Duke Comprehensive Cancer Center

DCCC Protocol Review and Monitoring System

Scientific Monitoring Subcommittee of the Cancer Protocol Committee

Institutional Clinical Trial Monitoring Procedures and Guidelines

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Table of Contents

Overview

All new cancer-related clinical trial applications proposing to involve Duke subjects (treatment and non-treatment, regardless of sponsorship) must be reviewed and approved by the Cancer Protocol Committee (CPC) of the Duke Cancer Center before they will be granted final approval by the DUHS (Duke University Health System) Institutional Review Board (IRB). These guidelines pertain to the scientific monitoring of clinical trials approved by the Cancer Protocol Committee and IRB. This process is conducted under the Scientific Monitoring Subcommittee of the CPC.

Applicability: It is recognized that clinical trials sponsored by NCI cooperative groups and industry are continually audited for compliance and monitored for progress. Institutional clinical trials without outside sponsorship are not, however, and are the focus of the monitoring system herein described.

Definition of a clinical trial: A clinical trial is herein defined as a prospective study involving human subjects designed to answer specific questions about the effects or impact of particular biomedical or behavioral interventions; these may include drugs, treatments, devices, or behavioral or nutritional strategies. Participants in these trials may be patients with cancer or people without a diagnosis of cancer, but at risk for developing it.

With regard to **diagnostic research** (molecular or imaging diagnostics), a study is considered to be a clinical trial if it uses the information from the diagnostic test in a manner that somehow affects medical decision-making for the study subject. In this way, the information from the diagnostic may have an impact on some aspect of outcome, and assessment of this impact may be a key goal of the trial. By contrast, studies that do not use information from the diagnostic test in any manner that can affect the outcome of study subjects, but whose objective is only the gathering of data on the characteristics of a new diagnostic approach are not clinical trials and are NOT covered by this policy, unless performing the diagnostic test itself imposes some risk on study subjects.

Behavioral clinical trials test interventions aimed at eliminating or reducing human activities associated with enhanced cancer risk, such as tobacco use, poor nutrition, and sun exposure, or eliminating or reducing morbidity associated with cancer screening, diagnosis and treatment.

Definition of an institutional clinical trial. An institutional (sometimes referred to as investigator-initiated) clinical trial is defined for the purposes of these guidelines as a clinical research study authored by a member of the Duke Faculty or staff, not primarily sponsored nor subject to monitoring by an outside agency (e.g. industry, cooperative group, NCI, NIH, other institution). Although an investigator may obtain investigational drugs and/or funding from an outside agency or industry in support of the research, if the clinical trial is not subject to monitoring by that agency it will be categorized as an institutional clinical trial and be internally monitored. Institutional clinical trials which are peer-reviewed by the NCI, but which are not subject to on-site monitoring by the NCI via contract organizations (those clinical trials which obtain investigational drug from NCI) are also internally reviewed through this mechanism.

Monitoring is conducted on all phase I and II therapeutic institutional clinical trials, regardless of support, and its level is determined by the degree of intervention and risk involved.

NIH-supported, large-scale, multi-site phase III therapeutic intervention clinical trials which involve significant risk are outside the scope of this system. Independent Data and Safety Monitoring Boards (DSMBs) for such studies would be established by the principal investigator and supported through the funding agency. NIH-supported phase III clinical trials which involve only low risk (i.e. behavioral and nutritional research) would be reviewed on a case-by-case basis, as their sample size may be too large to be practically monitored by this system. In some cases, these studies would require an independent DSMB.

Scientific Monitoring Subcommittee of the Cancer Protocol Committee (CPC)

1. **Charge.** As an NCI-designated Comprehensive Cancer Center, the Duke Cancer Center wishes to assure that research data generated by Cancer Center investigators are of high quality, reliable and verifiable. To accomplish this objective, the Cancer Center has charged the Scientific Monitoring Subcommittee of the Cancer Protocol Committee with the mission of developing and enacting quality assurance procedures to monitor the overall progress of institutional clinical trials and for ensuring adherence to clinical trial and procedural requirements. This includes review of the overall progress of each study to insure the safety of participants, validity of data, that the projected accrual goals are met on a timely basis, that excess accrual is avoided, that eligibility and evaluability rates do not fall below minimum acceptable standards, that risks are not excessive, and that adverse events are appropriately monitored and reported to the appropriate agencies. Inherent in this process is the goal of enhancing the quality of the research by providing the investigator with constructive criticism.

