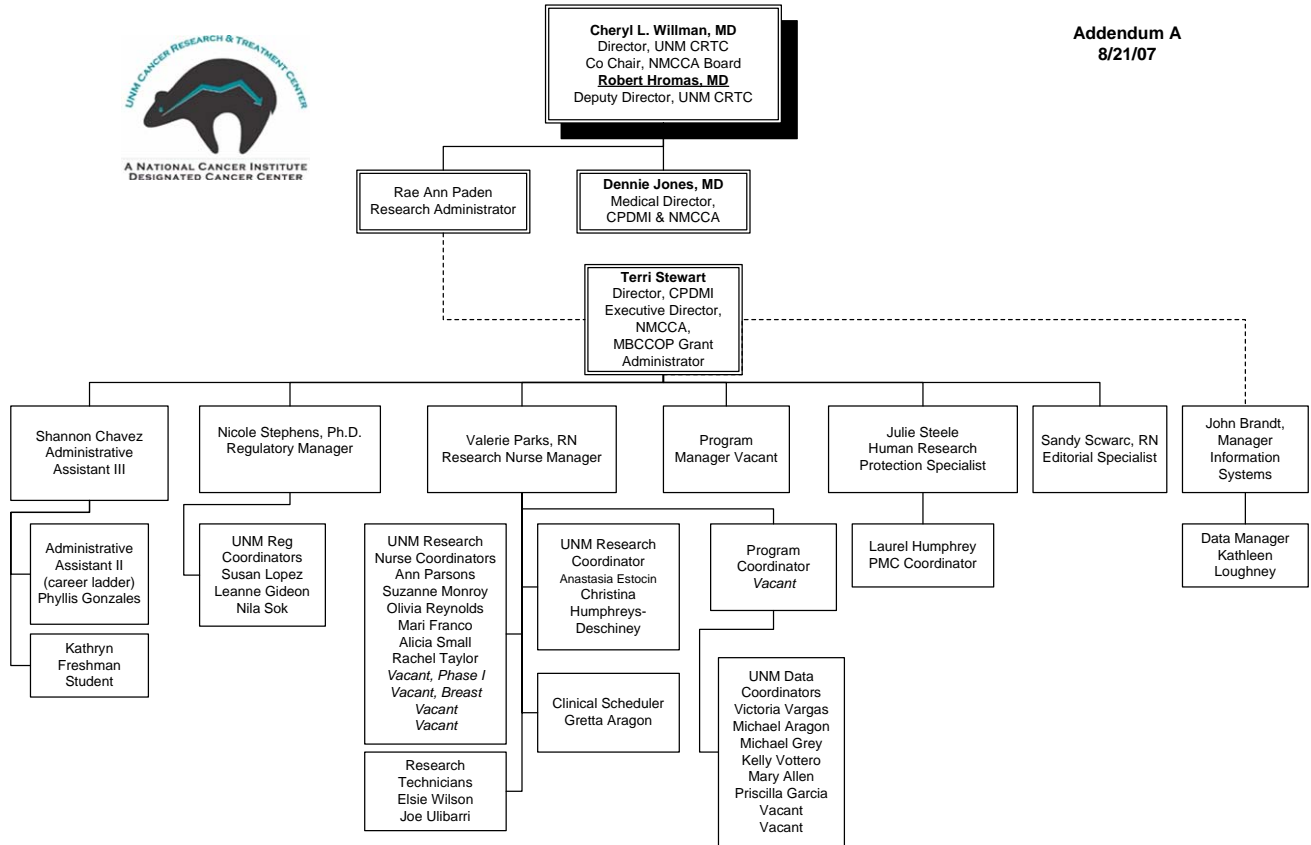
- For institutional career development programs (e.g., K12, R25T) in which clinical trials are an integral part, applicants should provide with their application a "Special Institutional Statement Regarding Human Subjects Research under K12 or R25T Support". This statement must be provided to NCI Program staff for evaluation and approved before the initial grant award can be issued, and submitted for evaluation and approval with each "Application for a Continuation Grant."
- For individual career development awards in which the grantee has direct responsibility for trial conduct or in which award funds directly support the trial, the DSM plan covering the trial may NOT be an institutional plan. The DSM plan must be tailored specifically to the clinical trial.
- A DSM plan does not need to be provided for individual career development awards in which:
 - The trial is a component of an NIH Cooperative Group trial;
 - The trial is a CTEP-supported protocol;
 - The trial is being partially or completely supported by an investigator-initiated NIH R-grant, with an approved DSM Plan.

