Norris Cotton Cancer Center
Dartmouth Hitchcock Medical Center

Institutional Data and Safety Monitoring Plan

April 15, 2002

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Norris Cotton Cancer Center
Clinical Research Program
Institutional Safety and Data Monitoring Plan

Summary

The Norris Cotton Cancer Center (NCCC) at Dartmouth Hitchcock Medical Center (DHMC) places the highest priority on ensuring the safety of patients participating in clinical trials. The Director of the Norris Cotton Cancer Center at Dartmouth and the Director of the Clinical Research Office (CRO) hold the overall responsibility for overseeing data and safety monitoring. Other groups with responsibilities for data and safety monitoring include the Clinical Cancer Research Committee (CCRC), the NCCC Safety and Data Monitoring Committee (SDMC), the internal auditing system of the CRO, individual data safety and monitoring boards for local phase III trials, the principal investigators of NIH grants and contracts supporting clinical trials, and, most importantly, the principal investigator of each clinical trial.

At Dartmouth, clinical protocol review and monitoring of all treatment, prevention, cancer control and interventional clinical trials is coordinated through Clinical Research Office of the Norris Cotton Cancer Center, an NCI-designated Comprehensive Cancer Center. The CRO currently manages approximately 150 active protocols, including Dartmouth Medical School (DMS), CALGB, POG, GOG, RTOG and ECOG, working group, and pharmaceutical trials. Since January 1996, two data and safety oversight committees have functioned at the NCCC, one to review each new clinical trial protocol prior to Institutional Review Board (IRB) review and the other to monitor safety and data throughout the trial. Prior to IRB review, the CRO submits the protocol to the Clinical Cancer Research Committee. The CCRC is responsible for the scientific review of all new studies of cancer treatment or cancer prevention in human subjects. This includes review of all scientific aspects of the study, including the required safety and data monitoring plan. Once a protocol receives CCRC and IRB approval, the protocol is considered for activation.

The CRO submits reports on all active Dartmouth clinical trials to the Safety and Data Monitoring Committee (SDMC). The NCCC SDMC, which oversees the monitoring of patient safety, scientific integrity, protocol enrollment, and progress toward protocol endpoints while trials are in progress and also at the completion of trials, operates in accordance with National Institutes of Health (NIH) guidelines for safety and data monitoring committees. The SDMC functions in this capacity for active clinical trials that are not monitored by another Data and Safety Monitoring Board (DSMB). A monthly internal audit system involves the intensive review of a random sample of study records to assess data accuracy and completeness, and adherence to protocol requirements for informed consent, pre-study tests and procedures, treatment, patient follow-up.

Every clinical trial conducted at the NCCC must include a plan for safety and data monitoring as part of the protocol. The monitoring plans and reporting requirements are

dependent upon the study sponsor, nature of the investigational agent (i.e. drug, biologic product or device), and phase of trial. Specific plans may vary based on the degree of risk involved in participation and the size and complexity of the clinical trial.

Investigator

The principal investigator 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:

- All protocols and amendments are submitted to CCRC and IRB for review. See Appendix I for flow chart of protocol and amendment review.
- All protocols include a data and safety monitoring plan and procedures for its implementation
- A study specific data safety and monitoring board (DSMB) is established if a proposed interventional study is:
    - A randomized, Phase III clinical trial
    - A multi-site clinical trial
    - Includes more than 100 participants
- A study specific DSMB may be established for a study that does not meet the above criteria
- 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.
- If the proposed protocol has additional clinical sites besides NCCC, the protocol describes procedures by which the investigator will notify sites of any problems identified by the DSMB if one is established
- 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 investigator submits individual adverse event reports to the funding agency(ies) (sponsor) in accordance with agency and FDA regulations
- Regularly (annual or quarterly as designated by the CCRC) submits data summaries to the designated DSMB. See Appendix II for flow chart of Safety and Data Monitoring Reports.
- Adverse events and serious adverse events are reported as required to appropriate agencies including the designated DSMB. See Appendix III for flow chart of serious adverse event reports.