2. **Membership**. The membership (Appendix I) of the Scientific Monitoring Subcommittee of the CPC is multidisciplinary and shall consist minimally of three physician members and representatives from oncology nursing, oncology data management, oncology regulatory affairs, pharmacy, radiology, and biostatistics. The Recording Secretary of the full committee, the Administrative Director of the Clinical Trials Research Shared Resource (CTRSR), shall serve as secretary to the Scientific Monitoring Subcommittee. The minimum membership shall be five.

   The Chair of the CPC shall appoint the Chair of the Scientific Monitoring Subcommittee. Members of the Scientific Monitoring Subcommittee shall be appointed by the Subcommittee chair in consultation with the CPC chair. The CPC Chair shall serve as Co-Chair of the Subcommittee.

   On-site case reviews are conducted by a monitoring team. The monitoring team is comprised of a core group with additional members selected as appropriate to the area under investigation, size and complexity of the study and level of risk. The core monitoring team consists of the Administrative Director, Clinical Research Manager, Assistant Clinical Research Manager (Senior CRA), the Cancer Center Pharmacist, and the Regulatory Specialist. Cancer Center Physician investigators, Clinical Research

Nurses, and Clinical Research Associates are selected from the Monitoring Board and assigned as needed. If cases from affiliate institutions are being monitored, the team includes the Administrative Director for the Duke Oncology Consortium. The Chair of the Scientific Monitoring Subcommittee periodically attends on-site monitoring reviews with the Team.

Conflict of interest. It is recognized that an institutional monitoring system must utilize its own faculty and research staff members to enable the system to function. Inherent in this type of system is the potential for a conflict of interest to exist. Even members of the core monitoring team may have a relationship, albeit indirect (such as preparation of IRB documents) with the study to be audited. Examples of indirect relationships would include staff members who are involved in the study's IRB reports, drug dispensing, and research laboratory procedures (such as PKs or assays). Direct relationships would include any physician who is a subinvestigator on the study; a radiologist responsible for determining tumor measurements (even though blinded) on the subject patients; CRAs or CRNs involved in study conduct, data management or consenting of patients; a statistician involved in the data analysis for the subject study; and any individual who is supported by the grant supporting the subject study**. No one is allowed to serve on a monitoring team with an indirect or direct relationship, as previously defined, to the subject study.**

3. **Meetings**. The Scientific Monitoring Subcommittee meets monthly on the first Thursday of the month, with meetings scheduled for the same day as the full Committee.

4. **Administrative coordination.** The Administrative Director of the Clinical Trials Research Shared Resource serves as recording secretary to the Subcommittee and is responsible for coordinating all meetings, monitoring visits, monitoring reports, and communications with the IRB. All records of the Subcommittee are maintained in the ccPAO.

Scientific Monitoring Procedures
Administrative Monitoring (all clinical trials)

All cancer-related clinical trials (treatment or non-treatment, regardless of sponsorship) must have the approval of the CPC before the IRB will grant initial approval or approval to renew the study (annually). All clinical trials as herein defined undergo IRB compliance monitoring through this system. Investigators are required to register centrally all subjects enrolled on cancer-related clinical trials with the Cancer Center Clinical Trials Administration Office (ccPAO). The central registry maintained there is a mainframe system (ProTRAK) built and supported by the Cancer Center Information Systems. This system enables IRB compliance monitoring as follows:

Initial and continuing IRB compliance: To ensure that subjects are not enrolled on studies prior to final IRB approval, a checkpoint is built into ProTRAK which rejects registrations of subjects if the date of final IRB approval has not been encoded or has lapsed. If an attempt is made to register a subject before evidence of final IRB approval exists, it sets into motion a system of checks and balances that enact appropriate notifications to the PI and the IRB.

