University of Kentucky
Markey Cancer Center
Institutional Data and Safety Monitoring Plan

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Date 04-29-2015
INTRODUCTION

The University of Kentucky (UK) Markey Cancer Center (MCC) places the highest priority on ensuring the safety of subjects participating in clinical trials and on the quality of data obtained from clinical and translational research. This document describes the data and safety monitoring plan (DSMP) for all therapeutic and non-therapeutic cancer clinical trials conducted by MCC investigators. All clinical trials involving humans and human specimens are monitored commensurate with the degree of risk involved with participation in the study. The MCC has implemented a process for routine real-time data monitoring and safety review of all trials, with a special focus upon investigator-initiated trials (IITs), which is based upon the Essential Elements of the National Cancer Institute (NCI) guidelines, the Food and Drug Administration (FDA) monitoring regulations, and Good Clinical Practice Guidelines. The MCC DSMP is maintained by the Associate Director for Clinical Translation and the Chair of the MCC Data and Safety Monitoring Committee (DSMC) and approved by the Director of the MCC. The MCC DSMP is reviewed and revised at least annually and is available at http://ukhealthcare.uky.edu/markey/data-and-safety/.

The MCC DSMP recognizes the NIH’s definition of a clinical trial available at: http://osp.od.nih.gov/office-clinical-research-and-bioethics-policy/clinical-research-policy/clinical-trials. Specifically, a clinical trial is a research study in which one or more human subjects are prospectively assigned to one or more interventions (which may include placebo or other control) to evaluate the effects of those interventions on health-related biomedical or behavioral outcomes.

The NCI also provides information regarding clinical trials and its clinical trials programs at: http://www.cancer.gov/clinicaltrials/nciprograms. In addition, the NCI defines “cancer health disparities” as differences in the incidence, prevalence, mortality, and burden of cancer and related adverse health conditions that exist among specific population groups in the United States.

MONITORING THE PROGRESS OF TRIALS AND SAFETY OF PARTICIPANTS

Overview

The MCC Director, Associate Directors and program leaders are actively engaged in the support of clinical and translational research to facilitate the safe conduct of human subjects research. The organizational structure for data and safety monitoring of the MCC is listed below in (Figure 1).

Institutional Oversight of Human Subjects Protection

Human research protection is a shared institutional responsibility encompassing diverse campus domains and personnel. All clinical cancer trials, that do not fall under NCI designated IRBs, are subject to institutional oversight by the UK Institutional Review Boards (IRB) with administrative support by the UK Office of Research Integrity (ORI) and subject to MCC oversight through this DSMP. The ORI Director reports directly to the Vice President for Research, who is the designated institutional official for human research protection in UK’s Federal Wide Assurance with the Department of Health and Human Services (DHHS). Through the Vice President for Research, UK grants the IRB the authority to act independently to bind all activities falling under the IRB to its decisions. In addition, direct responsibility for ethical conduct of human research and protection of research participants is the responsibility of each individual investigator. The University has transferred IRB review responsibilities for select cooperative group clinical trials to the NCI Pediatrics and Adult IRBs, consistent with NCI requirements. MCC and ORI responsibilities for NCI’s IRBs reviewed studies are outlined in the Coordinator SOP: http://www.research.uky.edu/ori/SOPs_Policies/C3-0400-NCI_CIRB_SOP.pdf
The MCC has a centralized process for monitoring the safety of research participants and the quality of the data for all clinical cancer trials conducted through the MCC and the MCC Research Network (MCCRN), as outlined in Figures 1 and 2. The Director of the MCC holds overall responsibility for overseeing data and safety monitoring and is assisted in this responsibility by the Associate Director of Clinical Translation, who oversees the function of the DSMC and the Audit Committee, the Quality Assurance Office and the Protocol Review and Monitoring System (PRMS). The QA Office reports directly to the Director and the DSMC. The Associate Director for Clinical Translation reports directly to the MCC Director on all aspects of clinical research. In addition, the Director and Associate Director for Clinical Translation are assisted by the leaders of the Clinical Protocol and Data Management Unit, which includes the Medical Director and Assistant Director of the MCC Clinical Research Office (CRO), who oversee the Clinical Research Office and facilitate the function of the Protocol Review and Monitoring Committee (PRMC), Clinical Care and Research Teams (CCARTs) and the Investigator-Initiated Protocol Development Unit (Figure 2).
**MCC Trial Monitoring Process**

Trials are monitored according to the type of sponsor, type of trial, and the assignment of potential risks. Monitoring for clinical trials involves a continuous review of the conduct of the trial, including adherence to study design and documentation of appropriate reporting of related toxicities.
IITs that are developed by investigators at the MCC and externally sponsored protocols of interest are vetted through a series of committees for scientific validity, feasibility, prioritization within our clinical trials portfolio, and patient safety (Figure 3a and 3b).

