

	Effective Date:	Procedure No: CRC001
Subject: Clinical Research Committee (CRC)	Function: Protocol Review and Monitoring System	

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 Clinical Research Committee which serves as the Protocol Review and Monitoring System at UMGCC.

Definitions

1. Principal Investigator (PI)

The PI is responsible for the completion of the CRC packet, which contains the information necessary for the CRC to properly review the protocol, and submitting the completed packet to the CRC by the CRC deadline. The PI is also responsible for proposing a DSM plan as part of the scientific review by the CRC.

2. Clinical Research Management Office (CRMO)

The CRMO is the physical space housing staff of the Clinical Research Shared Service (CRSS). It maintains a clinical research database of all protocols open at UMGCC. CRMO staff may be called upon by the PI to assist in preparation of materials for CRC review. Should the PI require such assistance the PI must provide the manager of the CRSS with a copy of the signed approval from the disease group head. However, the PI is ultimately responsible for the accuracy of the information and should review the entire packet prior to submission to the CRC Coordinator.

3. Clinical Research Oversight Committee (CROC)

The CROC defines and adjusts physical and personnel resources of the CRSS. It also 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.

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

The DSM/QAC is responsible for ongoing safety and quality assurance review of protocols at UMGCC.

5. 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 to receive communications regarding protocols under their jurisdiction.

6. Human Research Protections Office (HRPO)

The HRPO is the coordinating office for the UMB IRB. CICERO is the electronic database utilized by the HRPO and IRB.

Purpose

The Clinical Research Committee (CRC) will provide scientific review and evaluation of all cancer clinical protocols throughout the institution involving clinical subjects. The CRC will provide initial review of these protocols for scientific merit, methodology, validity of statistical analysis, potential for successful completion based upon anticipated accrual and scientific priority, availability of resources and funding including P30 Protocol Specific Research Support funding. CRC will require the submitted new protocols to be prioritized by the Disease Group Head or the investigator in the event of competing protocols prior to submission to insure appropriate accrual strategy, and in the event of an excessive queue of protocols, the CRC may review the queue with the Disease Group Head and require withdrawal of protocols. The CRC will also review the adequacy of accrual during the course of the study. The CRC will provide continuing scientific review of ongoing protocols if an issue arises during the annual accrual review or if the DSM/QAC or University of Maryland IRB so requests. Such continuing review may be occasioned by receipt of new information concerning a

treatment in the protocol or questions concerning the continuing scientific importance or methodology.

Approval by the CRC will be required in order to gain access to the Clinical Research Shared Service and Investigational Pharmacy of the Greenebaum Cancer Center.

The CRC is composed of a chair and representatives from all the relevant areas of the Cancer Center (e.g. biostatistics, hematology/oncology, surgical oncology, radiation oncology, and pharmacy). Members either volunteer or are assigned based on need and availability from the relevant areas. There is no fixed term length to committee service. Current membership, including voting and non-voting members, is shown in the Appendix. Ad hoc voting CRC members appointed by the Chair for a particular meeting and indicated in their review as “ad hoc” may be used when necessary to address specific areas of expertise not covered by standing committee members or to assure independent review if the required expertise resides in a member with a conflict of interest. In addition, an observer from the IRB is invited to allow IRB awareness of issues that arise in protocol review. A quorum consists of three voting members plus a chair or acting chair.

Objectives of the CRC:

1. To review all new cancer-related protocols for scientific merit, methodology, human resources, security of funding source, ethical appropriateness, and reasonableness of accrual goals prior to submission to the IRB.
2. To ensure that expert biostatistical planning regarding clinical trial design, calculation of sample size and monitoring for early closure will be part of each institutional protocol.
3. To provide review as needed of Medicare coverage and PI determinations of research v. standard of care procedures.
4. To work with the Disease Group Heads to assure proper prioritization of new and existing protocols.
5. To review on a continuing basis accrual to all studies supported by the Clinical Research Shared Service and to oversee the development of corrective action plans or require closure of poorly accruing trials.
6. To provide scientific review of issues that may arise in continuing review by the CRC, the DSM/QAC or the University of Maryland IRB.

The committee will judge the acceptability of the proposed research, based upon scientific merit, which includes the scientific question being posed, from which the study derives. The committee will also review the scientific design, statistical endpoints, study calendar, rules for monitoring as well as the likelihood of completing accrual in a defined time period (usually 3-4 years for institutional sponsored protocols). The review criteria are described below. The committee will have the authority to decline activation for protocols which do not meet scientific criteria or for which priority is not high compared to other protocols in the same disease area.