Clinical Research Office (CRO)

The NCCC CRO provides support for all clinical trials at the NCCC. CRO activities specifically related to data and safety monitoring are as follows:

- Assists investigators in the preparation and submission of local, investigator-initiated studies for review by the CCRC and Dartmouth IRB
- Distributes information on active cancer clinical trials
- Facilitates utilization of available patient resources
- Provides centralized patient registration for all investigator-initiated studies
- Collects, maintains and updates data on patients enrolled including data on accrual, toxicity and adverse events
- Provides information to and assists in review and monitoring of clinical studies
- Ensures that cancer clinical trials are conducted in accordance with federal, state and institutional regulations
- Assists in the training of investigators and clinical trial staff in the development and conduct of clinical trials
- Collects quarterly and annual data and safety monitoring reports from study principal investigators of trials monitored by the NCCC SDMC and distributes them to SDMC members

Clinical Cancer Research Committee (CCRC)

The Clinical Cancer Review Committee (CCRC) is a multidisciplinary committee charged with providing peer review of the scientific merit of all clinical research protocols for treatment, prevention, control or intervention of cancer, developed by investigators at the NCCC. The CCRC has the authority to approve, require modifications in, or disapprove all research activities that fall within its jurisdiction. All new clinical cancer research protocols and amendments to existing protocols are subject to review by the CCRC.

Committee members are appointed by the Director of the NCCC, and serve for a period of five years. Membership includes representatives from medical oncology, hematology, radiation oncology, surgical oncology, pediatric oncology, pharmacology, biostatistics, basic science research, oncology nursing, and clinical research administration. Presence of fifty percent (50%) of the CCRC's voting members constitutes a quorum. In order for a study or an amendment to receive approval, it must obtain an approval vote from the majority of the Committee quorum. The CCRC meets on a monthly basis, usually the second Thursday of each month. Administration of the CCRC (paperwork, meeting coordination, minutes) is provided by the CRO. Minutes reflect the members present, substantive issues discussed, and voting results (including members abstaining due to conflict of interest).

For each new study, the principal investigator is required to submit a cover letter addressing the following points:

- Justification for opening the protocol and explanation of how it fits into the overall research program for the specific disease site
- The number of potentially available patients per year
- The number of patients expected to be accrued annually and over the life of the protocol

- Funding source or sponsor
- Proposed project dates
- A Risk/Benefit analysis
- Plans for data and safety monitoring
- Statement regarding any other active studies that would compete for the same patient population, and how competing studies will be prioritized

New protocols submitted to the CCRC are first reviewed by the administrative staff of the CCRC to assure that all required components of a research protocol are included. They are then forwarded to the CCRC Chairman for preliminary review. At this time, the CCRC Chairman determines the study level of risk as one of two levels:

Low risk: Studies involving no therapeutic intervention, i.e. studies involving patient questionnaires, blood draws, or other low-risk tissue sampling (i.e., hair, urine, sputum), voice or video recordings, moderate exercise, existing data, documents, pathologic or diagnostic specimens, behavioral, cognition or perception. Studies involving intervention with standard doses of nutritional agents available over the counter (i.e., vitamins, minerals).

High Risk: Studies involving cancer-directed chemotherapy, biologic therapy, radiation therapy, or surgical intervention. Studies involving higher-risk tissue sampling (i.e., bone marrow, or sampling requiring any type of anesthesia). Studies involving non-standard doses of agents available over the counter.

There are two levels of CCRC review: full committee review and expedited review. The CCRC chairman determines the level of CCRC review, based on the following guidelines:

Expedited review: All national cooperative group studies or study amendments, and low risk studies initiated by in-house investigators or the pharmaceutical industry. Amendments that do not change the level of risk to patients, and do not substantively affect the scientific integrity of the study.

Studies or amendments subject to **expedited review** are reviewed by the CCRC Chairman, who is responsible for approval or disapproval. The decision of the Chairman is communicated in writing to the principal investigator. If the study or amendment is approved, it is sent on for IRB review. If the study or amendment is disapproved, the principal investigator is notified in writing of the reason(s) for disapproval. The outcomes of expedited reviews are reported in writing to the full committee at the next monthly CCRC meeting.

Full Committee Review: High risk studies initiated by in-house investigators (including NCI funded studies) or the pharmaceutical industry. Amendments that change the level of risk to patients, or substantively affect the scientific integrity of the study.