At the time of annual renewal of the clinical trial, the renewal application is submitted to the ccPAO. At that time, the subject accrual data reported in the renewal application are verified against the subject registration data in the database. Approval of the renewal application is not granted until the data are made consistent.

The subject registration process is also verified at the time the on-site monitoring reviews of institutional clinical trials are conducted. If subjects have been enrolled on the subject study and not registered centrally with the ccPAO, this is considered a major deficiency.

Institutional (Investigator-initiated) Clinical Trial Monitoring

Scientific progress and accrual: All institutional clinical trials are monitored yearly for scientific progress, accrual, and IRB compliance. The first page of the Institutional Clinical Trial Monitoring form (Appendix IIIa) is completed on each study being reviewed for scientific progress. IRB compliance is reviewed and summarized and accrual is reported. These reports are then reviewed at the next meeting of the Scientific Monitoring Subcommittee for any necessary actions.

The Scientific Monitoring Subcommittee reviews each study on an individual basis. In evolving to the present model, it has been learned that each institutional clinical trial may represent a unique set of factors affecting activation and accrual. Guidelines have been developed to assist the Scientific Monitoring Subcommittee in its actions, but it regards this process as a dynamic, constructive one, rather than punitive, designed to make investigators aware that if accrual is slow or nil, certain measures can be taken to overcome this. Taken into consideration are such factors as phase of study, rarity of the disease under clinical trial study or the collective eligibility criteria, and delays in activation (activation may be delayed for justifiable reasons such as FDA cross-filing, contractual matters, obtaining investigational drugs from sponsors, NIH review, NIH funding). All of these factors are taken into account in making a recommendation.

To assist the Scientific Monitoring Subcommittee in its decisions, at the time institutional clinical trials are initially reviewed by the CPC, their statistical sections are reviewed to ensure that an accrual rate forecast relative to the characteristics of the study participants and estimated duration of the study is stated (See Clinical trial Review Forms, Appendices IIa and IIb). If this is not stated, it becomes a required modification.

It is also noted at the time if the study is multi-center. All subjects participating in the study, including non-Duke subjects, must be registered centrally with the ccPAO to enable the Scientific Monitoring Subcommittee to judge the aggregate accrual and stopping rules for the study. If this is not stated in the clinical trial, the investigator is asked to insert it. At the time on-site subject monitoring is conducted, if no subjects have been registered from other centers, the status of this is specifically addressed to ensure that this is being captured. The general principles followed by the Scientific Monitoring Subcommittee in its recommendations regarding scientific progress and accrual are as follows:

1. **Underaccrual**. At the end of the first year following activation, accrual to the study is reviewed by the Scientific Monitoring Subcommittee. Based on the principal

investigator's accrual forecast, if there is less than 25% of the accrual projected, a letter to the investigator would call attention to the original projection and remind the investigator that the accrual is being monitored in fulfillment of the Scientific Monitoring Subcommittee's NCI/NIH commitment. Accrual and scientific progress are reviewed yearly thereafter and if accrual continues to lag behind the predicted rate, the study is placed on probation unless there are extenuating circumstances and the investigator is asked to justify continuing the study. These responses are taken into consideration on an individual basis. If no accrual has taken place after 2-3 years, termination of the study is recommended.

It is emphasized that each study is treated on an individual basis. If it is learned that study activation is delayed due to delays in awards or FDA filing, for example, extensions are granted. Letters to investigators are intended to alert them to low accrual situations and offer constructive suggestions as to how to improve accrual. These might include altering the design or eligibility criteria, seeking extramural funding, activating the study at affiliate centers or through the outreach network, etc.

The Scientific Monitoring Subcommittee regards a situation of zero accrual as a potentially fatally-flawed study. In this situation, the above rules may be adjusted and a recommendation for closure made at year two.