The CRC will additionally consider the adequacy of the suggested Data Safety Monitoring plan for each individual protocol. The CRC may impose a stricter level of monitoring for “high or highest risk” studies.

The CRC has the authority to close protocols due to poor accrual. On an annual basis the CRC will review accrual to all UMGCC trials to assure timely recruitment of subjects to trials. Typically timely accrual will entail accrual averaging at least 20%-33% of total target accrual per year, but consideration will be given to prevalence of the indication and other factors outside the PI’s control. This will also entail the assessment of progress in reaching protocol-defined clinical response endpoints

Subcommittees and Delegation

In December 2005, the Department of Radiation Oncology, in conjunction with UMGCC and the Clinical Research Committee, formed the Technology Research Review Committee (TRRC) as a sub-committee of the CRC. The TRRC was formed as a subcommittee under the CRC to supplement the review capacity of technology protocols. This sub-committee reviews research proposals that do not affect patients' treatment modalities, but instead study technology to help advance treatment planning or improve the use of technology assessment tools.

The subcommittee meets on the first Monday of every month, and members include representatives from the Department of Radiation Oncology, the Department of Radiobiology, the Department of Biostatistics, the Greenebaum Cancer Center, and CRC.

Faculty of the University of Maryland School of Medicine Department of Pediatrics are members of the Children’s Oncology Group, which is the source of most of their clinical research protocols. The CRC delegates to the Department of Pediatrics the review of pediatric cooperative group studies. Pediatric protocols are reviewed by the Department of Pediatrics according to departmental guidelines and receive second level review by the Associate Director for Clinical Research, UMGCC per IRB guidelines. On a quarterly basis, the CRC coordinator obtains a list of the approved cooperative group protocols and accrual statistics for these protocols and presents them to the CRC for ratification.

The CRC will review investigator-initiated and industry-sponsored pediatric protocols with usual review process, after signoff by the pediatric departmental reviewer, and at its discretion, the CRC can elect to review any specific cooperative group protocol.

Procedure

1. Initial Review of Protocols

CRC Packets

The CRC packet includes the information necessary for the CRC to properly review the protocol. The CRC packet includes (samples of each form and a checklist provided in the Appendix):

- Investigator & Disease Group Worksheet – this form allows the protocol to be properly categorized and prioritized. The PI in particular should make sure that sponsorship of the protocol is clear (e.g., “Industry-sponsored” studies imply provision of drug if not standard practice plus a per patient fee; “PI-initiated” studies may utilize drug provided by a sponsor and have partial financial support but not a full per patient reimbursement). The PI must also indicate the expected duration of the accrual period across all sites and provide justification for UMGCC participation for protocols for which the study is unlikely to be open to accrual for at least 18 months. The disease group head and Associate Director for Clinical Research must sign this form.
- A printout of the CICERO protocol – this allows the CRC to view the protocol in the form in which it will appear before the IRB
- Consent Form adapted to local IRB requirements, including 7th grade reading level (Industry studies need to have consent form approved by sponsor before IRB submission.)
- Data and Safety Monitoring Level Designation (see DSM/QAC materials)
- Website Form – any proposed advertisement will be reviewed by the IRB and must be available to the CRC for review. For industry sponsored trials, the proposed advertisement should be reviewed by the sponsor. In addition, the PI should ensure that the protocol is registered with clinicaltrials.gov
- Copy of the Sponsor’s Protocol. For PI-initiated studies, all co-investigators including the statistician should initial the face page of the submitted protocol.
- PDF file of the Investigator Brochure (if applicable)
- HIPAA Authorization – the IRB will not review a protocol until this form is available
- Study Schedule marked with R (research procedure) and C (standard of care procedure). The study calendar should be generated in Oncore®, the CRSS research database. The PI must sign this calendar, which will become the basis for a billing plan to be used by UMMC to ensure that research subjects are not charged for research procedures, or to review the consent to define that such charges are explicitly outlined.
- Plans for funding (part of the Disease Group Head or AD Clinical Research approval). If the PI is requesting use of P30 Protocol Specific Research Support (PSRS) funding, the PI will need to address the additional information described below under Criteria for Review.
- Model chemotherapy order set if required by the Pharmacy to allow generation of pre-printed orders

- A preliminary Medicare coverage analysis showing whether the trial is “deemed” according to Centers for Medicare & Medicaid Services criteria for coverage by Medicare

Chart reviews and other minimal risk studies not involving therapy can be submitted with documents pertaining only to therapy (e.g., chemotherapy orders) omitted.