**IIT Protocol Development and Approval Process**

Clinical Care and Research Teams: Initial Concept Review and Prioritization

Clinical trials are identified or developed by MCC investigators and presented to disease-specific CCARTs. First, the investigator conceives and develops a trial concept or full protocol or identifies an externally sponsored trial for potential participation. The investigator reviews the protocol or concept with the relevant CCART, which is responsible for the coordination of care and clinical research opportunities for the pertinent tumor type under study. The CCART reviews the concept or protocol for feasibility, clinical appropriateness, and anticipated scientific gain and considers its endorsement in light of other research commitments ongoing or already in development in its clinical care and research teams.
Non-IIT Trial Approval Process

Cooperative Group trial  
| Industry partner invites participation |
|----------------|----------------|
| Clinical Care and Research Teams (CCART) review concepts |
| CCART endorsed | CCART Rejected |

Protocol Review and Monitoring Committee (PRMC)

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<tr>
<th>PRMC approved</th>
<th>PRMC rejected</th>
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<td>Protocol Initiation Meeting (PIM)</td>
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<td>Institutional Review Board (IRB)</td>
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<td>IRB approved</td>
<td>IRB rejected</td>
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Figure 3b. Flow diagram of the development of cooperative group and industry sponsored clinical trials.

trials portfolio. The CCART may approve the protocol or concept, reject the protocol or concept, or refer the investigator to the Investigator-Initiated Trial Protocol Development Unit (IIT-PDU), which functions independently of the PRMC, for additional direct mentoring and support in clinical protocol development. The standard operating procedures (SOPs) of the MCC CCARTS are available at: http://ukhealthcare.uky.edu/markey/data-and-safety/.

Protocol Review and Monitoring Committee

The PRMC is charged with overseeing the scientific integrity of clinical cancer trials at the MCC. The PRMC is a separate entity from the MCC DSMC and Audit Committee, with distinct and clearly defined authorities and responsibilities. The PRMC reviews studies for scientific significance, feasibility with available resources, scientifically meaningful accrual goals, complementary and non-competitive study population within the current trials portfolio, relevance to the programmatic goals of the MCC, and appropriate study design, including appropriate statistical analysis.

All studies of cancer or specific to patients with cancer that require the consent of participants and are conducted by MCC faculty on the MCC campus, or by MCCRN investigators, are reviewed by the PRMC. An investigator may send a concept to the PRMC prior to developing a full protocol for scientific guidance and review or may submit a fully developed protocol. In general, cancer investigators send full study protocols to the PRMC first and then to the UK IRB once they have been either approved by the PRMC or deemed exempt from PRMC review. To coordinate IRB review with PRMC review and approval, the IRB application form includes a section to identify cancer-related studies and ensure review by the PRMC. In addition, monthly the UK IRB sends study listing of all cancer trials for which it is responsible to the ADCT and CRO leadership. If a researcher submits a clinical cancer research protocol to the IRB without having obtained prior PRMC review, the IRB notifies the PRMC and requests a review. The MCC will not activate any non-exempt (see PRMC definition below) cancer study without PRMC review and approval and IRB approval.

The Chair of the PRMC is appointed for a three-year term by the MCC Director. Committee members are appointed by the Chair and the ADCT and approved by the Director and serve three year terms. Ad-hoc members may be appointed by the Chair, as needed. One of the voting members will serve as the Vice Chair appointed by the Chair. Membership of the PRMC is comprised of a broad representation with a focus on senior cancer investigators and includes clinical cancer expertise from all disciplines at the MCC, the Biostatistics and Bioinformatics Shared Resource Facility (BBSRF), MCC Pharmacy, MCC basic science programs and the MCC Cancer Prevention and Control Program, MCCRN, as well as a patient representative. There is no limit on the number of terms a member may serve. The MCC Director approves the nomination of PRMC members. The current roster of the MCC PRMC is available at: http://ukhealthcare.uky.edu/markey/data-and-safety/.

PRMC SOPs define required attendance and quorum rules. Members are required to adhere to the UK Financial Conflict of Interest in Research policy, to sign an on-line conflict of interest declaration.
annually, and to update it, as necessary (see Conflict of Interest section below for further details). Investigators with a conflict of interest with the protocol being reviewed must recuse themselves. If a conflict of interest exists between a reviewer and his/her assigned project, it is the reviewer’s responsibility to notify the PRMC Chair upon receipt of the meeting packet.

Clinical research protocols received by the PRMC ultimately require one of three possible levels of review: 1) exempt (termed “not a clinical trial” in communication to PI), 2) expedited or 3) full committee review. Exempt studies do not involve cancer research, do not consent cancer patients, or do not reflect the NCI’s definition of a Clinical Trial. The PRMC Chair completes assessment certifying the level of review most appropriate and as outlined in SOPs:


Research studies are exempt from PRMC review if they: 1) do not require the consent of participants, or 2) do not involve cancer research, or 3) do not reflect the NCI’s definition of a clinical trial. The PRMC Chair determines whether a research study is exempt using the above criteria. If the PRMC chair is conflicted, the Vice Chair makes the determination.

Protocols derived from a cooperative group member of the National Clinical Trials Network or those that have undergone external peer review qualify for an expedited review by the PRMC Chair or designee after the CCART has completed its review. This expedited review does not duplicate the review that these protocols receive at the NCI or other external peer review process, but focuses instead on local feasibility and the place of the protocol within the prioritization scheme of the relevant CCART. If the facilitated review is performed outside of a PRMC meeting, the results of the facilitated review are presented at the next PRMC meeting. In addition, screening, supportive care, basic science, diagnostic, health services research, may undergo expedited PRMC review.

Protocols endorsed by a CCART that are not eligible for PRMC exemption or expedited review are reviewed by the full PRMC at a twice-monthly meeting. Protocols are evaluated by assigned reviewers who are members of the PRMC or ad hoc reviewers if additional expertise is requested by the PRMC Chair. All investigator-initiated and pharmaceutical company sponsored trials must undergo a full review, where two clinical investigator reviewers, an oncology pharmacist, and a statistician review these protocols and present their findings to the convened PRMC.