For **full committee reviews**, the Chairman of the CCRC identifies three appropriate reviewers, including a statistician. The entire protocol or amendment is made available

for review, and each reviewer is required to comment on specific items regarding the scientific merit of the study and submit their remarks on a CCRC Review Questionnaire. The CCRC Review Questionnaire appears as Appendix IV. At the CCRC meeting one of the three primary reviewers presents a summary of the study or amendment, and a summary of any concerns raised by the three primary reviewers. The principal investigators are encouraged to attend CCRC meetings, so they can help explain the study and answer questions from the Committee. After the principal investigator has answered questions, he or she must leave the room prior to final Committee deliberations and voting. The Committee can vote to approve, conditionally approve, or disapprove a protocol.

Approval or disapproval of the study or amendment is communicated in writing to the principal investigator, along with any reason(s) for disapproval. If the Committee approves the protocol except for minor, easily remediable changes, the Committee may conditionally approve the study pending these changes. Once a study has been approved, it is forwarded for IRB review. If the Committee notes any potential issues regarding the ethical treatment of human subjects, it will notify the IRB in writing of the concerns. principal investigators may appeal CCRC decisions in writing to the chairman of the CCRC.

If a protocol falls outside the expertise of the current CCRC membership, or if members are not available, the Chair will identify one or more members of the NCCC to act as ad hoc reviewers. They submit a written review and may attend the CCRC as non-voting members, to participate in the discussion of the study.

Several specific actions are taken to avoid conflict of interest in the CCRC voting process:

- In the event that the CCRC Chairman serves as the investigator or co-investigator for the study or amendment in question, another CCRC member will be responsible for establishing the level of risk, establishing the need for a full committee review, and assigning reviewers.

- All committee members involved as principal investigator or co-principal investigator of a study must abstain from voting, and are required to leave the meeting room prior to final Committee deliberations and voting.

- All committee members with a significant personal financial stake in the sponsor agency must abstain from voting, and are required to leave the meeting room prior to final Committee deliberations and voting.

Safety and Data Monitoring Committee (SDMC)

The Safety and Data Monitoring Committee (SDMC) is the DSMB for the NCCC at Dartmouth. It is a multidisciplinary committee charged with overseeing monitoring of safety of participants, conduct, progress, and validity and integrity of the data of all

clinical trials at NCCC at Dartmouth. The committee is chaired by the Director of the Clinical Research Office, and meets quarterly to review the progress and safety of all active research protocol that are not reviewed by another safety and data monitoring committee. If a study is already being monitored by a safety and data monitoring committee formed by a national cooperative group, a pharmaceutical sponsor, or a study-specific committee for a phase III trial, the NCCC SDMC does not actively monitor the study. The SDMC oversees the process of adverse event reporting to assure that the requirements are met. The SDMC has the authority to require amendments, suspend or terminate any research activities that fall within its jurisdiction. The SDMC reports to the Clinical Cancer Review Committee (CCRC). The SDMC can institute any other appropriate conditions needed for subject safety.

With the exception of the Director and Associate Director of the Clinical Research Shared Resource, who are standing members, all members serve a five-year term. Committee membership and voting status are assigned by the Director of the NCCC. The Committee includes representatives from the following disciplines: medical oncology, hematology, radiation oncology, pharmacology, bio-statistics, ethics, oncology nursing and data management. Presence of three or more of the SDMC voting members constitutes a quorum. Members may be appointed on an ad hoc basis by the Chairman of the SDMC, should additional expertise be required in the review of certain studies.

The SDMC meets on a quarterly basis. Special meetings may be convened when necessary, for urgent concerns regarding patient safety or data integrity. Administration of the SDMC (paperwork, meeting coordination, minutes) is provided by the Clinical Research Office. Minutes reflect the members present, substantive issues discussed, voting results, and members abstaining due to conflict of interest.

The frequency of SDMC monitoring for a particular study depends on the level of risk (low or high risk) assigned to the study by the Chairman of the CCRC, as described above. Low risk trials are reviewed on an annual basis by the SDMC. High risk trials are reviewed on a quarterly basis by the SDMC. The size and complexity of a trial also determines the frequency and level of review. 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.

