 UNIVERSITY of MARYLAND MARLENE AND STEWART GREENEBAUM CANCER CENTER	Effective Date:	Procedure No: DSM001
Subject: Data & Safety Monitoring Plan	Function: Data & Safety Monitoring	

UMGCC governs clinical research through a parent Clinical Research Oversight Committee (CROC), which oversees the function of the Clinical Research Shared Service, and two under committees: the Data & Safety Monitoring/Quality Assurance Committee (DSM/QAC) and the Clinical Research Committee (CRC). These committees coordinate to oversee the conduct of clinical research at UMGCC. The relationships between and the flow of protocols through these committees are shown in the attached Figures.

This SOP describes the actions and procedures of the Data and Safety Monitoring/Quality Assurance Committee (DSM/QAC).

I. DSM/QAC Scope and Function

The DSM/QAC will ensure patient and research subject safety and integrity of research in clinical trials conducted by the University of Maryland Marlene and Stewart Greenebaum Cancer Center (UMGCC). It is the responsibility of the DSM/QAC to review ongoing clinical studies for patient safety and quality control. The DSM/QAC has the authority to request modifications of the protocol and consent forms to incorporate safety information, to suspend trials pending investigation of toxicity and corrective action of protocol conduct which has led to deviations and exceptions from the intended protocol, and to require additional patients be treated at a current or previous cohort for Phase I studies. The DSM/QAC may refer recommendations to the CRC to permanently close trials in which it is felt that the demonstrated risks outweigh the potential benefits of the study or where the expected trial outcomes cannot be achieved with further patient enrollment. The DSM/QAC can refer protocols for re-review by the Clinical Research Committee in the event that there is a question about the continuing scientific value or methodology that may warrant revisions of the protocol or warrant closure of the protocol for loss of scientific progress or priority. The DSM/QAC has the following functional tasks:

A. Annual and semi-annual review

The DSM/QAC will provide ongoing safety review for UMGCC protocols which lack their own existing DSMB. These protocols include:

- Investigator-initiated protocols except those for which the IRB has granted a waiver of consent (e.g., retrospective chart reviews)
 - NCI-sponsored Phase I and Phase II trials not conducted within the purview of an NCI-sponsored cooperative group, or where the relevant NCI-sponsored cooperative group does not have an appropriate external DSM.
 - Industry-sponsored studies for which an external DSM group is not active.
- Other protocols may be considered for ongoing review at the request of the CRC or the IRB. Review may be conducted more frequently than semi-annually if there is a specific reason and request from the CRC or IRB.

B. Track Adverse Events

- Review Internal and External Serious Adverse Event (SAE) and Adverse Event (AE) experiences on the above designated protocol categories either semi-annually (high-risk studies) or annually (routine or low risk studies) to ensure that potential benefits of continuing research projects exceed potential harm from SAE and AE.
- Review on a monthly basis external SAE and DSM reports submitted to UMGCC investigators by trial sponsors, including reports from independent Data Safety Monitoring Boards for external randomized Phase III trials. For those external SAEs which do not meet UMB IRB criteria for immediate submission, the DSM/QAC will serve as the reviewing entity of record after receipt from the sponsoring organization. A table of such external SAEs for each protocol is available for submission to the IRB with the protocol annual renewal.
- Assess Phase I studies for dose limiting toxicities after each cohort prior to dose escalation

C. Review the results of internal Monitoring of Investigator Initiated Therapeutic Trials

D. Review the results of University of Maryland HRPO audits of UMGCC clinical trials.

DSM/QAC functions are in addition to, not in place of, the IRB, FDA or other sponsor reporting/monitoring that may be required within certain timetables.

II. Definitions and Scope of Responsibilities

A. Clinical Trial

The DSM/QAC follows the IRB's definitions for activities constituting human subjects research (i.e., clinical trial) as provided in the University of Maryland, Baltimore Human Research Protections Program and Institutional Review Board

Policies and Procedures Manual. This manual may be accessed at <https://medschool.umaryland.edu/hrpo>

B. Definition of an Investigator-Initiated Clinical Trial

An *investigator-initiated* (sometimes referred to as *institutional*) clinical trial is defined for the purposes of these guidelines as a clinical research study authored by a member of the UMGCC faculty or staff. Such studies are not primarily sponsored or subject to scientific review or monitoring by an outside agency (e.g., industry, cooperative group, NCI, NIH, FDA, or other institution). An investigator-initiated trial is therapeutic if a drug substance is administered or the intent of the protocol activity is to affect therapeutic decision making. 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 is categorized as an investigator-initiated clinical trial and internally monitored by the DSM/QAC. Those investigator-initiated clinical trials that are peer-reviewed by the NCI, but are not subject to on-site monitoring by the NCI via contract organizations (clinical trials that obtain investigational drugs from NCI) are also internally monitored through this mechanism.

C. Monitoring

Monitoring involves UMGCC Clinical Research Management Office staff or external sponsors scrutinizing the actions of UMGCC investigators without a requirement that the monitor be independent of the study team or sponsor. Monitoring activities at minimum include verifying that research documents (e.g. informed consent, eligibility checklist, case report forms), and the regulatory binder are complete and current, in order that a detailed audit may be conducted. The scope of monitoring activities may be expanded to include examination by Clinical Research Shared Service staff of case report forms and comparison of case report forms with source documentation for Investigator Initiated therapeutic clinical trials at the request of the DSM/QAC or IRB; as indicated by a prior or current record of deficiencies; as a precautionary measure in the case of exceptionally complex studies.

D. Audit

Audit activities by definition involve staff external to UMGCC. UMGCC trials may be audited by various external agencies including the UMB IRB, NCI or its contractors, or the FDA. Audit activities will involve a detailed review of the conduct of the clinical trial, including, but not limited to, subject enrollment, verification of source documentation of eligibility and data collection, review of serious adverse events, review of protocol exceptions and deviations, regulatory documents, drug accountability.

E. Principal Investigator (PI)

The PI is responsible for collecting and reporting adverse events on his/her clinical trials in a timely fashion to the UMB IRB, UMGCC DSM/QAC, FDA, trial sponsors, external IRBs for multi-institutional trials, as well as all other relevant committees and agencies. The PI is also responsible for proposing a DSM plan (Attachment 1) as part of the scientific review by the Clinical Research Committee and IRB submission packages for new trials.

F. Clinical Research Management Office (CRMO)

The CRMO is the physical space housing staff of the Clinical Research Shared Service. It maintains a clinical research database of all protocols open at UMGCC. This database allows for the collection of AEs and SAEs, both internal and external, providing a framework for DSM/QAC review. Further, a senior CRMO staff member coordinates DSM/QAC activities and CRMO staff may be called upon by the DSM/QAC to assist in data collection and auditing.