The PRMC has authority to close a study at the MCC or recommend against IRB continuation renewal if accrual plans and/or scientific progress are not being achieved. Each study is reviewed by the CCART monthly, as each CCART is provided information detailing open and pending trials on an ongoing basis. Guidelines for study closure target studies meeting less than 50% accrual goal for intervention and provide a framework to balance appropriate resource use and maximize opportunities for current and future patients with cancer. Investigators and CCARTs are encouraged to share information about extenuating circumstances before the review, monitor accruals in real time, and continuously reconsider the feasibility of the science proposed. An investigator may appeal PRMC recommendations for closure to the MCC Director, though investigators are strongly encouraged throughout the life of their study to work with the PRMC liaison in the respective CCART and to self-evaluate the feasibility of their proposed and ongoing work.

**Investigator-initiated Trial Protocol Development Unit**

The IIT PDU supports investigators who are in the process of protocol development and optimization, consistent with the goals of the PRMC and thus functions as an available complementary resource. The purpose of the IIT PDU is to identify and promote high-quality,
therapeutic-intent IITs at each stage, from the inception of a scientific concept to trial development, protocol writing, statistical support, and submission to the MCC protocol review process. Investigators may request IIT PDU support directly, be referred by their CCART, or be referred by the PRMC or the PRMC Chair. The IIT PDU is designed to provide a support mechanism to assist investigators in improving the potential of the IIT for success and meaningful discovery. The IIT PDU Executive Committee, made up of senior MCC leadership meets on a quarterly basis to review the MCC’s portfolio of IITs and to help facilitate promotion of new IITs by contributing scientific review, facilitating study development, and identifying funding when appropriate. The Executive Committee is also charged with prioritization and approval of IITs that request use of the Clinical Research and Data Management shared resource and other shared resources.

Office of Research Integrity

The UK ORI provides administrative support for seven federally mandated review committees: four Medical and one Nonmedical IRBs, the Institutional Animal Care and Use Committee, and the Radioactive Drug Research Committee. ORI also supports the institution in promoting ethical conduct of research and educating UK students and employees regarding research misconduct regulations, data ownership and animal care regulations. The ORI reports directly to the UK Vice President for Research. Additional information is available on the ORI website: http://www.research.uky.edu/ori/.

Institutional Review Board

UK’s human research protection program is fully accredited by the Association for the Accreditation of Human Research Protection Programs Inc. Any activity that meets the federal definition of both "research" and "human subjects" or the FDA definition of "clinical investigation" requires review and approval by a UK designated IRB. The UK IRB is charged with protection of the rights and welfare of human participants involved in research and conducts the following reviews: 1) initial IRB review for new protocols, 2) modification review for changes made to IRB-approved studies, 3) continuation review for ongoing approved studies, 4) review of unanticipated/anticipated problems/adverse events (AEs) associated with a study, and 5) protocol violations. Review types include exempt, expedited or full review. The IRB has the authority to approve, disapprove, or modify research; conduct continuing review; monitor consent process/conduct of research; suspend/terminate approval; investigate allegations of noncompliance. No individual at the UK MCC or committee of the MCC may permit the conduct of human research that has not been approved by the University of Kentucky’s IRB or a University of Kentucky designated IRB such as the NCI Central IRB.

The University recognizes the requirement of the NCI for Central IRB review of certain NCI-sponsored cooperative group clinical trials and the University has adopted the NCI required independent model for these studies.

The Vice President for Research appoints members to standing university research committees and, as authorized by the President, appoints Chairs, Vice Chairs, and members to the UK IRBs. Approximately once a year and as appropriate, the ORI submits recommendations for membership to the Vice President for Research. Appointments for IRB Chairs, Vice Chairs, and IRB members (including alternates) are for staggered three-year terms beginning the fall of each academic year. UK has no limit on the number of terms IRB Chairs, Vice Chairs, members, and alternates may serve on the IRB. Four Medical IRBs review research emanating primarily from the Colleges of Dentistry, Medicine, Nursing, Pharmacy, Health Sciences, and Public Health. These review boards comply with the federal and state regulatory requirements for human research protection. Each IRB at UK has a minimum of five voting members sufficiently qualified through experience and expertise to promote respect for its advice and counsel in safeguarding the rights and welfare of human
subjects. The membership includes regular members who have designated alternates with qualifications comparable to the regular member. Additionally, in accord with Office for Human Research Protections (OHRP) policy, a regular member of any of the UK IRBs may serve as an alternate for any comparably qualified member on any other UK IRB. While not listed on the OHRP/FDA roster, consultants and *ex officio* members provide guidance and input regarding IRB operations and protocol review.

IRB membership complies with federal requirements outlined in 45 CFR 46.107 and 21 CFR 56.107 to ensure appropriate diversity of the members through consideration of multiple professions, disciplines, ethnicities and cultural backgrounds, gender, and sensitivity to such issues as community attitudes. In addition, the IRB includes members who can determine the acceptability of proposed research in terms of institutional commitments and regulations, applicable law and standards of professional conduct and practice. If the IRB regularly reviews research involving a vulnerable category of subjects, the IRB membership includes individuals who are knowledgeable about and experienced in working with those populations. Each IRB includes at least one member with each of the following primary affiliations: nonscientific, scientific, and nonaffiliated (i.e., not affiliated with UK and not part of the immediate family of a person affiliated with UK), as well as a physician (on IRB committees that review FDA regulated studies). In addition, the IRB invites individuals with competence in special areas to assist in the review of issues which require expertise beyond or in addition to that available on the IRB. To meet OHRP/FDA registration requirements and in order to hold convened meetings, the scientist and nonscientist member designations are clearly defined and separate.