For each SDMC protocol review, summary information regarding toxicity and accrual patterns is prepared by the CRO, and submitted to the SDMC. The study Principal Investigator is required to review and sign all SDMC reports. Specific information submitted for review includes:

- The expected and actual numbers of patients entered to date, as well as for the most recent reporting period
- Number of patients treated
- Description of any changes to the study design since the last SDMC review
- Exceptions in eligibility or treatment
- Dates of patient enrollments

- Dose tier for each patient, for Phase I studies
- Best response to treatment for each patient, for Phase II and III studies
- Treatment arm for each patient, for Phase III studies
- The type and grade of adverse events for each patient using CTC 2.0 grading
- The duration and outcome of adverse events for each patient
- Current disease, vital, and study (on- or off-study) status of each patient
- Copies of all adverse event reports submitted since the last SDMC review are also sent to the SDMC, so they can be reviewed for accuracy and timeliness
- Significant literature reporting developments that may affect the safety of participants or the ethics of the study
- Results of any interim analyses required by the protocol
- Copies of abstracts or papers written using study data

Members receive this information approximately one week prior to Committee meetings, to allow for preliminary study and review. Each study is assigned to a specific Committee member for presentation during the Committee meeting. In the event that a Committee member is either a principal investigator or co-principal investigator for a study under review, or has any other conflict of interest (including substantial financial interest in the study sponsor agency), that member may be present to answer questions regarding the study, but must abstain from voting and leave the room prior to final deliberations and voting on that study. In the event that the Chairman is the principal investigator for the study, another member of the Committee will oversee the Committee deliberations and voting.

The Committee may vote to take one of the following actions for each protocol reviewed:

- **Full Approval:** enrollment may continue; no outstanding questions regarding toxicity or accrual

- **Conditional Approval:** enrollment may continue conditional upon satisfactory response by the principal investigator to SDMC concerns regarding toxicities and/or accrual.

- **Suspension:** enrollment immediately suspended pending principal investigator response SDMC concerns regarding toxicity and/or accrual patterns.

- **Closure:** study closed due to unacceptable toxicity and/or accrual patterns.

All SDMC decisions are conveyed in writing to the study principal investigator. Principal investigators may appeal SDMC decisions in writing to the chairman of the SDMC. If the decision regarding the appeal is unsatisfactory to the investigator, a second appeal may be made to the CCRC.

Temporary or permanent suspension of any NCI-sponsored clinical trial by either the NCCC Safety and Data Monitoring Committee or the Dartmouth Committee for the Protection of Human Subjects (the Dartmouth IRB) 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.

Internal Audit System

The purpose of the NCCC Internal Audit System is to assess and enforce NCCC Clinical Research Office compliance in the following areas:

- Presence of all NCI required elements in informed consent document
- 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

Audits are performed on a monthly basis. Each audit lasts approximately one day. All NCCC protocols (in-house, cooperative group, and pharmaceutical) are eligible for audit. The Associate Director of the Clinical Research Office (CRO) selects two protocols per month, and from these, randomly selects several patients from each protocol to be audited. The responsible principal investigator and clinical research administrator (CRA) are notified at least three weeks in advance of the audit, and are asked to supply all research records and patient medical records for the audit.

The audits are carried out by the Associate Director of the CRO and the Quality Assurance Coordinator of the CRO. Audit format follows the NCI guidelines for national cooperative group audits. Following intensive review of the research and medical records, a formal written report of the audit findings is also sent to the principal investigator, CRA, and the NCCC Safety and Data Monitoring Committee.

At the request of the NCCC Safety and Data Monitoring Committee, targeted audits may also be carried out when there is specific concern regarding patient safety or data integrity. For targeted audits, all patient records are typically reviewed for the study in question, rather than a sampling.

Interrelationship of Safety and Data Monitoring Activities within NCCC

A diagram showing the relationships between committees involved in safety and data monitoring activities appears as Appendix V. Reporting responsibilities between the various groups are as follows:

- The CCRC reports to the Dartmouth IRB, which is known as the Committee for the Protection of Human Subjects (CPHS). Minutes from the CCRC are sent to the CPHS. In addition, if the CCRC notes any potential issues regarding the ethical treatment of human subjects, it notifies the IRB in writing of the concerns.