G. Clinical Research Committee (CRC)

The CRC is responsible for the scientific review of new protocols. Their review is conducted prior to IRB review and includes a consideration of the adequacy of the DSM plan proposed by the PI. The CRC may impose a stricter level of monitoring for “higher-risk” studies (see Attachment 2). The Chair of the CRC will designate the appropriate level in the approval letter to the PI and CRC minutes, and will forward a copy of this designation to the coordinator of the DSM/QAC. The CRC is also responsible for reviewing accrual to all UMGCC trials on at least an annual basis to assure timely recruitment of subjects to trials. The CRC may be asked by the DSM/QAC or the IRB to provide continuing review of protocols about which questions have arisen in relation to the continuing scientific value or importance of the research question of the protocol. The CRC may also be asked by the DSM/QAC or the IRB to review whether, in light of new information received during the prior review period, the protocol in question is still scientifically of high priority.

H. Clinical Research Oversight Committee (CROC)

The CROC oversees both the CRC and the DSM/QAC and is responsible for setting policies and processes for clinical research at UMGCC. The CROC also has the authority to consider disciplinary sanctions against clinical investigators.

I. Data and Safety Monitoring / Quality Assurance Committee (DSM/QAC)

The DSM/QAC will consist of a chair and UMGCC staff representing various disciplines and disease groups, including representation from Medical Oncology/ Hematology, Surgical Oncology, Radiation Oncology, and Clinical Pathology Disease Groups, Nursing, Pharmacy, and Supporting Services (Infectious Diseases,

Biostatistics, Palliative Care, Administration). DSM/QAC activities will be coordinated by a senior member of the UMGCC Clinical Research Management Office. The DSM/QAC will meet monthly and requires a quorum of three members. Members may designate a proxy of comparable expertise to attend in their place. See appendices for membership.

J. University of Maryland School of Medicine Institutional Review Board (UMB or IRB)

The IRB is an administrative body, accredited by the Association for the Accreditation of Human Research Protection Programs, established to protect the rights and welfare of human research subjects recruited to participate in research activities conducted under the auspices of University of Maryland, Baltimore, which includes UMGCC. The IRB has the authority to approve, require modifications in, or disapprove all research activities that fall within its jurisdiction as specified by both the federal regulations and local institutional policy. The IRB makes use of an electronic database system (CICERO) to receive communications regarding protocols under their jurisdiction. The DSM/QAC accepts the IRB definitions of what constitutes SAEs and AEs, currently located in the IRB policies found at <http://medschool.umaryland.edu/orags/hrpo/policies.asp>.

K. Human Research Protections Office (HRPO)

The HRPO is the coordinating office for the UMB IRB. The HRPO will be responsible for providing periodic audits of designated trials.

II. Monitoring and Auditing of UMGCC Clinical Trials

A. Monitoring of UMGCC Clinical Trials

Industry sponsored clinical trials that have their own independent monitoring service, and perform monitoring on a routinely scheduled basis, will not be subject to additional monitoring by the CRMO. Likewise, NCI-sponsored trials that have periodic computerized data submission and independent auditing groups (e.g., Cooperative Groups) will also not be routinely monitored. However, all therapeutic investigator-initiated trials will be subject to monitoring by the UMGCC.

1. Monitoring Procedures

The manager of the CRMO and a designated senior member of the research team together will act as the Monitoring Team Coordinators and will be responsible for coordinating the monitoring of these trials. Designated members of the CRMO will function as monitors for these trials. The Coordinator of the DSM/QAC will be provided with the dates the trials will be monitored. Therapeutic Investigator Initiated

trials which do not have external monitoring will be monitored on an at least an annual basis.

2. Notification

The Principal Investigator and Study Coordinators are notified in advance of a scheduled monitoring session in which subjects have been randomly selected for review by the Monitoring Team Coordinators. The Monitoring Team Coordinator contacts the study team to arrange for a mutually agreed upon time for the monitoring session. The investigator and the research staff are responsible for gathering all of the materials germane to the review including medical records, case reports forms, and any other research records requested. If affiliate centers are enrolling subjects, materials needed for the review from the outside centers must be provided to the Monitoring Team.

Specific information requested for the monitoring session includes:

- Regulatory Folder, to include copy of most current protocol, amendments, Investigator Brochure, availability of form 1572
- Accrual listings from Oncore/Research Database
- Hospital medical record
- Patient-specific research record, which would include at a minimum the eligibility checklist, data collection forms, copies of serious adverse event reports
- Access to the Investigational Drug Pharmacy to ensure the presence of drug accountability forms specific to the clinical trial

3. Monitoring Session Implementation

The monitoring team will perform quality assurance review on the requested records to ensure compliance for an audit by the HRPO. The monitoring team will complete the checklist (Form Attachment 5), and the findings will be presented at the next DSM/QAC monthly meeting. A letter will be sent from the DSM/QAC to the Principal Investigator summarizing the findings and any recommendations. Any queries to the PI will need to be addressed by the next meeting of the DSM/QAC. Accrual findings will be presented to the CRC.

B. Auditing of UMGCC Clinical Trials

The UMGCC has many trials that are audited by external reviewers, including NCI contractors and industry representatives for data that is to be submitted to the FDA. However, a significant number of in-house trials, e.g. Investigator-Initiated, Phase I, or Phase II, do not have external auditors. In order to assure the proper conduct of the clinical trials under the purview of the DSM/QAC, the UMGCC will submit to periodic audits by the IRB/HRPO. In any given year, the HRPO/IRB will audit the patients accrued during the preceding calendar year on 100% of investigator-initiated

therapeutic trials and approximately 50% of the charts from the preceding calendar year for open and accruing therapeutic trials in the following categories: Phase 2 studies without external data safety monitoring, NCI Phase 1 studies and corporate/industry trials without external data safety monitoring. Members of the DSM/QAC will review the results of the audits.

Standard auditing tools will be used. Specific issues to be examined include:

- The proper maintenance of the regulatory file and database record with all necessary documents on hand, including the original IRB protocol approval, IRB approval of modifications, SAE reports and other regulatory documents
- Demonstration of an adequate consent form process
- Properly dated consent form
- Properly executed consent form, with the appropriate signatures
- No protocol related treatment starting before the date of consent
- PI's attestation document stating that the informed consent has been properly delivered
- Documentation that the protocol-specific therapy was delivered in the specified manner, including doses, schedules and infusion times
- Documentation that appropriate study-related investigations, i.e., laboratory, radiology and study visits, were accomplished
- Verification of responses in those studies where clinical responses are to be noted
- Verification of toxicities where toxicities are an endpoint
- Verification that all SAE's were reported in a timely fashion.