The MCC recognizes the independence and importance of the IRB and seeks to complement the IRB’s role in the protection of participants through its DSMP, DSMC, and Audit Committee. Regular and reliable communication between the IRB and the MCC is ensured through collaborative SOPs and direct contact between the Director and Chairs of the Medical IRB and the MCC Director and Associate Director for Clinical Translation in an ongoing manner. The IRB and the MCC have developed SOPs of collaboration to define the responsibilities of each entity and to ensure effective coordination of review processes, available at: [http://www.research.uky.edu/ori/human/SOPs_&_Policies.htm](http://www.research.uky.edu/ori/human/SOPs_&_Policies.htm)

**Data and Safety Monitoring Committee**

The MCC DSMC assures patient safety and protocol compliance and is overseen by the DSMC Chair who reports to the MCC Associate Director for Clinical Translation and ultimately the MCC Director. Data and safety monitoring functions are separate from other oversight processes of the MCC and are supervised by the Associate Director of Clinical Translation (ADCT). While the Protocol Review and Monitoring System (PRMS) is charged with overseeing the scientific aspects of cancer clinical trials at the MCC, data and safety monitoring remains a separate process. DSMC SOPs are available at: [http://ukhealthcare.uky.edu/markey/data-and-safety/](http://ukhealthcare.uky.edu/markey/data-and-safety/).

The Chair of the DSMC is appointed for a three-year term by the MCC Director. Committee members are appointed by the Chair and the ADCT and approved by the Director and serve three-year terms. Ad-hoc members may be appointed by the Chair, as needed. One of the voting members will serve as Vice Chair appointed by the Chair.

- **Voting members**
  - The Chair
  - Four (4) members who are active investigators appointed for a three-year term.
  - The Associate Director for Clinical Translation
• A biostatistician from the BBSRF
• A pharmacist from within the MCC and/or Investigational Drug Service (IDS)
• A nurse

**Non-voting members:**
• The Assistant Director of the MCC Clinical Research Office (CRO)
• The Medical Director of the Clinical Research Office (CRO)
• DSMC Coordinator for the meetings
• Member, Cancer Research Informatics Shared Resource Facility (CRI SRF)
• Patient Care Manager, MCC Chemotherapy and Infusion Center
• Quality Assurance Program Manager
• MCCRN Project Coordinator

The DSMC meets monthly. In order for the meeting to take place, at minimum, the following must be present at the meeting: Committee Chair or designee, three clinician members of the DSMC, a biostatistician from the BBSRF. The current roster of the MCC DSMC is available at: http://ukhealthcare.uky.edu/markey/data-and-safety/.

The DSMC will act as the Data and Safety Monitoring Board (DSMB) for studies approved by the PRMC that meet the NCI’s requirement for a DSMB (available at: http://www.cancer.gov/clinicaltrials/conducting/dsm-guidelines/page2#dsmb_req) and that do not have an external DSMB that meets the requirements for DSM by the NCI, unless otherwise specified by this plan or the IRB of record. The DSMC will review and monitor study progress for all MCC IITs. Concurrently, the Early Therapeutics CCART closely monitors the progress of all phase I and complex phase II trials, as well as MCC IITs on a monthly basis, and reviews all AEs and serious adverse events (SAEs), study accrual, and study progress. AE levels are determined by the NCI’s Common Terminology Criteria for Adverse Events (CTCAE), with version specified by each protocol and with current versions available at: http://ctep.cancer.gov/protocolDevelopment/. In addition, the DSMC monitors the progress of all MCC study participants on industry-sponsored trials, NCI National Clinical Trials Network (NCTN), or cooperative group trials or any trial designated by the PRMC. The DSMC also has access to the external DSMB reports of these entities.

The DSMC meets monthly to conduct monitoring reviews as outlined by the initial PRMC review and on an ad hoc or emergent basis at the discretion of the Chair, the MCC Director or Associate Director for Clinical Translation. The DSMC will review study-specific reports regarding study status, safety, and progress as designated by the risk assignment and level of review. These reports will include protocol deviations, subject accruals, and analysis of SAEs, at a minimum. In addition, for all IITs, AEs will be included in the review. The DSMC will monitor the following elements:
• AEs (at a minimum all CTCAE Grade 3, 4 and 5 AEs) for IITs
• SAEs for all studies
• Protocol deviations
• Audit Committee reports, if applicable
• Previous DSMC reviews, if appropriate
• Study-specific MCC DSMB reports
• Suggested actions from other committees such as the IRB, Indemnification Committee, Conflict of Interest Committee, Early Therapeutics CCART, if applicable
• DSMC and/or DSMB Reports from outside entities such as cooperative groups and industry of studies involving MCC subjects
• Analysis of primary and secondary efficacy parameters and outcomes if required (i.e., early stopping rules, interim monitoring, etc.)
• Suggested actions, if applicable

The DSMC has the option of two levels of review: expedited and full. Full review will be performed for all trials that are not low risk as defined by the MCC (see Table 1). At the discretion of the MCC Director, the ADCT, or the DSMC chair, the DSMC may also choose to perform full review of selected low risk studies. The Chair of the DSMC reviews each study in full committee with a review outcome determined at the meeting. If there is insufficient data for a complete review, the study is re-reviewed at the next meeting. If appropriate, the DSMC will designate and monitor corrective action(s) based on review outcome. The DSMC will have the authority to terminate protocols based upon issues of safety or scientific misconduct, and will notify the MCC Director and ORI’s Research Compliance Officer of such decisions, as outlined in the University of Kentucky's Administrative Regulations 7:1. The DSMC will make the following recommendation for all trials reviewed during the DSMC meeting:

• Approved – Enrollment may continue
• Close to accrual – Close enrollment
• Temporarily Close to Accrual – delinquent progress report, need for corrective action plan

If appropriate, the DSMC will designate and monitor corrective action(s) based on review outcome. Corrective action plans will be reviewed at the next DSMC meeting with a determination by the entire committee: approval, approval with amendment, table, or decline approval. The DSMC Chair will convey the results in writing to the principal investigator (PI). If the PI does not feel that the issues have been addressed in a satisfactory manner, the PI may appeal to the Associate Director for Clinical Translation and/or the Director of the MCC.

If the DSMC recommends amendment and/or termination of a protocol based upon issues of safety or study misconduct, a cover letter summarizing the nature of the discrepancies and their resulting requirements and/or decisions by the DSMC will be sent to the PI, the Medical Director of Clinical Research Office (CRO), the MCC Director, the Associate Director for Clinical Translation, the DSMC Chair and the PRMC Chair. Additionally, if it is determined that the study should be closed or suspended, all sponsoring agencies, the UK ORI RCO, and other relevant regulatory agencies will be notified promptly.

Expedited reviews may be performed by the Chair for low risk studies. The Chair has the right to request a full review, call a committee meeting, or request other action if the Chair finds the expedited review insufficient. Studies which are non-interventional and therefore do not record SAEs or deviations in the MCC electronic clinical trials database, OnCore, will require annual review by DSMC, with staff required to provide IRB records of any SAEs or deviations reported during the review period.

DSMC Audit Review
The DSMC receives and reviews final audit reports from the Audit Committee and renders decisions based on these reports. Audit Committee reports are presented by the Audit Committee Chair or designee for discussion with the DSMC. The DSMC will determine the appropriate action based on the audit report as follows: “Acceptable”, “Acceptable needs follow-up” or “Unacceptable” to each audit component. Audits are reviewed on a study-by-study basis, and components found to be unacceptable, require corrective and preventive action as defined by the DSMC. In addition, based on the findings, the DSMC may choose to suspend a study or an investigator until all deficiencies have been adequately addressed in writing to the DSMC Chair and approved by the DSMC. The PI
may present a formal appeal to the DSMB. The PI may request to be present at the DMSC meeting and must notify the DSMB Chair of the request to attend the DSMB meeting after the audit report is received. The PI should prepare and submit to the DSMB a formal written response to the audit findings prior to the scheduled meeting. The PI will have the opportunity to present and discuss the details of the audit with the DSMB members. In addition, the DSMB will have a closed session to review both the Audit Committee’s review and the issues presented by the PI and make a determination. If the PI does not feel that the issues have been addressed in a satisfactory manner, the PI may appeal to the Associate Director for Clinical Translation and/or the Director of the MCC.

Temporary or permanent suspension of any NCI-sponsored clinical trial by either the DSMB or the IRB will be reported immediately to the NCI project manager for that trial. If Cancer Therapy Evaluation Program (CTEP) drugs are used in the study, the suspension will also be reported immediately to CTEP. If the suspension is temporary, the NCI and CTEP will also be notified in a timely manner regarding the resolution of the issues that caused the suspension and the date that the suspension was lifted. The DSMB Chair forwards a copy of the major audit findings and the DMSC decision to the UK ORI Research Compliance Officer, who forwards the report to the IRB and/or ORI Director in accord with standard ORI/IRB operating procedures. In addition, any review by the DSMB that results in suspension of any NCI-CIRB monitored study, will follow the notification policies of the NCI CIRB Review SOP: http://www.research.uky.edu/ori/SOPs_Policies/C3-0400-NCL_CIRB_SOP.pdf and, if applicable, the MCC/IRB/ORI Coordination SOP: http://www.research.uky.edu/ori/SOPs_Policies/C6-0400-Markey_SOP.pdf.

All DSMB members complete an annual significant financial interest disclosure, as listed below and must abide by UK’s Confidentiality Agreements and Conflict of Interest Forms. Abstention from monitoring review or voting by committee members will be accepted only if the committee member has a conflict of interest and/or a lack of expertise in the scientific subject of the protocol. A committee member who is an investigator on a study will be asked to recuse him/herself from the review process.

Investigational Drug Service (IDS) Oversight and Collaboration

The IDS supports all clinical drug-related research conducted by investigators at the UK Medical Center. The IDS reviews protocols for study drug and device concerns; receives and maintains investigational and/or study drugs and devices; and stores, prepares, and verifies and dispenses study drugs and devices. The IDS is managed by the Department of Pharmacy and provides the support needed to assure safe and efficient conduct of clinical drug trials including compliance with federal, state, and The Joint Commission (TJC) requirements regarding investigational drugs. All inpatient studies are required by UK HealthCare policy to utilize the IDS. Any exceptions must be arranged in advance between the IDS and the PI. The MCC utilizes the IDS for all outpatient drug studies involving investigational agents. The MCC and the UK Center for Clinical and Translational Science advise the IDS regarding policy, performance metrics, and needs of the centers as they pertain to investigational pharmaceuticals. As part of this oversight, the MCC Associate Director for Clinical Translation serves on the IDS Steering Committee.