2. **Stopping rules**. At the time of annual review, any early stopping rules for toxicity or response analysis described in the statistical section of the clinical trial are also reviewed to determine if a data review point has been reached. The investigator is asked to provide the Scientific Monitoring Subcommittee with an update on the status if accrual has reached that point. This is also scrutinized during on-site reviews.

3. **Overaccrual.** Overaccrual within the range of 10-15% is not regarded as a serious deficiency. However, beyond that, actions will be geared in accord with the level of over-accrual.

Level of Monitoring

Determination of level of monitoring: At the time of initial review of the institutional clinical trial by the Cancer Protocol Committee, a determination of the degree of monitoring is made commensurate with the phase, endpoints, level of intervention, degree of risk, size (single site vs. multiple sites) and complexity of the trial (Appendix II). At the time of initial review, the clinical trial is reviewed to ensure that the following are adequately addressed:

- Procedures to ensure the safety of subjects in accord with the degree of risk
- Validity and integrity of the data (an adequate biostatistical design must be present and procedures to ensure adequate data capture and how the data will be evaluated)
- Expected duration of the study based on a realistic predicted enrollment rate based on the characteristics of the participants.
- Data management systems that will ensure subjects' eligibility for the trial and data completeness and for multiple-site studies, an operational plan (i.e. eligibility checklist and data collections forms)

- Adverse event reporting (to the Cancer Center, IRB, FDA, NIH, and Office of Biotechnology Activity, as appropriate to the clinical trial, funding agency, and test agent)

If any of the above areas are not adequately addressed, they are made required modifications with approval subject to their inclusion. Clinical trials are not approved by the CPC until the above have been adequately described. Adherence is then verified by the on-site monitoring reviews.

For studies proposing enrollment at multiple sites, the application will be required to state a plan of organization (i.e. if dose escalation is involved, how this will be managed operationally). Investigators will be asked to describe a central reporting entity that will be responsible for preparing timely summary reports of adverse events for distribution among sites and their IRBs. The frequency of the summary reports will depend on the nature of the trials. If it is later observed at the time of on-site monitoring reviews that a trial has evolved from a single site (Duke only) to a multiple site study, the investigator will be asked to provide a description of the operational plan as a condition of the audit.

In determining the level of monitoring, a study is first categorized into one of the following classes:

1) **therapeutic intervention**
2) **non-therapeutic intervention**
3) **non-therapeutic, non-physical intervention**

Therapeutic Intervention studies: These are institutional clinical trials proposing any form of treatment of a cancer-patient population. This includes all primary forms of anti-neoplastic therapy (chemical, biological, internal and external radiation, surgery) and also includes all forms of supportive treatments, prophylactic or otherwise (hematologic growth factor support, anti-infectives, anti-fungals, narcotics, etc).

All treatment studies (phase I and II) undergo on-site case monitoring after the first three patients have been enrolled and treated. This is accomplished functionally by the insertion of an accrual flag into ProTRAK to signal that the time point for monitoring has been reached. **The CPC determines in its initial review of the clinical trial if the minimum level of monitoring (described below) is adequate. If it determines that a more rigorous monitoring plan is required, a plan specific to the clinical trial will be determined and its details conveyed to the principal investigator and IRB at the time of initial review.**

Pivotal to this determination is the phase of the study. For example, since the level of risk is usually significantly higher in Phase I and pilot studies, the level of monitoring is commensurate with this. Reviews would be triggered by accrual based on the anticipated level of risk, but if in their monthly review of adverse events for all institutional clinical trials it became apparent to the subcommittee that toxicity was higher than anticipated, intervening actions would be taken.

If the study contains a primary response endpoint, response evaluations by the investigator will be reviewed on a selected case sample.