To ensure independence of review, the HRPO/IRB will typically select the trials and charts to be audited, but the DSM/QAC may select up to 10% of the auditing capacity based on the results of its annual and semi-annual reviews. HRPO audit reports will be sent to the DSM/QAC and the HRPO Director of Quality Improvement. If required, audit results will be reported to a fully convened UMB IRB panel. The DSM/QAC has the authority to suspend and ultimately close trials in which adherence to good clinical research practices are lacking. The IRB, if not already so informed, and affiliated sites will be notified of all audit results. PI's at affiliated sites will be notified of audit results as well. The HRPO/IRB will have the discretion to adjust the selection percentages based on accrual or return to studies that have closed to accrual. The HRPO/IRB and/or the DSM/QAC may also audit additional charts/trials pending results of these audits or issues that may arise in relation to a particular trial or investigator.

III. Procedures

A. Types of Reviews and Assignment of Risk

Annual Review (Routine and High Risk)

Phase II and III therapeutic studies shall be designated as at least high risk by the Clinical Research Committee (CRC) (Form Attachments 1 and 2). Chart reviews and other non-therapeutic studies are typically designated by the CRC as routine risk, but may be assigned a higher risk category based on the complexity of the study. Studies designated by the CRC as routine and high risk will be reviewed annually. The DSM/QAC will also have the discretion to review on only an annual basis highest risk studies where the sponsor monitors appropriately and conducts cohort reviews but lacks an independent DSM. More detail on the process is provided in III.B. below.

Semi-Annual Review (Highest Risk)

All Phase I therapeutic trials and at the determination of the CRC investigator-initiated Phase II/III therapeutic studies are designated as highest risk. Studies designated by the Clinical Research Committee (CRC) as highest risk will be reviewed annually for subject accrual by the CRC and by the DSM/QAC for conduct of trial and semi-annually for safety. More detail on the process is provided in III.B. below.

Phase 1/Cohort Review

A member of the DSM/QAC will act as a protocol monitor to review the toxicity experience in all treated patients prior to escalating into the next cohort. It is understood that in some cases with accelerated dose escalation designs, the cohort may be composed of a single patient. Since the DSM/QAC meets monthly, to avoid delay in the study the review of the previous cohort can be done by a member of the DSM/QAC prior to the scheduled meeting with reporting to the full DSM/QAC on these activities. Documentation of this cohort review will be kept in the study file and forwarded to the IRB with the annual report. The PI of a Phase I study must receive explicit approval from the DSM/QAC member before proceeding to the next dose escalation cohort. This cohort escalation review is in addition to the review process described in detail below.

Ad Hoc Review of SAEs and DSM reports

The DSM/QAC will review in real time external SAE and DSM reports submitted to UMGCC investigators by trial sponsors for all protocols, including reports from independent Data and Safety Monitoring Boards for external randomized Phase III trials. More detail is provided in Section III.C. below.

B. Annual and Semi-Annual Review Procedures

To insure that DSM/QAC and IRB oversight of protocols is optimally coordinated, DSM/QAC annual review will be timed for completion prior to the IRB anniversary date. For those studies requiring DSM/QAC review, UMGCC clinical investigators will compile the IRB annual renewal submissions 90 days before IRB annual review in the IRB's software system. The DSM/QAC will assign a committee reviewer who will present their evaluation at the DSM/QAC meeting no later than 60 days prior to the IRB annual review. The DSM/QAC will provide feedback and requests for clarification to the PI no later than 45 days prior to IRB annual review. The PI will complete response to DSM/QAC inquiries no later than 30 days prior to IRB annual review, and the DSM/QAC will review at the meeting approximately 30 days prior to the IRB anniversary date.

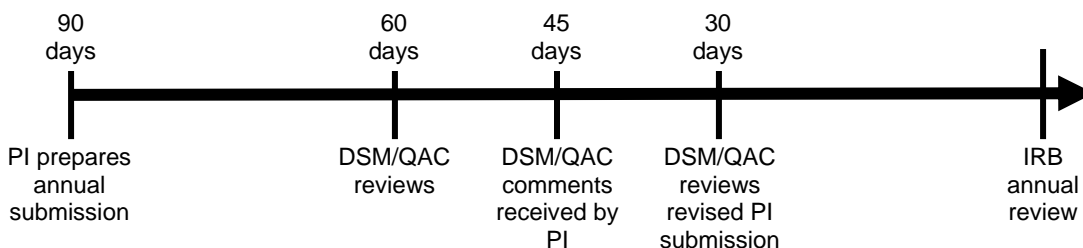


Fig. 3 Timeline for DSM/QAC annual review process

Semi-annual reviews will be conducted on the same timeline to coincide with the IRB annual review date and also six months from same. PIs are expected to attend DSM/QAC meetings where their protocols will be discussed.

The below items will be considered in DSM/QAC annual review and appropriate recommendations made. The semi-annual review will include only those items below related to safety.

- All adverse events, internal and external, including those that have previously been reported to the DSM/QAC. The DSM/QAC will have a full report on all SAE's concerning that clinical trial, including the nature of the SAE, grade, therapeutic agents involved, whether they were reported to all appropriate agencies within the mandated timeframes, and the investigator's assessment of whether the toxicity was study related. The DSM/QAC may recommend to the CRC to close studies with adverse event profiles that deviate in a substantial way from expected patterns of events.
- The consent form to determine whether it needs modification based on the accumulated AEs and SAEs. The DSM/QAC may require amendment of consent forms to reflect new or continuing information.
- The protocol regulatory binder maintained by the CRMO for any relevant items that may not be available electronically. The DSM/QAC may

recommend to the CRC to close studies when the PI or research team show a pattern of persistent non-compliance with Good Clinical Practices policies.

- If available, interim outcomes and other results will be assessed to see if response rates conform to estimates used to develop the statistical analysis. The DSM/QAC may close studies early with poorer than expected response rates that cannot meet stated outcomes targets even if the trial accrued fully. Conversely, response rates significantly greater than expected may lead to early termination of trials to prevent further assignment of patients to the inferior treatment arms in comparative trials.
- Periodic audit results, if available. The DSM/QAC may recommend to the CRC to close studies when the PI or research team show a pattern of persistent non-compliance with Good Clinical Practices policies.

Upon conclusion of review, the DSM/QAC will make one of four possible final decisions regarding the disposition of the protocol:

- Award final DSM/QAC approval to the protocol
- Find that minor revisions are still needed for final DSMB approval
- Find that major corrections are still needed to the protocol
- Recommend to the CRC to close the protocol for uncorrectable deficiencies

Additionally, the DSM/QAC may refer for scientific re-review by the CRC those protocols in which new information may have called into question the original hypothesis underlying a particular study.

DSM/QAC actions will be approved by majority committee member vote. Members with conflicts of interest will not serve as reviewers for protocols for which they are conflicted and will recuse themselves from voting on such studies. DSM/QAC review information will be added to the IRB's electronic database record, and the IRB will only conduct annual review for those protocols that have completed or are undergoing DSM/QAC review.