Data and Safety Monitoring Boards

A DSMB is required by the NCI for all phase III randomized trials, excluding low-risk behavioral and nutritional trials, which require a DSMP but not necessarily a DSMB, depending on the anticipated level of risk to participants. The PRMC will determine whether or not a DSMB is required in the case of low-risk or nutritional studies. All MCC investigator-initiated phase III clinical trials must have a DSMB appointed prior to initiation of the trial. If no independent DSMB exists, the MCC will assist in the creation of a DSMB. Guidelines for the structure of DSMB are as follows. The PI will suggest
members of the DSMB, which will be approved by the MCC Director and the MCC Associate Director for Clinical Translation. Voting members will include physicians, biostatisticians, other scientists based on expertise and knowledge of the clinical trial proposed, pharmacist, and ad hoc members at the discretion of the MCC Director. A majority of voting members should not be directly affiliated with the MCC, and no voting member may be directly involved with the design, enrollment, or analysis of the trial.

Members will receive the written trial, plans for data and safety monitoring, planned monitoring for study progress (i.e., interim monitoring, early stopping rules, etc.), randomization procedures, and accrual estimates. The DSMB will determine the number of reviews based on risk, study timeline, and study endpoints, but should meet at least twice per year. At each meeting, an open session including a study summary prepared by the PI, study statistician and CRO staff will be presented, as well as any relevant new information from the scientific field that would impact the current study. All safety data, study accrual, and progress should be included in these reports. The DSMB will then move to a closed session to review the general conduct of the trial, review outcome and toxicity results, and determine whether the study: 1) should continue as originally designed, 2) requires modification, or 3) should be terminated based on the data reviewed. Following the meeting, the DSMB provides the PI and study staff with a written report of their findings, deliberations, and recommendations, as well as plans for the next meeting. DSMB activities will continue until the study completes enrollment and no further patient safety issues require monitoring, as determined by the DSMB. These written reports will not contain any confidential data from the protocol (including outcomes data, blinded information, or other proprietary information). The DSMB is charged with maintaining strict confidentiality regarding all elements of the study and is required to adhere to the UK Conflict of Interest Policies. The DSMB also provides this report to the MCC Director, Associate Director for Clinical Translation, the IRB and relevant external entities. If requested, the study PI will respond in writing to any queries, recommendations or requests for further information from the DSMB. The ORI’s guidance document on DSMB creation is available at: http://www.research.uky.edu/ori/QIP/DSMP.htm.

Conflicts of Interest

As a public land-grant institution, the University has an obligation to the citizens of the Commonwealth and the general public to conduct its activities transparently and with integrity. The University is committed to avoiding financial conflicts of interest that may compromise, or appear to compromise, the integrity and objectivity of research and the safety of human research subjects. Because the University encourages its members to engage in outside activities and relationships that enhance its missions, real or perceived conflicts of interest may arise.

The keystone of an effective program for identifying and dealing with financial conflicts of interest is full disclosure of those financial interests that reasonably appear related to one’s institutional responsibilities. UK Conflict of interest regulations provide guidance and procedures for disclosure by investigators of their relative significant financial interests.

Pursuant to Federal regulations, the Institutional Official shall inform each Investigator about this regulation and of his/her responsibilities to comply. Prior to engaging in sponsored research, each Investigator shall complete training regarding the disclosure of significant financial interests and the management, reduction or elimination of financial conflicts of interest. Training shall be repeated at least every four years or when (a) this regulation is substantially revised; (b) an Investigator is new to the University; or (c) if an Investigator is determined to not be in compliance with this regulation. After the disclosure, the University can make an informed judgment about a particular activity and require appropriate oversight, limitations, or prohibitions in accordance with its Administrative
To summarize, an individual investigator shall complete at least annually a Financial Interests Disclosure Statement (Disclosure Statement) whether or not he or she has financial interest to report. The Disclosure Statement shall include the financial interests of the Investigator and those of his or her spouse and dependent children. An individual investigator shall submit an updated Disclosure Statement within 30 days of acquiring a new financial interest that reasonably appears related to his or her institutional responsibilities. New employees who are required to disclose under this regulation shall complete a Disclosure Statement within 30 days of their employment start date. An individual covered by this regulation shall submit a Disclosure Statement prior to submitting a proposal seeking external funding, or prior to participating in any research activity regardless of the source of funding. Investigators, who apply for or receive funding through a PHS grant, cooperative agreement, or contract, shall disclose each instance of reimbursed or sponsored travel (i.e., paid on behalf of the Investigator rather than being reimbursed) that reasonably appears related to their institutional responsibilities within 30 days of the completion of such travel. Disclosure Statements shall be reviewed by the Institutional Official or designee to assess whether or not a significant financial interest constitutes a financial conflict of interest. If a financial conflict of interest appears to exist, the Institutional Official shall involve the appropriate dean or director and shall refer the case to the Research Conflict of Interest Committee as needed for review and input.

In cases where the investigator is a member of the MCC, the Center Director and the Associate Director for Clinical Translation also receive notification of the conflict of interest plan for the investigator, from the Research Conflict of Interest Committee of the University of Kentucky. The Associate Director for Clinical Translation reviews the conflict of interest management plan, and the DSMC reviews these plans yearly or more frequently when deemed necessary by the Director or Associate Director as an additional assurance that mediation is ongoing and appropriate. Any deviation from the management plan or problems arising during the conduct of the study will be communicated to the Research Conflict of Interest Committee of the University. The DSMC of the MCC is not involved in the Conflict of Interest Committee’s decision making or due process but serves as an internal check that the process is proceeding as defined by the committee. Federal regulations governing financial conflicts of interest for Public Health Service-funded activities are promulgated at 42 CFR Part 50 and 45 CFR Part 94.