- The SDMC reports to the CCRC. On a twice-annual basis, a summary table of SDMC actions is reviewed at a meeting of the CCRC. This summary table includes information on approvals, suspensions, and closures of studies, and the dates and reasons for these actions.

- Written reports containing the results of monthly internal audits are submitted to the SDMC, and are reviewed by the full SDMC at its quarterly meetings.

Adverse Event Reporting

Adverse event (AE) reporting is conducted in accordance with guidelines for Expedited Reporting for Phase I and Phase II studies, as published in the NCI Investigator Handbook (http://ctep.info.nih.gov/handbook/handbook/HandBookIEPF.htm). In addition, 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. Finally, all unexpected and severe AEs are reported to the Dartmouth Committee for the Protection of Human Subjects (the Dartmouth IRB) within 24 hours of occurrence. The SDMC and IRB are empowered to immediately suspend accrual until concerns related to the AE are addressed. They are also empowered to close a study immediately due to an unacceptable level of risk to the study subjects. A flow diagram of serious adverse event reporting appears as Appendix III.

- Adverse events are reported to the SDMC in the quarterly report.
- Serious adverse events are reported to all the following:
    - CRO
    - SDMC
    - IRB
- Serious adverse events are also reported to one or more of the following as required:
    - If the NCI holds the IND the NCI Guidelines for Expedited Adverse Event Reporting Requirements for NCI Investigational Agents are followed as published in the NCI Investigator Handbook (http://ctep.info.nih.gov/handbook/handbook/HandBookIEPF.htm)
    - If NCI is not IND holder the controlling regulations followed are those of the Food and Drug Administration (21 CFR, Part 312.32; Expedited

Safety Reporting Requirements for Human Drug and Biological Products), (http://www.fda.gov/cder/aers/fr07oc97.htm)
  - FDA if commercially available agents/devices (no IND involved), reported through FDA Medwatch (http://www.fda.gov/medwatch/index.html)
  - If trial involves recombinant DNA molecules (gene transfer), in addition to following reporting requirements for investigational agents as above, NIH Guidelines for Research Involving Recombinant DNA Molecules (Gene Transfer) (http://www4.od.nih.gov/oba/guidelines.html) are followed
  - If a post-marketing vaccine trial, in addition to following reporting requirements for investigational agents as above, applicable FDA regulations are followed, (http://www.fda.gov.cbervaers/vaers.htm)
  - If a Phase III multi-center study a central reporting entity collects and reports to all necessary destinations including co-principal investigators at participating institutions

- Individual investigators will define suitable grades for adverse events occurring in trials involving behavioral or nutritional interventions that do not use and investigational agent. These will be reported as required above.

Categories of Trials Monitored and Level of Monitoring

Sponsor: National Institutes of Health

- The following types of ***NCI-sponsored cooperative group trials*** are currently conducted at the NCCC: Cancer and Leukemia Group B (CALGB), Gynecologic Oncology Group (GOG), Radiation Therapy Oncology Group (RTOG), Southwest Oncology Group (SWOG), Pediatric Oncology Group (POG), and Eastern Cooperative Oncology Group (ECOG). Phase I, II and III clinical trials 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 NCCC Safety and Data Monitoring Committee, but they are included in the monthly internal audits conducted by the NCCC Clinical Research Office.

- All ***NCI or CTEP-sponsored phase I or II trials*** must include specific plans for data and safety monitoring using NCI data monitoring systems. Early phase I trials will normally require full and detailed reporting using the Clinical Trials Monitoring System (CTMS) of which, Theradex, Inc, of Princeton, NJ is the contractor. Later phase I trials may be selected for abbreviated reporting via the Clinical Data Update System using reporting of summary data on a quarterly basis. These trials are also monitored on a

quarterly basis by the NCCC Safety and Data Monitoring Committee, and they are included in the monthly internal audits conducted by the NCCC Clinical Research Office.

- ***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 are also monitored on a quarterly basis by the NCCC Safety and Data Monitoring Committee, and they are included in the monthly internal audits conducted by the NCCC Clinical Research Office.