The record of DSM/QAC actions for a particular UMGCC protocol will consist of:

- Chair notes documenting initial DSM/QAC review, discussions, decision of the DSM/QAC, and specific corrective actions requested from the PI
- DSM/QAC correspondence with the PI
- PI responses to DSM/QAC inquiries
- Subsequent DSM/QAC review including final decision by the DSM/QAC

Chair notes will consist of findings of the DSM/QAC reviewer, decisions by the DSM/QAC and specific issues requiring remediation. The PI will be sent a letter specifying the actions to be taken and the acceptable turnaround time for response. PI responses will be reviewed at the next DSM/QAC meeting. The PI will then be provided with a final DSM/QAC review. Records of these reviews will be made available to the IRB. (See Form Attachments 3-4)

C. Ad Hoc Reviews of SAEs and DSM reports

The DSM/QAC will review in real time external SAE and DSM reports submitted to UMGCC investigators by trial sponsors, including reports from independent Data Safety Monitoring Boards for external randomized Phase III trials. This does not supplant the PIs responsibility to report directly to the IRB in established timelines all internal SAEs and those external SAEs that present serious risk of harm to patients.

External SAEs will be captured in the Oncore® database maintained by the CRMO as per Figure 2. Designated DSM/QAC members will review these reports no less than every four weeks and review the following determinations:

- Related or unrelated to the study therapy
- Seriousness
- Expected or unexpected
- Requires IRB submission immediately or with annual report

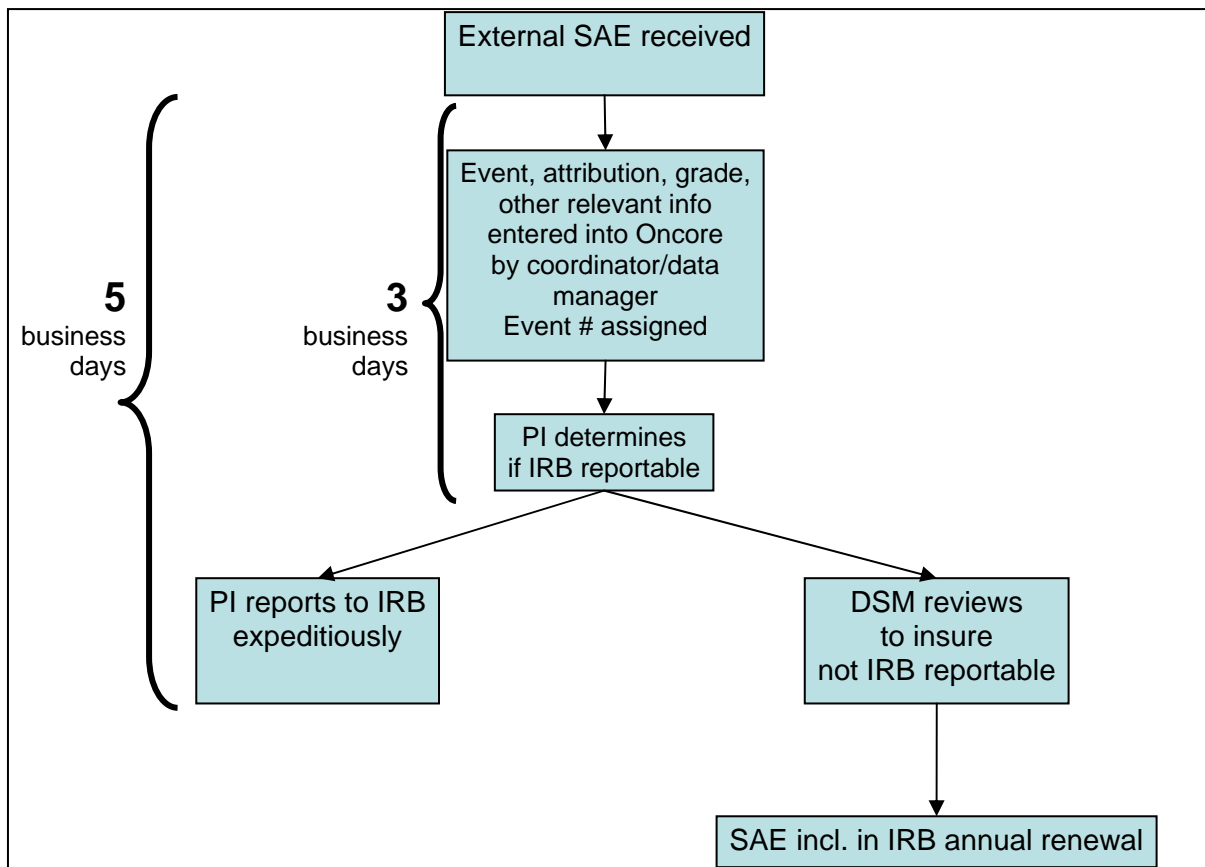


Fig 4. Flowchart for review of external SAEs

All of these decisions will be captured in the database record for the protocol, along with relevant reporting dates. For those external SAEs which do not meet UMB IRB criteria for immediate submission, the DSM/QAC will serve as the reviewing entity of record after receipt from the sponsoring organization. Summaries of these SAE reviews will be presented at the next DSM/QAC meeting.

The CRMO research database has the capability to send out email alerts if the number/severity/expectedness of SAEs in a certain time period reaches a specified level which may be indicative of a troubling pattern of SAEs. When the DSM/QAC members receive such an alert, they will review the protocol on an ad hoc basis to determine if further action is needed.

IV. DSM/QAC Meetings

DSM/QAC agendas for the monthly meetings will be maintained by the DSM/QAC coordinator. This individual will maintain, with the assistance of the research database, lists of all protocols that are subject to semi-annual and annual review, all protocols for which the DSM/QAC serves as the DSMB, and all Phase I trials which will require dose escalation approval. Protocols will remain subject to their DSM plan until all enrolled patients are beyond the time period when study-related adverse events would likely be seen. Under some circumstances, the DSM/QAC may still review protocols for certain IRB, GCP, and data integrity issues. The coordinator will make sure that all protocols from each of the above categories are added to DSM/QAC agendas at the appropriate time points. The coordinator will also schedule follow-up discussion of PI responses to protocols reviewed at prior meetings. The coordinator will also print for review at each meeting the summary reports of the external SAEs that have been assessed in the intervals between meetings.

Minutes of the DSM/QAC meetings will consist of a record of attendance, the chair notes for each of the protocols reviewed, DSM/QAC reviewer summaries of protocol reviews, letters to the PIs, and PI responses received for studies reviewed at earlier meetings, and chair documentation of any other issues discussed (see Attachments 3 and 4).