The **minimum level** of monitoring for institutional treatment studies is the initial monitoring review (described above) followed by repeat on-site monitoring based on the findings for the initial review. If the review is rated "satisfactory" by the Scientific Monitoring Subcommittee, the study is subsequently reviewed annually for scientific progress and accrual. On-site case-reviews are not routinely repeated. In reviewing these studies annually, the progress report is reviewed and if the Scientific Monitoring Subcommittee notes anything in the annual report that would warrant an on-site review (such as a concerning volume/severity of adverse events), a monitoring visit will be scheduled and a case sample selected at random for review. Subsequent remonitoring would be based on those findings.

Studies are automatically scheduled for re-monitoring if the initial review is rated anything less than satisfactory (marginal, unsatisfactory). Each study and its review findings are judged on a case-by-case basis and follow-up actions are taken in accord with the type and degree of the deviations or violations, and the investigator's response in terms of corrective actions. The norm is to re-review the study after 3-5 additional patients have been enrolled. At that time, if a corrective plan of action has been proposed its impact will be assessed.

2. Non-therapeutic intervention studies: These are clinical trials which do not involve treatment of human subjects, but involve a physical intervention. There may be some degree of invasiveness, but the risk must be significantly less than that imposed in therapeutic trials. Because there is no therapeutic intent, these studies are closely scrutinized since there may be no overt benefit to human subjects from participation. Examples are diagnostic clinical trials as previously defined (radiology, biopsy, endoscopy, phlebotomy), tumor oxygenation studies, normal wound healing, biological sample collection for laboratory correlates (use of discarded tissue is considered in the next category), and radiation treatment planning. Because of their variability, these studies are treated on a case-by-case basis in determining the degree and frequency of monitoring. Essential to this determination is the level of risk imposed weighed against potential benefits.

Non-therapeutic intervention studies are reviewed initially by the Cancer Sciences Subcommittee of the CPC. Similar to the model for therapeutic studies, each new proposal will be assigned a level of monitoring based on the degree of risk, complexity, and nature of the trial at the time it is initially reviewed. Studies in this category may undergo the same minimal level of monitoring as described above for therapeutic studies (initial on-site monitoring after first 3 patients enrolled; remonitoring based on findings). However, If a study involves only minimal risk (e.g. phlebotomy only), no on-site case monitoring would necessarily be done.

3. Non-therapeutic, non-physical intervention studies: Studies in this category involve no physical intervention. Research of this type includes cancer control investigations, quality-of-life inventories, epidemiology research, smoking cessation, cancer risk assessment, and use of excess discarded tissue.

Studies in this category are reviewed annually for scientific progress and IRB compliance. Because this type of research does not involve any physical intervention, no on-site case monitoring is done routinely. It is emphasized that if a study in this category imposes the potential for untoward psychological reactions due the area under investigation or the type of

disease being investigated, or there are factors of a sensitive nature that are felt to require surveillance, the Scientific Monitoring Subcommittee may decide to perform some form of monitoring beyond the annual progress review.

On-Site Case Monitoring Procedures

On-site case monitoring is done in accord with the monitoring plan determined upon initial review of the clinical trial. This plan is enacted through the cancer center database, ProTRAK. An accrual flag is keyed in so that the monitoring coordinator is notified when the required number of cases to prompt monitoring has occurred. This system can accommodate reviews required at any time during the course of the study. If a study is monitored initially after the enrollment of the first 3 subjects and the findings are less than satisfactory, the Scientific Monitoring Subcommittee will determine when to remonitor the study based on the accrual of additional subjects and that flag will be coded into ProTRAK.

Case sample. Once a clinical trial is identified for monitoring, the Monitoring Coordinator will contact cancer center biostatistics, download the subject registration listing, and the required case sample will be selected at random by the cancer center statistical office. Studies active at affiliate centers will have cases from those sites randomly selected.

Notification. The principal investigator and study coordinators of the study being monitored receive written notification that the clinical trial will be monitored (Appendix III) and the cases selected. The Monitoring Coordinator contacts them to arrange a convenient time for the visit by the Monitoring Team. The investigator and the research staff are responsible for gathering all materials germane to the review - medical records, case reports forms, office and research records. If affiliate centers are enrolling subjects, materials needed for the review from the outside centers must be provided to the Monitoring Team. The investigator is advised that the assessment will be based on the materials present at the time.

