UNIVERSITY of MARYLAND
MARLENE AND STEWART GREENEBAUM
CANCER CENTER

NCI Cancer Center
A Cancer Center Designated by the National Cancer Institute

Clinical Investigators Handbook for

UNIVERSITY OF MARYLAND
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(Note: Attachments requiring institutional approvals have been approved separately. These may be subject to change without modification to this handbook.)

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Introduction

Clinical Research is an integral part of the mission of the University of Maryland Marlene and Stewart Greenebaum Cancer Center (UMGCC). Funding to support Clinical Research typically comes from the following sources: industry sponsors, grants, the University of Maryland Medical System and from funds available to the Director, UMGCC. Because funding is limited, UMGCC has adopted a series of policies and processes to prioritize research, making certain that adequate resources are available to support selected clinical trials. UMGCC has also put into place a number of committees to oversee all research conducted.

The Clinical Research Management Office (CRMO) is organized to support clinical research. Comprising over 35 FTEs, it is charged with managing patient interactions, data and regulatory actions related to clinical trials. The Director of the CRMO reports to the Associate Director for Administration with professional guidance from the Associate Director for Clinical Research. As a rule, CRMO staff do not report to individual PI's. There may be times when a specific project has resources allocated for a dedicated CRMO staff member however, the Director of the CRMO will make the determination if additional resources are needed to support the trial and be responsible for the oversight of the individual. See Attachment 1 for the CRMO Organizational Chart.

Initiation of Research

Investigators are often the first to initiate a protocol at UMGCC, either by contact with industry sponsors, national cooperative group colleagues or internal discussions and drafting of a protocol. Regardless of mechanism of initiation, the processes outlined in this handbook are applicable for all research conducted at UMGCC.

Operational review (for logistical and resource feasibility considerations) of the proposed protocol is the first consideration at UMGCC. As an NCI-funded Cancer Center, UMGCC is also required to review scientific merit and safety of protocols as well as accrual to protocols via a Protocol Review and Monitoring System (PRMS). For UMGCC, the PRMS in place is the Clinical Research Committee (CRC). See Attachment 2 for CRC Standard Operating Procedure. IRB approval is sought after CRC approval is obtained.

Concurrent with and/or subsequent to feasibility and scientific review, contractual and budgetary issues including investigational agent supply, administration of agent, correlative study funding etc. For the protocol must be settled. The General Clinical Research Center (GCRC) is a possible resource to be considered for complex trials. Application to the GCRC is made within CICERO after discussion with the Director of the CRMO.

The protocol may be initiated after all scientific, regulatory, contractual and budgetary concerns have been addressed.

Contracts & Budgets

The proper conduct of clinical research is a resource intensive endeavor. Contracts and their associated budgets are an integral mechanism for obtaining sufficient funding to support clinical research.

Federal cooperative group trials are generally conducted under a master contract that covers the conduct of all trials from the cooperative group and often no contractual work is required prior to initiation of these studies (although there is some preliminary evidence that this model will be changing). Budgets for cooperative group trials are generally nonnegotiable and seldom fully cover the costs of conducting the trial. NCI P30 funds and other funds available to the UMGCC leadership subsidize the cost of running these scientifically meritorious, nationally important trials. Occasionally cooperative group trials have "special" funding set aside to cover the cost of research only procedures (e.g., PET scans or ECHOs that cannot be justified as billable to patient insurance). This special funding is usually described in the protocol and/or consent; the CRC should be made aware of any such special circumstances.

Industry-sponsored trial contracts should contain a budget that fully covers the estimated cost of conducting the trial at UMGCC. The UMGCC Director of Contracts works with the University's Office of Research & Development to negotiate for an adequate budget with the sponsor. If negotiations fail to produce a budget that fully covers the cost estimate for the trial, the Associate Director for Clinical Research must give permission for the trial to proceed due to the scientific merit or expected patient benefit from the trial. In no case does a PI have the authority to approve a budget deemed inadequate by the Director of Contracts.

An important component of the budget development process is the Medicare Coverage Analysis, as this analysis guides the determination of what procedures in the protocol may be billed to patient insurance. While CRMO and ORD staff routinely consult National Comprehensive Cancer Network (NCCN) guidelines to help justify denoting a procedure as "standard of care" or a "routine cost," PIs may occasionally need to assist by providing peer-reviewed literature as evidence of the standard practice for a particular disease.