The CRC submission packet can be accessed on the G drive at g:\protocol\reports\irb\packet or on the S drive s:\CRC Submission. Copies of the template documents follow this plan.

The packet should be submitted via hard copy. An electronic version or disk version should be submitted to the CRC Coordinator.

The CRC meets on the second Tuesday of the month. The deadline for submitting a packet for consideration at the CRC is the last Monday of the prior month but in no case less than 2 weeks prior to the meeting. In rare cases where time is of the essence and there is a valid reason why the protocol cannot be reviewed at a regularly scheduled committee meeting, the CRC chair may convene an ad hoc meeting to review a specific therapeutic protocol.

In the event of a queue of protocols in excess of the capacity of the CRC or the CRSS, the Disease Group Head may be requested to prioritize and eliminate trials from the queue pertinent to their area of responsibility. If this measure is inadequate to reduce the queue of protocols to a manageable number, a Disease Group Head may be invited to a CRC meeting to present a streamlining plan for the Disease Group. If the Disease Group Head is unable to reduce the queue of protocols to a manageable number, the CRC will review the queue at a meeting and require the Disease Group Head to withdraw certain protocols summarily.

Reviewer Assignments

Reviewers are assigned based on scientific expertise. For NIH Cooperative Group trials (e.g. CALGB, RTOG, NMDP) and trials sponsored by major pharmaceutical companies of at least 500 employees and/or with a prior track record of having submitted at least one well-constructed statistically sound trial to UMGCC, one primary reviewer is assigned as these studies have already received extensive review. For all other Industry and PI-initiated protocols two reviewers are assigned; one primary reviewer and one secondary reviewer. For chart reviews and other minimal risk protocols not involving therapy, a single reviewer is assigned and the chair decides whether the protocol may be reviewed ad hoc with a report of review at the meeting or whether the entire committee should discuss the results of the review. Reviewers are generally committee members, although additional reviewers may be recruited to provide specific expertise. Only non-cooperative group trials will require statistical review. The pharmacy representative will review the model chemotherapy orders if necessary. The complete CRC packet, except for those documents only required for

administrative processing, will be distributed to reviewers five days in advance of the meeting with other members receiving only the proposed CICERO submission.

Procedures at Meeting and Criteria for Review

The meeting will be led by the CRC Chair or an Acting Chair appointed by the Chair. The PI is expected to be available by pager at the time of review of the protocol by CRC. At the meeting, the assigned primary reviewer will give a brief synopsis of the protocol followed by a critique. Secondary and statistical reviewers then add any additional comments. Reviewers provide written synopses of their comments to the CRC Coordinator. Minor editorial or typographical comments do not require discussion at the meeting.

The criteria for review include appropriate prioritization within the disease group, biostatistical input and review, scientific justification, if the study design is appropriate, if the risks are appropriate for the nature of disease, if the standard of care is maintained, potential for accruing at acceptable pace, adequacy of the consent form, consideration of the Medicare coverage analysis and designation of research procedures in the study calendar, and if the data and safety monitoring plan described is appropriate. The study is rated adequate or not adequate for each of these criteria as shown in the template documents following this plan.

Additional Criteria for Protocols Requesting PSRS Funding

To gain access to P30 PSRS resources, investigators will have provided the following, in addition to the usual information currently required for a CRC submission:

- Describe how the protocol is innovative in achieving the goal of attaining a novel cancer diagnosis, treatment, imaging, or prevention strategy
- Describe the correlative science to be enabled as a result of PSRS funding and indicate whether translational collaborators and assays are in place
- Describe the independent funding applications that will be developed for the activity and indicate the anticipated total cost of conducting the trial

The CRC weighs each of these criteria using a 1–5, NIH-like priority scale. Protocols that achieve an aggregate ranking (equally weighted) of 2.0 are considered for PSRS resources.

Following discussion of the review criteria and DSM plan, a member will make a motion to approve, approve with minor or major modifications, scientifically disapprove, or defer.

The CRC Coordinator will take notes at the meeting and ultimately compile the comments of the reviewers. The review letters distributed to the PIs constitute the minutes of the meeting.