Decision to Suspend or Make Recommendation to Close

Should the DSM/QAC exercise its authority to suspend or make a recommendation to the CRC to close a trial under any of the above review mechanisms, the DSM/QAC will promptly notify the IRB of this decision. The DSM/QAC will require that the PI notify the sponsor, collaborators, grant program director if applicable, any and all appropriate governmental agencies (i.e. FDA, NCI), and any other appropriate party. The PI will provide the DSM/QAC with copies of all such notifications. If the trial is suspended or closed by any other party, the PI is expected to promptly provide the DSM/QAC with copies of the suspension or closure, and documentation that

appropriate parties have been notified. The CRMO research database is configured such that a trial that is suspended or closed by the DSM/QAC is unavailable for further patient registration. While the PI is responsible for primary notification to appropriate treating physicians and nurses about protocol closure, the research database provides a secondary notification system.

V. Types of Trials and Adverse Event Reporting

The requirements for adverse event reporting for clinical trials are complex. DSM/QAC review of protocols will include checking whether AE and SAE reports have been properly reported to the sponsor, the IRB, the FDA if applicable, co-investigators at participating institutions, and any applicable government agencies. The CRMO research database has specific capacity to record the reporting dates of adverse events for tracking purposes (Fig. 3). Research staff for protocols will be expected to avail themselves of this capacity unless they can provide alternate adequate documentation of adverse event reporting, as perhaps in the case of multi-institutional studies that may have other established systems. If the trial involves federal or other grant funding, the PI will be responsible for summarizing adverse events in grant progress reports as per the requirements of the funding agency. More specific guidelines for the various types of trials expected to be undertaken at UMGCC are described below.

Subject SAE		MRN: 1234567		Name: Jones, JJ	
Event Date (MM/DD/YYYY)	08/21/2005	Reported Date (MM/DD/YYYY)		Reported By	
Death Date		Death Occurred		Did the SAE occur at your site or at a site for which the PI is responsible?	
Intervention					
Treating Physician Comments					
PI Comments					
Protocol Attribution		Outcome		Consent Form Change Required	
SAE Classification		No information entered			
Toxicity		No information entered			
Tracking Details					
		Action	Action Date		
		Notified SAE Coordinator			
		Notified Sponsor			
		Notified DSMC			
		Notified Protocol Coordinator			
		Notified Test Communication			
		Notified IRB			
		Team Reviewed			

SAE Report | Back

Fig 5. CRMO research database has the ability to record notification dates of SAEs to appropriate agencies.

The DSM/QAC has the authority to temporarily suspend or make a recommendation to the CRC to permanently close trials if review indicates that investigators or research staff are failing to follow adverse event reporting guidelines for the trial. Investigators or research staff who have a consistent history of problems with meeting reporting guidelines will be referred to the CROC for potential disciplinary action.

A. Phase I Trials (Highest Risk)

UMGCC conducts Phase I trials both with NCI-sponsored and industry-sponsored agents.

As described above, UMGCC regards these Phase I trials as highest risk studies, so in addition to NCI- or sponsor-mandated reporting and review, UMGCC also requires local continuous monitoring of patient safety.

All NCI Phase I studies go through detailed audits by NCI’s clinical trials monitoring system using private contractors. Data are submitted to the appropriate NCI clinical trials monitoring system using standardized forms. It is an NCI requirement that any serious, unexpected adverse event possibly related to the study drug be reported immediately via an adverse event expedited reporting system. Details of this process are available at <http://ctep.info.nih.gov>.

Industry-sponsored studies in most cases have external safety monitoring boards. Where this is not the case, the investigator can request that the DSM/QAC serve as the safety monitoring committee of record provided that the sponsor agrees to make the group aware of external site SAEs.

Irrespective of sponsor, for all agents UMGCC adopts NCI’s guidelines for determining reporting requirements to the IRB (see table below). UMGCC will also report to NCI or other sponsor as per their specific requirements.

Phase 1 Trials								
	Grade 1	Grade 2	Grade 2	Grade 3		Grade 3		Grades 4 & 5 ²
	Unexpected and Expected	Unexpected	Expected	Unexpected with Hospitalization	Unexpected without Hospitalization	Expected with Hospitalization	Expected without Hospitalization	Unexpected and Expected
Unrelated Unlikely	Not Required	Not Required	Not Required	10 Calendar Days	Not Required	10 Calendar Days	Not Required	24-Hour; 5 Calendar Days
Possible Probable Definite	Not Required	10 Calendar Days	Not Required	24-Hour; 5 Calendar Days	24-Hour; 5 Calendar Days	10 Calendar Days	Not Required	24-Hour; 5 Calendar Days
All deaths on study require both routine and expedited reporting regardless of causality. Attribution to treatment or other cause must be provided.								
Any medical event equivalent to CTCAE grade 3, 4, or 5 that precipitates hospitalization (or prolongation of existing hospitalization) must be reported regardless of attribution and designation as expected or unexpected with the exception of any events identified as protocol-specific expedited adverse event reporting exclusions.								
Any event that results in persistent or significant disabilities/incapacities, congenital anomalies, or birth defects must be reported								
Adverse events of Grade 3 with hospitalization or prolongation of hospitalization, Grade 4 unexpected or any Grade 5 with attribution of possible, probable or definite that occur greater than 30 days after the last dose of treatment must also be reported.								

B. Phase II Trials – UMGCC

Phase II trials constitute the most common investigator-initiated trials at the UMGCC. In addition, UMGCC investigators participate in industry or NCI sponsored Phase II studies, in some cases as a lead Institution, and in other cases as a partner with Institutions holding a NCI-funded Phase II contract. Both investigator initiated and NCI-sponsored Phase II trials will be subject to at least annual review by the DSM/QAC. Industry-sponsored Phase II trials lacking an independent DSM will also be reviewed by the DSM/QAC. In-house Phase II trials will receive the level of oversight appropriate to the risk involved in the trial (i.e., high, highest, etc.) as assigned by the CRC.

Irrespective of sponsor, for all agents UMGCC adopts NCI's guidelines for determining reporting requirements to the IRB (see table below). UMGCC will also report to NCI or other sponsor as per their specific requirements.