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

- Local, investigator-initiated ***Phase I and Phase II clinical trial protocols*** must include specific plans for data and safety monitoring. The principal investigator is required to continuously monitor Phase I trials and frequently monitor Phase II trials. Quarterly safety and data monitoring reports are submitted to the NCCC SDMC. Adverse events are reported as described in the Adverse Event section. These trials are monitored on a quarterly basis by the NCCC Safety and Data Monitoring Committee, and they are included in the monthly internal audits conducted by the NCCC Clinical Research Office. Therapeutic clinical trials, initiated by an investigator at another institution, to be carried out at a **limited number of institutions** including the NCCC are monitored on a quarterly basis by the NCCC Safety and Data Monitoring Committee, and they are included in the monthly internal audits conducted by the NCCC Clinical Research Office.

Sponsor: 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 CCRC and the Dartmouth Committee for the Protection of Human Subjects (the Dartmouth IRB). 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. The NCCC SDMC will not monitor these trials.

Special Circumstances

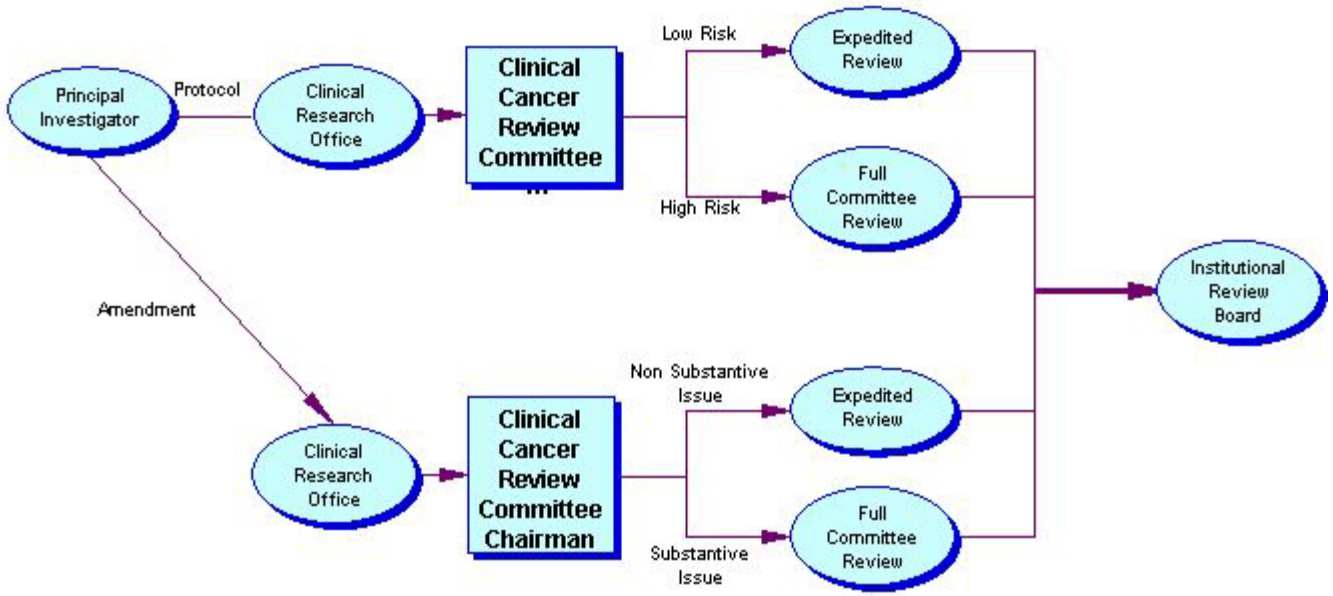
Behavioral and nutritional studies are required to have a DSM plan in place appropriate to the anticipated level of risk involved. Level of review will vary dependent upon whether the investigator anticipates the possibility of early stopping based on emerging differences in either risk or benefit.

NCI's DSM policy covers **NCI career and training awards** that support clinical trials, directly or indirectly. Responsibility for compliance rests with the grant recipient, either the trainee or the training program director. Documentation that the NCCC has an institutional DSM plan that covers all trials supported by the grant will be included in the application submission.