Monitoring Team visit. Prior to the onsite visit, the Administrative Director reviews the clinical trial and the statistical section and completes the initial part of the monitoring form (Appendix IIIa). The other members of the team also preliminarily review the study prior to the visit. The Administrative Director compares the subject registration log to the statistical section to determine if the study has met a data review point so that this can be addressed at the time of the visit. The investigational pharmacist reviews the adverse event files to determine what has already been filed on the study.

The monitoring team uses the primary medical record as the central document. The primary source documents are checked to ensure that subjects were not treated on clinical trial prior to final IRB approval, informed consent was properly obtained and executed, and pre-therapy requirements, eligibility criteria, treatment delivery, and adverse event reporting are in accordance with the clinical trial. The clinical trial staff is interviewed to ascertain their data management systems and whether subjects are being enrolled off-site (or initially seen at Duke and thereafter being treated offsite), either through a formal affiliation or because of geographical exigencies. If subjects of the Duke Oncology Consortium or DOORS outreach

sites are enrolled, those cases are reviewed at the time Duke subjects are reviewed. The

required materials are obtained from the sites and provided to the Monitoring Team.

Following the on-site visit, the Administrative Director completes the "Summary of Scientific Monitoring Findings" form (Appendix IIIc.) These are distributed, along with any other study summaries provided by the investigator addressing scientific progress, to the Scientific Monitoring Subcommittee. These forms describe IRB compliance, consent, accrual, study endpoints, data management systems, AE reporting, and the findings regarding subject eligibility and treatment delivery. Any areas where there does not appear to be satisfactory compliance are noted.

Scientific Monitoring Subcommittee Ratings and Recommendations

The findings of the monitoring team are reviewed and discussed by the full Scientific Monitoring Subcommittee. The overall rating given a study is a composite of scientific progress, accrual, and the onsite-monitoring findings of the conduct of the study. If a study were found to have no deficiencies in its conduct, for example, but was seriously lagging in accrual or violating its stopping rules, the rating would reflect the latter, and be unsatisfactory or marginal, depending on the level of deficiency in the latter areas. In rating the conduct of the study, the Scientific Monitoring Subcommittee categorizes deviations as "MAJOR" or "MINOR". The Scientific Monitoring Subcommittee exercises reasonable judgment in determining if a deviation should be considered major or minor. **Major deviations** would be those variances from clinical trial-specified criteria or procedures that make the resulting data questionable. Examples of these would be findings that render the subject ineligible, failure to meet regulatory requirements (including failure to document properly obtained informed consent or not obtain properly executed informed consent prior to the start of treatment), failure to comply with IRB approval and/or re-approval guidelines, treatment deviations (substantial alternation or modifications of doses not in agreement with the clinical trial specifications), and poor general data quality. **Minor deviations** would be those that do not affect the outcome or interpretation of the study and are not described above as major deviations. For example, if a hematology value were within a small percentage of variance from the requirement, this would be categorized as a minor deviation. A significant variance from a required measure of cardiac function, such as a MUGA, would be considered major. An unacceptable frequency of minor deviations will be treated as a major deviation.

Verification of adverse drug reaction (ADR) reporting: All new clinical trials are required to contain a description of procedures for adverse event reporting at the time they are reviewed by the CPC. Depending on the type of intervention proposed, the clinical trial must contain a grading system for adverse events (i.e. NCI Common Toxicity Criteria), reference the reporting forms to be used (investigational vs. non-investigational drug reporting), and describe oversight by the investigator for grading and attribution to the study intervention.

Cancer Center investigators are required to report all adverse events to a central review system operated by the Pharmaceutical Research Service. The investigational pharmacist reviews all adverse events in Duke patients and compiles data by compound into a central database. The pharmacist also reviews the AE reports for appropriate reporting to the IRB (serious adverse events and unexpected events). This review also enables consistency of grading to occur.