The budget will in all cases contain some degree of effort for the PI. PIs should keep in mind, however, that if the Medicare Coverage Analysis indicates that the physical exams, medical history, etc are billable to patient insurance, then the PI effort component of the industry budget will only comprise effort for the strictly research activities of the PI (e.g., participating in investigator teleconferences, evaluating adverse events, signing case report forms). CRMO staff have algorithms for the average percent effort for PIs on clinical trials based on trial complexity, phase, etc.

In addition to the budget component, industry-sponsored trials also require negotiation of the contractual language. Each industry-sponsored trial will have two components to its

contractual language: one component for the university and one for the hospital. While a contract may be fully negotiated ahead of IRB approval, current UMB policy is that final execution of the contract will be held until IRB approval is obtained. An industry-sponsored trial will not open to enrollment until contract documents have been signed by the university and the hospital. CRMO staff meet monthly with university and hospital staff to discuss the current state of all pending contracts. Studies being opened at the VA or at other affiliate hospitals may have additional contractual issues.

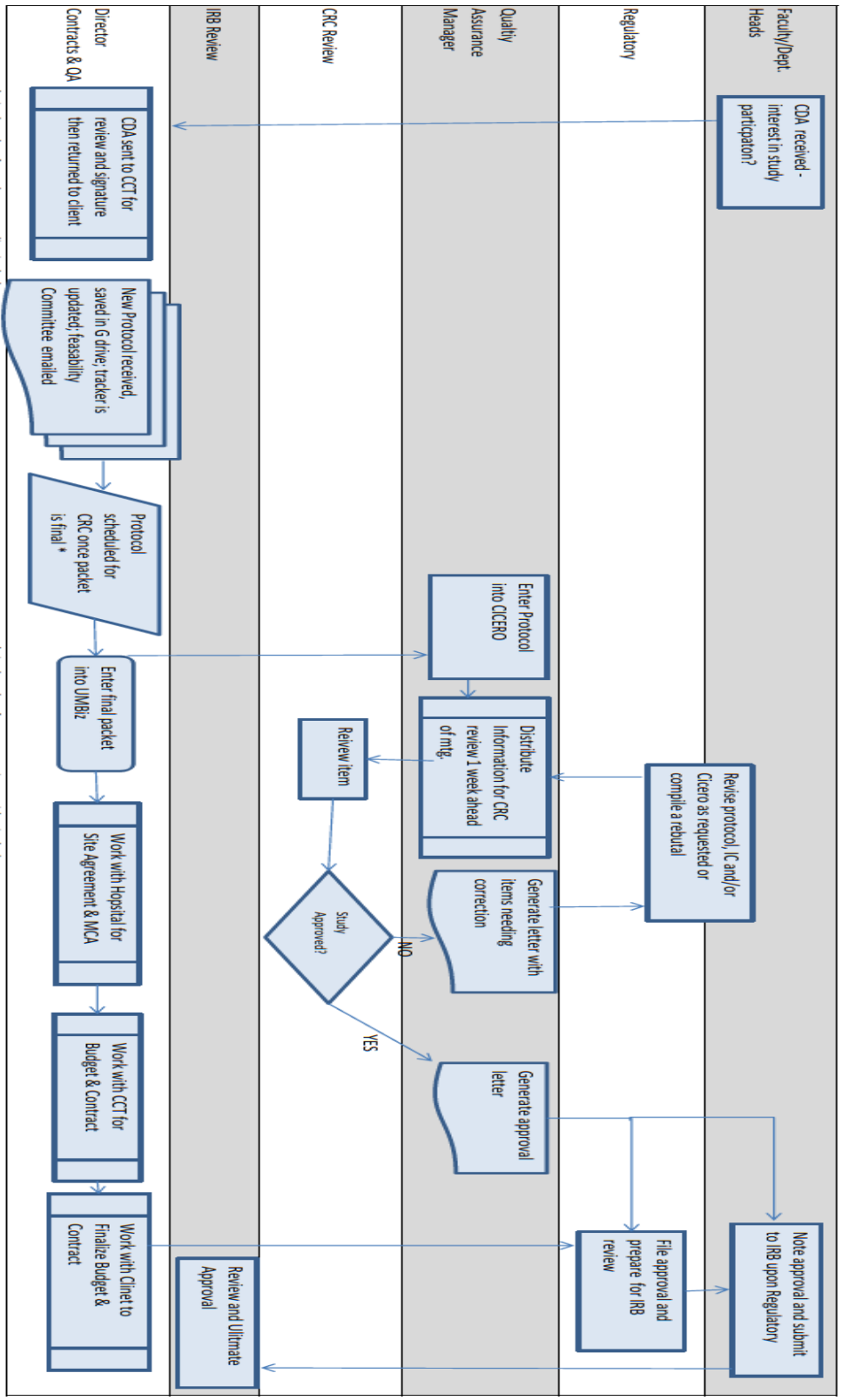
Funding for investigator-initiated studies can come from a variety of sources: federal or foundation grants, pharmaceutical collaborators, philanthropic funds, pilot funding available to UMGCC, and other funds controlled by UMGCC leadership. From an NCI-designated Cancer Center perspective, investigator-initiated trials are considered the most important. For that reason, UMGCC leadership will make every effort to identify sufficient funds to allow their conduct.