In addition, UK has established institutional conflict of interest policy, Regulation 7.9 Institutional Conflicts of Interest Involving Research intended to provide clear guidance and procedures for the disclosure and management, or elimination, of institutional conflicts of interest, whether real or perceived, that may otherwise compromise processes for the review or oversight of research. This policy can be found at: http://www.uky.edu/regs/files/ar/ar7-9.pdf.
**Definition of Levels of Risk in Clinical Trials**

All studies opened at the MCC are assigned a risk level at the time of review by the PRMC. The levels of risk described are a guide for the PRMC to assign review intervals by the DSMC, and are also used by the Audit Committee and by the UK Indemnification Committee to determine frequency of auditing and to define risk.

Table 1. Determination of Level of Risk in Clinical Trials

<table>
<thead>
<tr>
<th>Level of Risk</th>
<th>Explanation</th>
<th>Examples</th>
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| **Low Risk**  |  Non-intervention trials (epidemiologic, outcome, observational, QOL, correlative lab/ancillary) | • Behavioral Studies  
• Nutrition/food supplement Studies  
• Observational Studies  
• Survey / questionnaire Studies  
• Correlative sample acquisition |
|               |  Interventionsal Trials that are behavioral, nutritional, psychosocial or pose no more risk than expected in daily life |          |
| **Moderate Risk** |  Phase II, III, IV therapeutic, palliative or prevention trials that are sponsored by national cooperative groups or NCI / NIH that already include independent appropriate/approved DSMPs | • Most cancer treatment studies  
• Cooperative group cancer treatment studies |
|               |  Phase II, or III therapeutic, palliative or prevention trials sponsored by industry that include appropriate / approved monitoring plans |          |
|               |  Investigator-initiated single institution phase III studies deemed moderate risk by PRMC |          |
| **High Risk** |  MCC IIT’s that are phase I, I-II and II or with early stopping rules / interim monitoring  
  Trials for which the MCC investigator holds the IND/IDE  
  Studies which involve the manufacture of agents by UK investigators  
  Phase III investigator-initiated multi center trials that do not have an industry-sponsored monitoring plan  
  Other phase I studies with industry or cooperative group sponsorship  
  Gene therapies that are not FDA approved  
  High dose studies (i.e., transplantation)  
  All viral, bacterial, or cellular based vaccine studies, regardless of whether or not the vaccine is “live”, attenuated or “killed” | • First in human device and agent studies, and studies determining maximum tolerated dose  
• A gene therapy study or research involving recombinant DNA molecules  
• Investigator-initiated multicenter trial  
• Study involves the manufacturing of agents by UK  
• Bone marrow support needed after chemotherapy |
Categories of Clinical Trials Monitored by the MCC and Level of Monitoring

The MCC monitors all clinical trials, and as described above, the extent of the monitoring varies by the degree of risk encountered by study participants, the study sponsor, the type of agent or agents involved, the phase of the clinical trial, and the complexity of the study.

MCC Investigator-Initiated Therapeutic Intervention Trials

**Phase I** - It is the responsibility of the PI, the study statistician, and study nurse of each phase I study to continuously monitor all subjects for central elements, including toxicities and their resolution and response to the intervention. The Early Therapeutics CCART also monitors severe adverse events and their resolution, deviations and reports these to the DSMC. In addition, for dose-escalating trials the Early Therapeutics CCART monitors the subjects at each respective dose level, dose escalations, interim analysis, and early stopping rules, to assure the conduct of the trial complies with protocol design. The DSMC monitors all phase I studies for study progress and study-defined endpoints.

**Phase II** - These studies are monitored by the study statistician, as well as the PI and study team. The DSMC will review study-specific reports regarding study status, safety, and progress as designated by the risk assignment and level of review determined by the PRMC. These reports will include protocol deviations, subject accruals, and analysis of AEs and SAEs. These reviews occur annually at a minimum.

**Phase III** – All phase III trials will require a DSMB which should be described in the protocol’s DSMP and must be approved by the PRMC and the IRB. The DSMC and the IRB will review the DSMB monitoring reports from these studies.

Multicenter Investigator-Initiated trials in which the MCC is the Coordinating Center

The MCC will require all sites to obtain approval from their IRB of record, under which each site will conduct its research. The MCC will identify a project manager/coordinator who is responsible for ensuring that MCC policies and procedures for conduct of multicenter clinical trials are followed, per the SOP: “Conducting Multi-Center Markey Cancer Center Investigator Initiated Trials” The MCC DSMC will have oversight over multicenter IITs per the guidelines of the MCC DSMP.

Other Therapeutic Intervention Trials

**Sponsor: The National Institutes of Health and/or National Cancer Cooperative Groups**

NCI-sponsored cooperative group trials are currently conducted by MCC either through direct membership in the cooperative groups or via the Clinical Trial Support Unit. Phase I, II, and III clinical trials that are sponsored by the NCI Cooperative Groups are monitored centrally by mandated, long-standing DSMCs at the cooperative group level. These cooperative group studies are not primarily monitored by the MCC DSMC, but they are included in the annual internal audits conducted by the MCC Audit Committee.