For individual career development awards in which a clinical trial will be conducted that does not require the submission of a DSM plan, the grantee must submit for evaluation a letter to NCI program staff describing their situation and explaining why a DSM plan is not needed. This letter must be co-signed by the institutional official authorized to evaluate issues pertaining to data safety and monitoring; and, in the case of mentored awards, by the grantee's mentor.

- If the clinical trial is not to be started immediately upon award of an individual career development award but will follow after a considerable lapse of time (years), submission of a DSM plan to NCI for approval may be delayed until the nature of the trial is clear and its initiation is in the near future. This will insure that the DSM plan suits the needs of the trial.
- For NCI career development awards for established investigators (K05, K24), a DSM plan does not need to be provided. However, a Restriction term will be included in each Notice of Grant Award requiring that the grantee remain in compliance with the NCI's policy on data and safety monitoring throughout the project period.



Addendum A
8/21/07



Addendum B

COMMITTEE MEMBERSHIPS

PROTOCOL REVIEW COMMITTEE MEMBERSHIP

NAME	POSITION	EXPERTISE
Melanie Royce, MD, PhD	Committee Chair – UNM Cancer Center	Oncology, Breast Cancer
Malcolm Purdy, MD	Committee Vice Chair – Hematology Oncology Associations	Community Physician, Hematology/Oncology
Teresa Stewart, MHA	Executive Director, NMCCA and CPDM	Senior Administrator
Dennie Jones, Jr., MD	Medical Director, NMCCA and CPDM	Oncology, Development, Lung Cancer
Valerie Parks, RN	Research Office Manager, CPDM and NMCCA	Clinical Trials Management, Nursing
Bernard Agbemadzo, MD	Member, Lovelace Medical Group	Community Physician, Hematology/Oncology
Stanley Cheshire, Ph.D	Member, UNM Cancer Center - Pharmacist	Pharmacy, Pharmacology
Michael Davis, MD	Member, Albuquerque VAMC	Community Physician, Hematology/Oncology
Elizabeth MacGuire, MD	Member, Albuquerque VAMC	Community Physician, Hematology/Oncology
Ginnie McClure, RT, CDT	Member, Clinical Trial Coordinator, NMCCA	Clinical Trials Management, Radiation Oncology
Sang-Joon Lee, Ph.D.	Member, UNM Cancer Center – Statistician	Statistician
James Lin, MD	Member, Hematology/Oncology Associates	Community Physician, Hematology/Oncology
Karen LoRusso, MD	Member, New Mexico Cancer Care Associates	Community Physician, Hematology/Oncology
Karen Moller, MD	Member, Southwest Gynecologic Oncology	Community Physician, Gynecologic Oncology
Carolyn Muller, MD	Member, UNM Cancer Center	Gynecologic Oncology
Ian Rabinowitz, MD	Member, UNM Cancer Center	Oncology, Urologic Cancer
Claire Verschraegen, MD	Member, UNM Cancer Center	Oncology, Drug Development, Gynecologic Oncology
Charles Wiggins, Ph.D.	Member, Director, SEER Registry	Tumor Registry
Debbie Winklejohn, RN	Member, Research Nurse, Hematology Oncology Associations	Clinical Trials Management, Nursing
Robert Winter, MD	Member, UNM Cancer Center	Pediatric Oncology

PROTOCOL MONITORING COMMITTEE

NAME	POSITION	EXPERTISE
Elizabeth McGuire, MD	Committee Chair	Community Physician, Hematology/Oncology
Carolyn Muller, MD	Committee Vice Chair	Gynecologic Oncology
Teresa Stewart, MHA	Executive Director, NMCCA and CPDM	Senior Administrator
Dennie Jones, Jr., MD	Medical Director, NMCCA and CPDM	Oncology, Drug Development, Lung Cancer
Valerie Parks, RN	Research Office Manager, NMCCA and CPDM	Clinical Trials Management, Nursing
Nicole Stephens, PhD	Manager, Regulatory Affairs, NMCCA and CPDM	Administrator, Regulatory Affairs
Julie Steele, BA, LPN	Human Protections Specialist, Quality Office	Administrator, Quality Assurance
Richard Heideman, MD	Member, UNM Cancer Center	Pediatric Oncology
James Lin, MD	Member, Hematology Oncology Associates	Community Physician, Hematology/Oncology
Robert Quinn, MD	Member, UNM Cancer Center	Orthopedic Oncology
Melanie Royce, MD	Member, UNM Cancer Center	Oncology, Breast Cancer
Amy Tarnower, MD	Member, UNM Cancer Center - Lovelace	Community Physician, Hematology/Oncology
Claire Verschraegen, MD	Member, UNM Cancer Center	Oncology, Drug Development, Gynecologic Oncology
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