Post-Meeting Activities

After the CRC meeting an e-mail will be forwarded to the PI from the CRC Coordinator including a detailed memo from the Chair regarding the protocol including reviewer comments and disposition. The CRC Chair will designate the appropriate level of DSM plan in the letter to the PI with copies to the DSM/QAC and the CRMO. The DSM plan will remain in effect until all enrolled patients are beyond the time period when study-related adverse events would likely be seen. Copies of this letter are sent to the Associate Director of Clinical Research and the DSM/QAC Coordinator. A copy is also included in the regulatory binder kept with the CRMO.

The PI is ultimately responsible for addressing the comments of the CRC and insuring that the appropriate changes are made before IRB submission. CRMO staff can be enlisted to assist in this process, but the PI remains responsible for the content of the submission. A response to the CRC's recommendations should be addressed within a month of the date of the memo unless more extensive communication with the sponsor dictates a longer turnaround time.

- 1) When a protocol is approved as written, no further review by CRC is needed.
- 2) When a protocol is approved with minor revisions, the changes are returned to the CRC chair. If in the opinion of the chair, who may consult the original reviewers at chair's discretion, approval can be granted by the chair.
- 3) When a protocol is approved with major revisions, a revised submission should be resubmitted for review at a CRC meeting. In most cases, the original reviewers should receive the revised package. PI may be invited to the meeting to discuss the points raised by the reviewers.
- 4) When a protocol is deferred, the CRC will provide the PI with written recommendations. Protocol can be re-submitted to a future CRC meeting with no prejudice.
- 5) When a protocol is scientifically disapproved, the CRC chair will be available to meet with the PI to discuss re-design of the study. If the PI chooses to resubmit, the CRC chair may designate independent ad hoc reviewers or CROC members to assure impartial re-review. The CROC and/or independent reviewers should be made aware of the prior issues in review by the CRC.

The PI response memo to the CRC chair should be forwarded to the CRC coordinator. The CRC coordinator reviews for technical compliance with the CRC review and then forwards to the CRC chair for final review. Once the chair, the full committee or the CROC subcommittee has reviewed the changes and approved them, the PI and PI's regulatory staff will be notified via e-mail that the PI may submit the protocol to IRB via CICERO. This notification may originate from the CRC Chair or CRC Coordinator.

Cancer Center Signatories will be informed of the submission as a reminder to sign off on the IRB submission once notified via CICERO e-mail.

The CRC letter to the PI, the PI's response to the CRC, and the CRC's final approval should be attached to the CICERO submission in Section S so that the IRB can see the record of scientific review.

2. Accrual Monitoring

All trials, regardless of whether an independent DSMB exists or not, will be subject to at least annual review of accrual by the CRC. The CRC may close studies with persistently poor enrollment, typically accrual averaging less than 20% - 33% of total target accrual per year, but consideration will be given to prevalence of the indication and other factors outside the PI's control.

The CRC will consider the following items in its review.

- Accrual of research subjects to the study for adequacy will be reviewed by the CRC. The CRC will determine if early closure is justified if anticipated accruals cannot meet stated study goals.

Following review of the accrual information, the CRC will make one of the following recommendations:

- Allow protocol to remain open.
- Request corrective action plan to improve accrual from PI
- Close the protocol

The CRC will not issue a determination letter for those protocols that may remain open without corrective action. The CRC will send the PI a letter either requesting a corrective action plan or informing the PI that the protocol will be closed. In the event of a closure recommendation, the IRB, any appropriate granting agency, the sponsor, and any other appropriate body will be sent a copy of the letter.

3. Continuing Review of Protocols

Upon referral from the DSM/QAC or the University of Maryland IRB, or if the CRC's own accrual monitoring indicates, the CRC will provide continuing scientific review of protocols in which questions have arisen as to the continuing scientific importance or appropriateness of the research question; which require proper consideration of significant new information; or for which questions have been raised by investigator or participant experiences since the last review. The CRC will not as a matter of routine re-review protocols without cause.

The process of the continuing review will be identical to the initial review with the following exceptions:

- The review packet will contain a summary from the IRB, the DSM/QAC, the CRC chair or designee as to why re-review is necessary. The PI will be expected to include a written response to the issue raised.
- The outcome of the review will have the following categories:
 - Continue protocol as previously
 - Modify protocol as specified by the CRC with or without suspension of accrual until amendment completed
 - Close protocol

In each case, the determination of the CRC will be final.