Appendix I

Norris Cotton Cancer Center

Flow Diagram: Protocol and Amendment Reviews



Appendix II

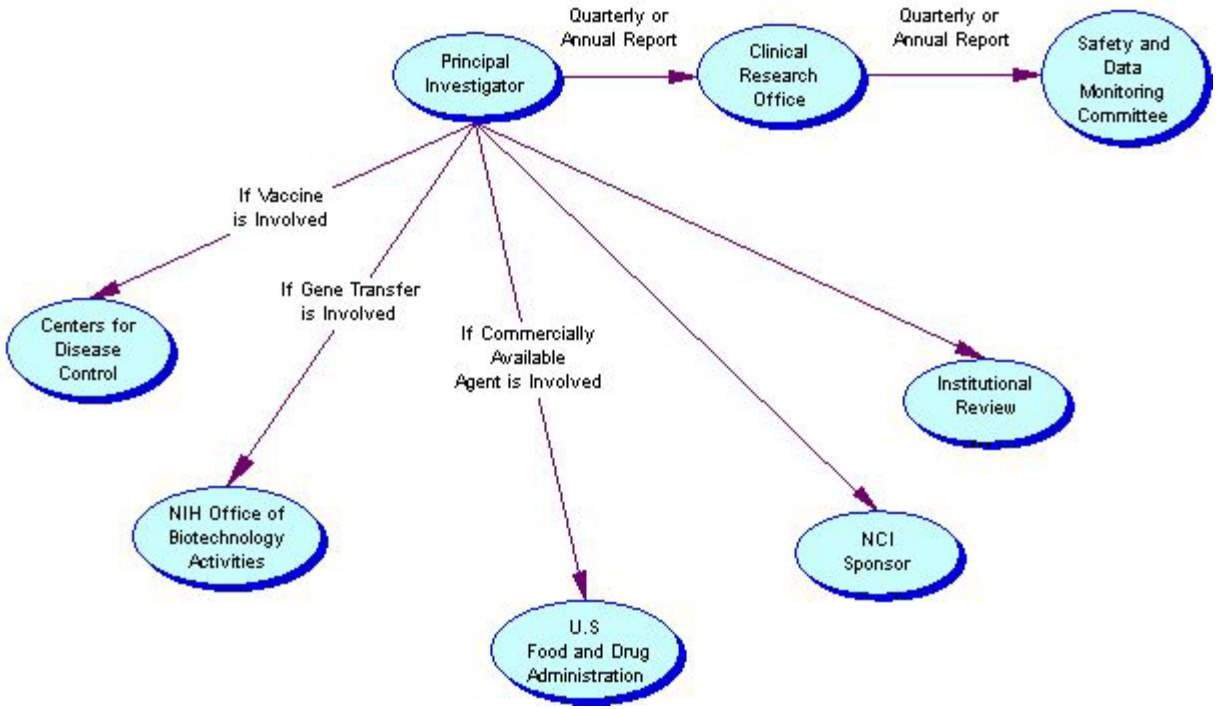
Norris Cotton Cancer Center

Flow Diagram: Safety and Data Monitoring Reports

Appendix III

Norris Cotton Cancer Center

Flow Diagram: Serious Adverse Events Reports



Appendix IV

CCRC Peer Review Checklist

Protocol Title:

Reviewer:__ _____ Date Reviewed:_____

1) Are protocol objectives described?	Yes	No	Comments:
2) Are objectives scientifically sound?	Yes	No	Comments:
3) Are these objectives achievable in the time frame anticipated by the protocol?	Yes	No	Comments:
4) Do the scientific questions addressed have adequate merit to justify experi-mentation involving human subjects?	Yes	No	Comments:
5) Is there a method to investigate this scientific problem without use of human subjects?	Yes	No	Comments:
6) Prior animal or in vitro studies are adequate to support human trials?	Yes	No	Comments:
7) Is the number of patients to be accrued clearly defined?	Yes	No	Comments:
8) Have the potential risks of the study been accurately and fully described?	Yes	No	Comments:
9) Are the study design and statistical input adequate to answer the questions being asked?	Yes	No	Comments:
10) Is there specific indication of what data will be collected?	Yes	No	Comments:

Please attach an additional page with further comments if you wish.

The question of whether there is an adequate patient population available to complete the study in the anticipated time frame will be addressed by the full committee at the next CCRC meeting with input from the Tumor Registry**.**

Appendix V

Norris Cotton Cancer Center
Relationship of Committees with Safety & Data Monitoring Responsibilities