Phase 2 and 3 Trials									
	Grade 1	Grade 2	Grade 2	Grade 3		Grade 3		Grades 4 & 5 ²	Grades 4 & 5 ²
	Unexpected and Expected	Unexpected	Expected	Unexpected with Hospitalization	without Hospitalization	Expected with Hospitalization	without Hospitalization	Unexpected	Expected
Unrelated Unlikely	Not Required	Not Required	Not Required	10 Calendar Days	Not Required	10 Calendar Days	Not Required	10 Calendar Days	10 Calendar Days
Possible Probable Definite	Not Required	10 Calendar Days	Not Required	10 Calendar Days	10 Calendar Days	10 Calendar Days	Not Required	24-Hour; 5 Calendar Days	10 Calendar Days
All deaths on study require both routine and expedited reporting regardless of causality. Attribution to treatment or other cause must be provided.									
Any medical event equivalent to CTCAE grade 3, 4, or 5 that precipitates hospitalization (or prolongation of existing hospitalization) must be reported regardless of attribution and designation as expected or unexpected with the exception of any events identified as protocol-specific expedited adverse event reporting exclusions.									
Any event that results in persistent or significant disabilities/incapacities, congenital anomalies, or birth defects must be reported									
Adverse events of Grade 3 with hospitalization or prolongation of hospitalization, Grade 4 unexpected or any Grade 5 with attribution of possible, probable or definite that occur greater than 30 days after the last dose of treatment must also be reported.									

C. Phase III Trials

Large randomized Phase III trials are the least common clinical trials at the UMGCC. Most of our Phase III efforts involve participation in multi-center trials, either pharmaceutical-sponsored or cooperative group-sponsored. These sponsored studies must have an independent DSM plan in place before the CRC will approve it. Should

UMGCC investigators participate in multi-site, non-sponsored trials coordinated by an outside institution, it will be the responsibility of the outside institution to provide a DSM plan and monitoring board, if appropriate. If the UMGCC is the coordinating center of a Phase III study, the DSM plan will require a Data and Safety Monitoring Board (DSMB) with appropriate qualifications. In accordance with published guidelines, the DSMB will be composed of at least three clinicians and a clinical biostatistician with relevant expertise. The DSMB will be appointed by the DSM/QAC. No member of the DSMB will be associated with the trial.

All blinded trials will require a randomization schema and specific criteria for unmasking any blinding. The individual protocol must specify the frequency of the DSMB meeting, list the data elements to be provided to the DSMB and list prospective members of the independent DSMB, along with their affiliations with any commercial interests which might constitute a conflict of interest.

Irrespective of sponsor, adverse event reporting to the IRB will follow the guidelines above for Phase II and III trials. UMGCC will also report to NCI or other sponsor as per their specific requirements. The DSM/QAC will review external SAE reports forwarded by the central IRB, NCI, other participating institutions, and study sponsor (if any) to the UMGCC PI. SAE's impacting UMGCC participation will be forwarded to the UMB IRB.

D. NCI-Sponsored Cooperative Group Studies (External)

The UMGCC is a member of the Cancer and Leukemia Group B (CALGB), Gynecologic Oncology Group (GOG), Radiation Therapy Oncology Group (RTOG), Children's Oncology Group (COG) and American College of Surgeons Oncology Group (ACOSOG). It may participate in occasional studies from other cooperative groups. Each of these groups develops peer-reviewed Phase I, II, or III trials, which include detailed DSM plans. Data management is handled through the standardized reporting forms and reported centrally. Adverse event reporting is handled as per the specific instructions from the cooperative group.

E. Multi-Institutional Cooperative Trials

Multi-institutional trials may or may not have industry sponsors. These trials, whether coordinated at UMGCC or at another affiliated research sites, will receive the level of oversight appropriate to the risk involved in the trial (i.e., routine, high, highest, etc.). NCI has specific guidelines for the conduct of multi-institutional trials using NCI-sponsored agents. UMGCC will follow these guidelines for multi-institutional trials sponsored by NCI or sponsored by any other entity which does not provide acceptable alternate coordination guidelines.

- The Protocol Chair is responsible for the overall conduct of the study at all participating institutions and for monitoring its progress. All reporting requirements are the responsibility of the Protocol Chair.

- The Protocol Chair is responsible for the timely review of Adverse Events (AE) to assure safety of the patients.
- Where UMGCC is the Coordinating Center, it will maintain documentation of AE reports. There are two options for AE reporting: (1) participating institutions may report directly to CTEP with a copy to the Coordinating Center (this option only available for NCI-sponsored trials), or (2) participating institutions report to UMGCC who in turn reports to the sponsor. The CRMO research database will be used to collect all AEs for the protocol.
- Audits may be accomplished in one of two ways: (1) source documents and research records for selected patients are brought from participating sites to the Coordinating Center for audit, or (2) selected patient records may be audited on-site at participating sites. If the NCI or another sponsor chooses to have an audit at the Coordinating Center, then the Coordinating Center is responsible for having all source documents, research records, all IRB approval documents, NCI Drug Accountability Record forms, patient registration lists, response assessments scans, x-rays, etc. available for the audit.
- The protocol will include the following minimum information:
 - The title page must include the name and address of each participating institution and the name, telephone number and e-mail address of the responsible investigator at each participating institution.
 - UMGCC as the Coordinating Center must be designated on the title page.
 - Central registration of patients is required. The CRMO research database is equipped to maintain these records. The procedures for registration will be stated in the protocol.
 - Data collection forms will be of a common format. Sample forms should be submitted with the protocol. The frequency and timing of data submission forms to the Coordinating Center will be specified.
 - Describe how AEs will be reported from the participating institutions
 - Describe how Safety Reports and Action Letters from NCI CTEP or any other sponsor will be distributed to participating institutions.

F. Gene Transfer Trials

Adverse event reporting for studies involving recombinant DNA-containing products will follow *NIH Guidelines for Research Involving Recombinant DNA Molecules* in addition to any other applicable federal, state, institutional or sponsor guidelines for adverse event reporting for the trial. Briefly, any serious adverse event that is both unexpected and associated with the use of the gene transfer product (i.e., there is reasonable possibility that the event may have been caused by the use of the product; investigators will not await definitive proof of association before reporting such events) will be clearly labeled as a “Safety Report” and submitted to the NIH Office of Biotechnology Activities (NIH OBA) and to the local Institutional Biosafety Committee. Any serious adverse event that is fatal or life-threatening, that is unexpected, and associated with the use of the gene transfer product will be reported to the NIH OBA as soon as possible, but not later than 7 calendar days after the initial

receipt of the information (i.e., at the same time the event must be reported to the FDA). Serious adverse events that are unexpected and associated with the use of the gene transfer product, but are not fatal or life-threatening, will be reported to the NIH OBA as soon as possible, but not later than 15 calendar days after the initial receipt of the information (i.e., at the same time the event must be reported to the FDA).