The investigator is responsible for submission of adverse event reports to the parties and agencies described in the clinical trial (as appropriate to the test agent and trial). These would include the pharmaceutical sponsor, NCI, NIH and/or FDA. Information on reporting requirements is periodically distributed to all clinical investigators.

The investigational pharmacist compiles a monthly summary report to the subcommittee depicting all adverse events that have occurred during the preceding month for Duke (and affiliate) patients enrolled on institutional clinical trials. This report is reviewed by the subcommittee and appropriate actions taken if the volume or severity of adverse events for a particular intervention or compound appears concerning.

During monitoring visits, if serious ADRs are found which have not been appropriately reported, the Scientific Monitoring Subcommittee will evaluate the number and severity of the ADRs and this will be taken into account in the overall rating. A primary intent concerning monitoring ADR reporting is to educate investigators and staff concerning the requirements. The monitoring team includes the ADR pharmacist who at the time of the visit reviews with the staff of the clinical trial the need to send ADR reports to both the IRB and the cancer center at the time of the occurrence.

Review Ratings

The following guidelines are used in determining an overall rating:

1. **Satisfactory.** No major deviations.

2. **Marginal.** One major deviation.

3. **Unsatisfactory.** Two major deviations.

Actions Based on Rating

The Scientific Monitoring Subcommittee determines the overall rating in accordance with the above guidelines, which is conveyed to the investigator by letter. If a study receives a satisfactory rating, it will thereafter be reviewed for scientific progress and accrual annually as long as it is active, but full monitoring is not repeated. Studies rated less than satisfactory are each judged individually and follow-up actions are taken in accordance with the type and degree of the deviations and/or violations. Depending on the nature of the findings and the investigator's response, early re-review will be decided on a case-by-case basis at the discretion of the Scientific Monitoring Subcommittee. For example, if a corrective plan is

proposed by the investigator, this may warrant an early re-review to determine its impact. If the only issue is underaccrual, the recommendation will follow the guidelines described above. If the case review reveals problems with eligibility, a repeat on-site visit would be conducted after a specified number of subjects have been enrolled (usually 3). The Scientific Monitoring Subcommittee may elect to recommend probation, suspension or termination of the clinical trial if the level of unacceptability warrants it.

The investigator also receives a copy of the summary monitoring report. The cover letter, summary report, and investigator's response are copied to the Chairman of the Duke IRB.

Recommendation of Clinical Trial Suspension or Termination

Grounds for recommending suspension or termination of a clinical trial to the IRB include, but are not limited to:

1. Zero accrual for 1-2 years or long-term low accrual.
2. Exceeding the accrual goal by more than 15%.
3. Stopping rule violations.
4. Major violations in the conduct of the study (including serious IRB violations) that result in an unacceptable audit rating.

The decision to recommend suspension or termination of a clinical trial is carefully considered and takes into account whether corrective actions had been requested at previous reviews and were not implemented. If the decision is made to recommend suspension or termination of a clinical trial, the recommendation will be made in a letter to the investigator. A letter will be sent simultaneously recommending suspension or termination of the clinical trial to the Chair of the IRB. The Duke IRB has the ultimate authority to effect termination or suspension of a clinical trial. Any recommendation for temporary or permanent suspension of an NIH-funded clinical trial will be reported by written communication to the NCI grant program director responsible for the grant. The principal investigator is required to report any FDA, IRB or commercial sponsor actions that affect an NCI-funded trial,

Internal and External Reporting of Scientific Monitoring Findings

Internal Reporting: Summary Scientific Monitoring Reports, all correspondence with principal investigators, including the Scientific Monitoring Subcommittee's final recommendations concerning re-review or corrective plans needed, are sent to the Chairman of the Duke Institutional Review Board and the Dean of the Medical School. Any correspondence and recommendations stemming from administrative monitoring findings and accrual review will also be sent to the IRB Chairman.

External Reporting: The Principal Investigator will be required to notify the ccPAO if an NIH award has been made in support of a clinical trial. At that time, the investigator will be asked to identify the appropriate agency head to whom actions of suspension or termination should be directed.