The following considerations should be kept in mind when designing investigator-initiated trials and negotiating for outside funding so that PIs can maximize their ability to conduct such trials:

- Procedures that cannot be billed to patient insurance should be avoided as much as possible (e.g., follow peer-reviewed guidelines as to timing of procedures such as biopsies, scans and cardiac tests);
- The local Medicare contractor currently does not cover routine costs for phase I clinical trials so other trial designs should be considered;
- The Director of Clinical Trials should be consulted as early in the trial development as possible. PIs should NOT attempt to estimate research nurse/study coordinator/data manager effort without consulting with the Director of Clinical Trials;
- Multi-centered trials coordinated by UMGCC need to have effort built in to budgets for coordination, monitoring and auditing of external sites; Statistical analysis should be built into budgets;
- Both the hospital and university have restrictions on their hiring processes and on the credentialing processes necessary to bring personnel on board. If a budget proposal supporting specialized staff (e.g., a technician with a special certification) is accepted by a funding agency, consult UMGCC leadership as soon as a funding decision has been offered so that a trial is not delayed by the need to comply with hiring processes.

The figure below provide an overview of the steps involved in the protocol start up process and the key personnel involved in each step.

Process Flow for New Potential Protocols



*** Final packet for Industry Studies include:**

Protocol
IB
Consent
Contract
Budget
Medicare Coverage Analysis

***Final packet for Cooperative Stuides include:**

Protocol
IB
Consent
Medicare Coverage Analysis

Management of Research

Every protocol is assigned a Study Coordinator, who works closely with the investigator to organize and conduct visits with patients being considered for research enrollment. Every protocol is also assigned a Data Manager, who works closely with the investigator to obtain needed signatures on protocol required assessments and enter all study information into the sponsor provided database as well as the UMGCC Clinical Trials Management System – OnCore®.

Ongoing protocol management includes annual renewals with the Data Safety & Monitoring Committee and IRB, routine monitoring and auditing with the sponsor or UMGCC Quality Assurance Manager, adverse event reporting, reporting of deviations, and submission of amendments to the IRB. See Attachment 3 for UMGCC DSM/QAC Standard Operating Procedure. See Attachment 4 for UMGCC Monitoring Standard Operating Procedure. Preparation of research records for audits is a time consuming process that will involve a host of CRMO staff. Whenever a PI receives notification of any upcoming audits, the PI must promptly notify the Director of the CRMO to ensure resources are allocated to assist with documentation preparation. The regulatory team at UMGCC will facilitate with the Investigator the annual renewal of a protocol with the DSM/QAC (as applicable) and with the IRB. Protocol renewal requests must be submitted to the IRB no later than 45 days prior to the protocol renewal date.

Adverse event (AE) reporting is required for all trials and must comply with the protocol as well as UMGCC and IRB policies. Adverse event collection and reporting are a routine part of every clinical trial. Requirements for collection and reporting of data are complex, and PIs should be aware that there are numerous reporting bodies, each of which may have different requirements.