VII. Conflict of Interest Policies

The DSM/QAC will follow the conflict of interest policies set out by the UMSOM IRB, which has the responsibility for monitoring conflict of interest. These policies are completely described at <http://medschool.umaryland.edu/orags/hrpo/policies.asp>. Briefly however, all investigators, including those operating or employed outside of UMB, and their study personnel must disclose in advance all outside activities and economic interests that might be or have the appearance of being conflicts of interest as described above to the UMB IRB. An economic disclosure form is provided by the IRB for easy reporting. If a conflict of interest occurs after the research study has commenced, the investigator must promptly notify the IRB in writing. A disclosure shall be sufficiently detailed and timely as to allow accurate and objective evaluation prior to making commitments or initiating activities that represent potential conflict situations. The information must be accurate and not known by the Investigator to be false, erroneous, misleading, or incomplete. Each individual has an obligation to cooperate fully with the IRB and the appointed Conflict of Interest (COI) Officer in the review of the pertinent facts and circumstances regarding any conflict of interest disclosed.

The IRB will determine whether the disclosed economic interest is likely to compromise or appear to compromise the design, conduct or reporting of the study. Specifically, the IRB will consider the impact of the economic interest on:

1. Study design;
2. Protocol;
3. Informed consent form (particularly representations of risks and benefits);
4. Data collection and reporting;
5. Eligibility determinations and application of inclusion and exclusion criteria;
6. Continuing consent;
7. Protecting the privacy interests of participants and maintaining the confidentiality of identifiable data;
8. Clinical determinations (e.g., dose modifications, removing patients from study, related care);
9. Determination and reporting of adverse events and their relationship with study mechanism for data and safety monitoring;
10. Data made available on continuing review (integrity and sufficiency);
11. Consequences from conflict affecting clinician researcher's clinical duties to participant as patient.

After a thorough review has been conducted by the IRB and input has been provided by the COI Officer as applicable, the IRB may disapprove research that involves a conflict of interest or it may require changes at the Investigator's or sponsor's expense to eliminate or manage the conflict. Required actions include, but are not limited to:

1. Requiring divestiture or termination of relevant economic interest;
2. Requiring Investigator recusal from a study;
3. Modification in participation in all, or a portion, of the research funded;
4. In case of equity, imposing a bar on insider trading, or requiring the transfer of securities to an independent financial manager or blind trust, or limiting the timing of sales or distributions;
5. Monitoring of research (i.e., independent review of data and other retrospective reviews for bias, objectivity, comprehensiveness of reporting versus withholding data);
6. Requiring independent clinical review of appropriateness of clinical care given to research participants;
7. Monitoring the consent process;
8. Requiring disclosure to institutional committees, research participants, journals, and data safety monitoring boards.

The DSM/QAC will follow any recommendations from the IRB with respect to conflict of interest and will reserve the right to impose even more stringent conflict management. It will assure that no reviews or audits are conducted by individuals with conflicts. The DSM/QAC will further assure that, even where no economic conflict exists, studies will not be monitored or reviewed by individuals who may have significant scientific interest in the outcome.

Figure 1

Committee Organization

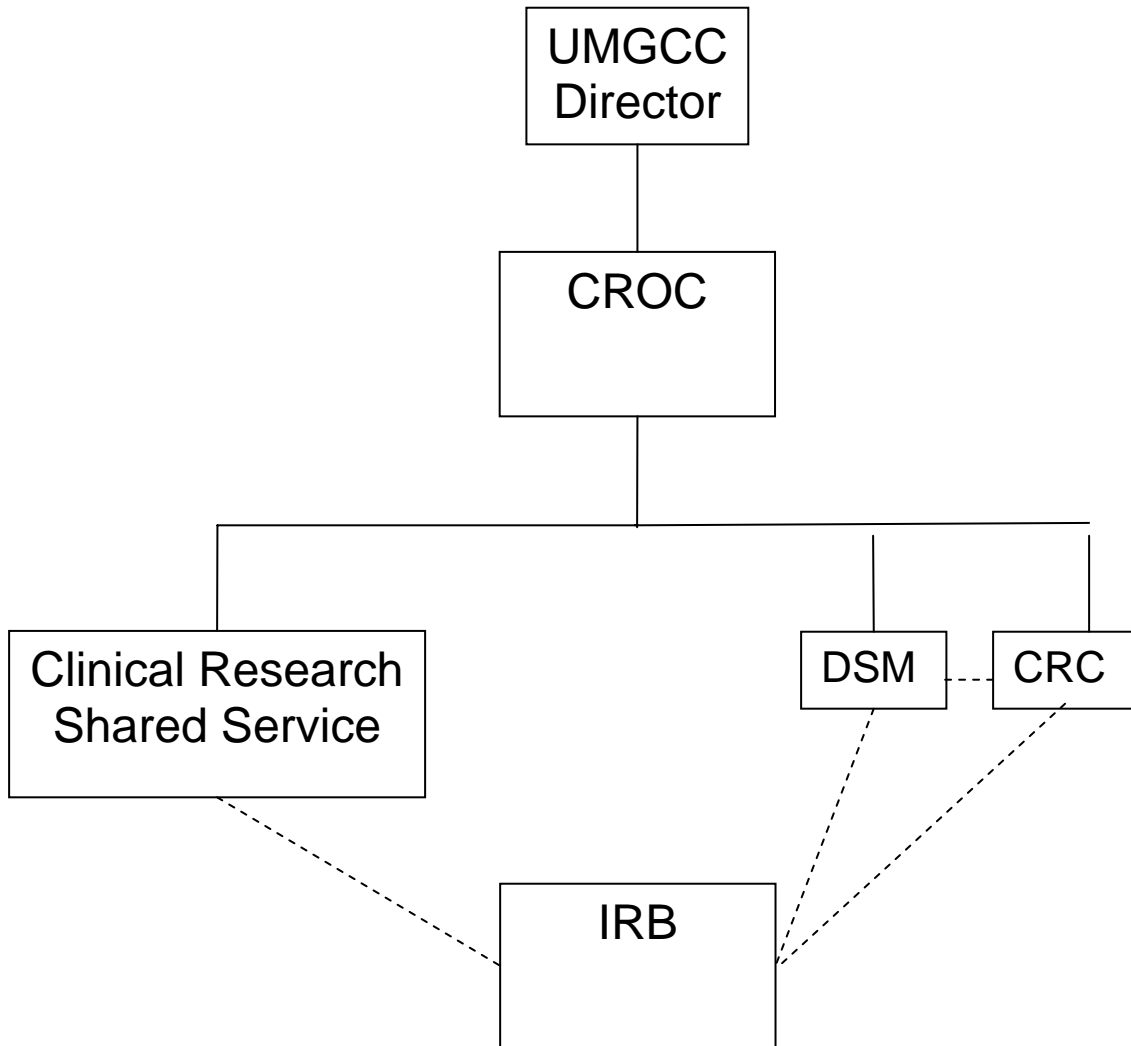


Figure 2

CLINICAL RESEARCH OFFICE
of the
GREENEBAUM CANCER CENTER
BUDGET AND PROTOCOL SUBMISSION PROCESS FOR NEW TRIALS

All new trials: GCC, Industry, NCI, Co-op group- PI submits all protocol and budget documents in **ELECTRONIC FORMAT**, to the manager of CRO.
Required: Protocol, Model Consent, Investigator Brochure, IND Safety Reports, FDA/ Sponsor Documents (see Appendix A), Budget and Contract