Reporting bodies include the IRB, the DSM, the FDA, NIH, and sponsors. Sponsors could include pharmaceutical companies, Cooperative Groups, or the NCI Cancer Therapy Evaluation Program (CTEP); there are also investigator-initiated trials. For most clinical trials, PIs will be required to collect and report information to sponsors on many more adverse events than those that eventually require reporting to the federal government. The requirements for collecting and reporting of adverse events should be clearly defined within the protocol, and as such, the protocol is a crucial but not exclusive point of reference to guide practice. UMGCC policy is that for all investigator-initiated trials, PIs are required to follow FDA regulations for IND studies in relation to collection of adverse event information; specifically, this means that the protocol must indicate that the PI will collect information on ALL adverse events irrespective of seriousness, expectedness or attribution.

The protocol Principal Investigator (PI) has the ultimate responsibility for identifying adverse events, and subsequently determining the seriousness of the event, the expectedness of the event, and the assignment of attribution of the study agent with relation to the event. Seriousness is not the same as severity. Serious is based on patient/event outcome associated with events that pose a threat to a patient's life or functioning. Severity is often used to describe the intensity of an event. Expectedness of an event refers to whether the adverse event is included in the informed

consent, protocol, investigator brochure and/or package insert. PIs should be aware that sponsors, regulatory agencies, and the IRB may require a determination of expectedness based on one, some or all of these documents. In particular, NCI has specific instructions on which column in its Comprehensive Adverse Event and Potential Risk (CAEPR) list should be used to determine expectedness. Attribution refers to the investigator's clinical judgment about the drug's relation to the event (unrelated, unlikely, possible, probable, definite). To ensure uniformity in the reporting and grading of adverse events, the Common Terminology Criteria for Adverse Events (CTCAE) is a tool that is frequently employed. This can be accessed at the following web address: ctep.cancer.gov

See Attachment 5 for UMGCC CRMO Standard Operating Procedure on AE Management.

Deviations to the protocol post enrollment into a trial will be captured in the OnCore database. UMGCC policy is that NO eligibility waivers whatsoever may be granted, irrespective of whether a sponsor is willing to allow the waiver. No other intentional prospective changes to the protocol should be taken unless required to eliminate an immediate hazard to a participant. CRMO staff are instructed to immediately inform UMGCC management of any intended eligibility deviation from a protocol by a principal investigator or any other staff member. At UMB, the IRB requires reporting of failures to follow the protocol due to the action or inaction of the research staff. Actions of the patient or those of hospital staff not on the delegation of authority log are not reportable to the IRB. For instance, if a research nurse fails to order a urinalysis, this failure is reportable to the IRB. However, if the research nurse orders the urinalysis, but the clinic staff fails to request the patient to provide a sample or the patient leaves the clinic without providing the sample, these are not reportable to the IRB. The IRB will assess the reported information as simple noncompliance requiring no further action, or as continuing and/or serious non-compliance. Determinations of continuing and serious non-compliance will result in the IRB reporting the investigator to the HHS OHRP and any federal funding sponsors. Therefore PIs must take extreme care to minimize any deviations from the protocol.

PIs should be aware that the UMB IRB has an extensive list of categories of Reportable New Information (RNI). Most of these are encompassed in the above. However, an audit by a federal agency must be reported to the IRB. PIs should familiarize themselves with the IRB's RNI policy located at https://www.umaryland.edu/media/umb/oaa/hrp/documents/study-tools-docs/Reportable-New-Information-Bulletin.pdf.

The PI is responsible for submitting any amendments to the IRB through CICERO as necessary. This is in addition to the requirement to submit amendments to the NCI, industry sponsors, and any other sponsors/coordinating centers. The CRMO will assist with this process, however, the PI should provide information on what sections of the protocol, consent and study schedule require changes. If the IRB requires any clarifications or modifications to the amendment, the PI and other designated staff will receive e-mail notification.

Committee Oversight of Research Conducted at UMGCC

Clinical Research Oversight Committee (CROC)

The Clinical Research Oversight Committee (CROC) is the committee that oversees the Clinical Research Management Office. The CROC defines and adjusts physical and personnel resources, is responsible for approving standard operating procedures followed during the conduct of clinical research, and has the authority to consider disciplinary sanctions against clinical investigators. The CROC does NOT participate in the review of protocols.

Clinical Research Committee (CRC)

The CRC functions as the Protocol Review and Monitoring System for the UMGCC NCI Cancer Center Support Grant. It reviews all protocols for scientific merit and approves them for submission to the IRB. The CRC also closes protocols for poor accrual following annual review or at the recommendation of the Data and Safety Monitoring / Quality Assurance Committee (DSM/QAC). To submit a protocol related to cancer treatment, diagnosis, imaging or prevention to the CRC, the investigator must obtain:

1) Concurrence and sign-off from their Disease Group Head AND the Associate Director for Clinical Research
2) Concurrence from the Feasibility Committee that appropriate resources exist to support the study.

Review by the CRC requires the submission of a packet of information. Following successful address of any CRC issues, the protocol and supporting documents can be submitted to the IRB. Since the CRC ratifies to the IRB the scientific value of the study and UMGCC's commitment to the study, the IRB will not review a protocol without evidence of CRC approval attached to the submission. The IRB submission system also requires electronic concurrence by the Associate Director for Clinical Research, as well as any departmental electronic signatures required by the University. Response to any IRB issues must then be made. Those protocols originating from the Radiation Oncology program which deal solely with technology-related matters are analogously reviewed by the Technology Research Review Committee (TRRC), a subcommittee of the CRC, prior to IRB submission.

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

The DSM/QAC reviews any trial without an independent external data and safety monitoring committee. Such trials largely consist of PI initiated trials and NCI sponsored Phase I and Phase II trials, but may include certain industry-sponsored trials that do not have adequate external

DSM plans. The DSM/QAC functions as the monitoring committee of record for institutional/PI-initiated clinical trials; NCI sponsored Phase I and II trials; and corporate trials that do not have a fully independent DSM. The Quality Assurance Manager conducts auditing of these trials and provides the DSM/QAC with the audit results. The annual renewal package for these trials must be reviewed by the DSM/QAC within 90 days of anticipated IRB renewal to allow timely response to DSM/QAC concerns prior to IRB submission. The DSM/QAC may recommend that the CRC close protocols for causes including compliances problems, failure to accrue successfully, exceeding of accrual goals, or where the risk vs. benefit ratio is not favorable given the safety data collected to date.

Feasibility Committee

The feasibility committee reviews intended protocols for logistical and operational considerations. Close attention is paid to the staffing level needed to support the proposed trial in relation to existing workloads currently managed by the CRMO. Attention is also paid to special equipment or procedures that are required in the proposed research. If special equipment is needed, the cost of this equipment will be built into the study budget, when appropriate. The timing of acquisition of this equipment is also considered. Members of the pharmacy team, CRMO, department heads and QAM are all represented on the feasibility committee. When a volume of work is proposed simultaneously, the disease group heads will assist the committee in determining the priority of submission of protocols to CRC.

Institutional Review Board (IRB)

The IRB reviews and approves all research prior to conduct at UMGCC, as outlined in their Investigator Manual (http://www.umaryland.edu/hrp/institutional-review-board-irb/). Annual renewal is also required. The IRB will automatically close any protocol for which a timely renewal is not submitted. Closure of the protocol requires resubmission of the entire package to the IRB for re-review.

The UM IRB requires the use of CICERO for the submission of new protocols, as well as amendments, adverse events and annual renewals. In order to use the CICERO system, a log in is obtained from http://cicero.umaryland.edu. All users are required to complete human subjects training (CITI training – Biomedical Research Investigators AND Good Clinical Practice) and HIPAA training prior to being granted a log in. Principal investigators are additionally required to watch short videos before receiving a log in.
Refer to the training materials provided by CICERO for complete information on how to use this system. The renewal submission to the IRB including accrual, deviation and adverse event information and must also be submitted to the DSM/QAC for these trials. The PI is responsible for ensuring compliance with reporting requirements to all reporting bodies as outlined in Attachment 3 UMGCC DSM/QAC Standard Operating Procedure.