Statement by Disease Group Head-Dr.Edward Sausville approving trial at GCC
CRO Manager to verifies Protocol within the capacity of CRO

Industry and GCC Trials

Manager of CRO will electronically submit: Service request form to the SOM clinical trials office CCT:
<http://www.medschool.umaryland.edu/cct>

Manager emails or faxes draft budget, contract, protocol, & study calendar to CCT
Fax: 410-706-4853
Email: cct@some.umaryland.edu

CCT will produce first budget draft. CRO/ Manager will review for accuracy and communicate with PI and Study Coordinator

CCT, upon completion of agreement negotiations, emails the Grants / Contacts Administrator of GCC (Helen Mourat)

Grants/ Contract Administrator of GCC routes the completed Routing Form with the CCT Cover Sheet stapled to the front and any necessary documents to the Office for Research and Graduate Studies for approval (Rm 14-021, Bressler Research Building)

CCT sends finalized Agreement to GCC Grants / Contract Administrator for Principal Investigator signature.

GCC Grants/ Contract Administrator returns signed agreement to the CCT.

CRO manager sends via fax or email a copy of IRB approval letter to CCT

NCI and Co-op Group

CRO will contact GCC Grants Office and work with Grants Administrator to Formulate Budget

Schedule of Events or Sponsor's Draft Budget required for budget negotiations**

Grants Administrator confirms budget and other grant items with PI.

Grants Office routes proposal through SOM channels.

REGULATORY PROCESS
CRO Regulatory Contact designated by Disease Specialty

CRC Submission
by Disease Group Reg. Coordinator
Includes entering info into CICERO: web based IRB

↓

CRC Review

↓

CRC Approval

↓

Essential Documents Coordinator (Terri Joneckis) completes pre reg. Documents and routes to sponsor)

↓

IRB Submission
**Materials should be submitted to the IRB as soon as possible. Do not wait for completion of clinical trial agreement negotiations

**CANCER CENTER
DATA AND SAFETY MONITORING PLANS**

(This form completed by PI at time of submission to CRC. CRC will review and either accept PI designation or assign a different level of risk. Form then included in initial IRB submission.)

Title of Study: _____

IRB#: _____

Level (check one):

___ **Routine** All SAEs reported to the IRB, FDA (if appropriate affiliated research sites) in a timely fashion. Summary of SAEs submitted with **annual** report for review by DSM/QAC and IRB.

___ **High** (Prospective review)

All SAEs reported to the IRB, FDA (if appropriate affiliated research sites) and DSM/QAC in a timely fashion. Summary of SAEs is submitted with annual report for review by CRC and IRB. Requires annual review by DSM. Includes high-dose treatments or those expected to cause significant risk of complications whether due to study drug or not, e.g. BMT, acute leukemia.

___ **Highest** Dose escalation studies – Phase I

All SAEs reported to the IRB, FDA (if appropriate affiliated research sites) and DSM/QAC in a timely fashion. Summary of SAEs submitted with annual report for review by the DSM/QAC and IRB. Expedited review by member of DSM/QAC before each new cohort. (This includes single- patient cohort, accelerated trial design.) Requires review of original patient records or case report forms.

___ **Special** Institutionally developed, single-site or multi-site Phase III trials require a Data and Safety Monitoring Board (DSMB). See GCC DSM planning document for details.

___ **External** External DSMB in place. All SAEs submitted to the IRB, FDA and sponsor. Summary of SAEs submitted with annual report.

Signature of Principal Investigator:

CRC CHAIR'S SUMMARY OF PROTOCOL

(This form included in CRC's initial review of protocol and communicates the designation of risk to the PI and the DSM/QAC).

	Adequate (may need minor revisions)	Not Adequate
<i>Appropriate prioritization within research group</i>	<input type="checkbox"/>	<input type="checkbox"/>
<i>Biostatistical input & review</i>	<input type="checkbox"/>	<input type="checkbox"/>
<i>Scientific justification</i>	<input type="checkbox"/>	<input type="checkbox"/>
<i>Study design appropriate</i>	<input type="checkbox"/>	<input type="checkbox"/>
<i>Risks appropriate for nature of disease</i>	<input type="checkbox"/>	<input type="checkbox"/>
<i>Standard of care maintained</i>	<input type="checkbox"/>	<input type="checkbox"/>
<i>Potential of accruing at acceptable pace</i>	<input type="checkbox"/>	<input type="checkbox"/>
<i>Consent form</i>	<input type="checkbox"/>	<input type="checkbox"/>
<i>Data and safety monitoring plan described</i>	<input type="checkbox"/>	<input type="checkbox"/>

DSM level recommended by the CRC:

_____ **Routine**
 _____ **High**
 _____ **Highest**
 _____ **Special**
 _____ **External**

Chair, Clinical Research Committee

Date

Serious Adverse Events	
Number of external SAEs reported since last annual review:	
Number of internal SAEs reported since last annual review:	
Number of SAEs reported expeditiously to the IRB:	
List Events Reported:	
Was consent form modified due to reported SAE: <input type="radio"/> YES <input type="radio"/> NO	
Adverse Event (s) Added to Consent:	
Deviations and Exceptions	Comments:
Trends in Safety Data	Comments:

DSM/QAC CHAIR'S SUMMARY OF PROTOCOL

(This form provided to PI and IRB following each DSM/QAC review of protocol)

Recommendation:

- Allow protocol to remain open
- Close protocol

Reason(s):

- Response rates
- Accrual not met
- SAE rates too high
- SAEs not reported to IRB
- Consent form issues
- Other: _____

Recommendation(s) for improvement: _____

Chair, Data and Safety Monitoring Committee

Date

Form Attachment 5

Monitoring Worksheet for Clinical Trials					
Protocol					Date:
Principal Investigator					
Members of Monitoring Team					
Regulatory Documents					Comments (if deficient)
Current version of protocol	Yes		Date	No	
Amendments	Yes				
Investigator Brochure	Yes			No	
Current version of informed consent	Yes		Date	No	
Form 1572	Yes			No	
Accrual Listing from Oncore	Yes		Up to date	Yes	
				No	
Hospital Medical Record	Yes			No	
Research Record (Patient)					
Eligibility Checklist	Yes			No	
Pathology Report	Yes			No	
Radiology Reports	Yes			No	
Data Collection Forms	Yes			No	
Serious Adverse Event Reports	Yes			No	
PK/PD Worksheets (if indicated)	Yes			No	
Investigational Drug Pharmacy					
Presence of Drug Accountability Forms	Yes			No	