National Institutes of Health R-series grant mechanisms provide funding for small pilot, phase I, or phase II clinical trials of agents. These grants supporting clinical trials are required by the sponsoring agency to provide specific DSMPs at the time of funding. Studies monitored under a Phase I contract will use the NCI-specified reporting mechanisms. These trials will be monitored by the DSMC, depending upon their level of risk, and they are included in the internal audits conducted by the MCC Audit Committee.
Industry Sponsors
Protocols sponsored by an industry partner or pharmaceutical company are monitored by the company holding the Investigational New Drug (IND) application; specific arrangements for monitoring are included in the agreement with the sponsoring company and outlined in the protocol-specific DSMP. These trials are reviewed at the MCC DSMC to ensure MCC participant safety and compliance with protocol requirements.

Multicenter Investigator-Initiated Trials in which the MCC is a Participating Site
The MCC will review the DSMP for any collaborative trial; the DSMC will ensure the monitoring by the other institution meets the minimum requirements of the MCC DSMP and that the specific responsibilities and oversight provided by the coordinating center are clearly defined. The MCC DSMC will monitor this study for all subjects enrolled at the MCC as required by the MCC DSMP. Subjects accrued at the MCC are subject to audits by the MCC Audit Committee.

Non-Intervention Trials and Low Risk Studies
For trials based upon survey research, questionnaires, blood or tissue sampling, observational studies, or limited interventional studies typically addressing research in cancer prevention and control, monitoring is primarily through the PI and research nurse or data coordinator. The protocol must contain DSM language which is appropriate to the study’s level of risk. The conduct of the study and any observed toxicities (including AE and SAE events) are reported in documentation to the IRB of record and reviewed yearly by the DSMC.

Training Grants
Certain types of NCI career and training awards may support clinical trials, directly or indirectly. NCI's DSM policy covers those career and training awards in which the trainee has direct responsibility for conduct of the clinical trial or in which award funds directly support the trial. Responsibility for compliance with NCI's DSM policies rests with the grant recipient; this may be either the trainee or the training program director, depending on the award (individual versus institutional). Trainees in a mentored career program should consult with their mentors about adapting or designing suitable DSMPs for their clinical trials. In most cases the trainees will be in a mentored stage of their career and will lack the experience needed to provide appropriate oversight of the trial. The DSMP must therefore clearly identify the senior individual responsible for monitoring the trial and the function of the trainee in this process.

For institutional career development programs (e.g., K12, R25T) in which clinical trials are an integral part, applicants should provide with their application a "Special Institutional Statement Regarding Human Subjects Research under K12 or R25T Support". This statement must be provided to NCI Program staff for evaluation and approved before the initial grant award can be issued and submitted for evaluation and approval with each "Application for a Continuation Grant."

For individual career development awards in which the grantee has direct responsibility for trial conduct or in which award funds directly support the trial, the DSMP covering the trial may NOT be an institutional plan. The DSMP must be tailored specifically to the clinical trial. A DSMP does not need to be provided for individual career development awards in which:

- The trial is a component of an NIH Cooperative Group trial;
- The trial is a CTEP-supported protocol;
- The trial is being partially or completely supported by an investigator-initiated NIH R-grant, with an approved DSMP.
For individual career development awards in which a clinical trial will be conducted that does not require the submission of a DSMP, the grantee must submit for evaluation a letter to NCI program staff describing his/her situation and explaining why a DSMP is not needed. This letter must be co-signed by the institutional official authorized to evaluate issues pertaining to data and safety monitoring and, in the case of mentored awards, by the grantee's mentor.

If the clinical trial is not to be started immediately upon award of an individual career development award but will follow after a considerable lapse of time (years), submission of a DSMP to NCI for approval may be delayed until the nature of the trial is clear and its initiation is in the near future. This will insure that the DSMP suits the needs of the trial.

For NCI career development awards for established investigators (K05, K24), a DSMP does not need to be provided. However, a restriction term will be included in each Notice of Grant Award requiring that the grantee remain in compliance with the NCI's policy on data and safety monitoring throughout the project period.

ASSURING COMPLIANCE WITH REQUIREMENTS FOR UNANTICIPATED PROBLEMS/ADVERSE EVENT REPORTING

IRB Requirements

MCC investigators follow the federal reporting guidelines of the NCI and the NIH, as well as the requirements of the IRB. The MCC and UK Office of Research Integrity (ORI) have developed a coordination SOP, available at: http://www.research.uky.edu/ori/SOPs_Policies/C6-0400-Markey_SOP.pdf. This document describes the communication and collaboration of MCC and IRB.

Regulatory guidance provided in 45 CFR 46.103(b)(5) and 21 CFR 56.108(b) requires the IRB to have in place written procedures for ensuring prompt reporting to the IRB, appropriate University officials, and applicable regulatory agencies of any unanticipated problems involving risk to human subjects or others. The UK reporting categories are as follows:

Prompt Reporting of an unanticipated problem involving risk to subjects or others (including unanticipated serious or life-threatening AEs) and anticipated or unanticipated related deaths to the IRB and Institutional Biosafety Committee.

Non-Prompt Reporting of anticipated problems/anticipated SAEs or unrelated deaths (required by sponsor but not by UK) to the IRB.

Continuation Review Reporting if any problems/AEs occurred within 12 months prior to the continuation review request for a written summary of all problems/AEs involving subjects since the study was initiated, whether anticipated or unanticipated, serious or not serious, life-threatening or not life-threatening, or related or not related to the IRB.

The UK IRB has processes in place for reporting of AEs that occur during research conducted at the MCC, as well as clearly defined policies and procedures that describe the mandatory reporting requirements of unanticipated AEs or SAEs to external sponsoring and/or regulatory bodies. IRB guidance in the prompt reporting of unanticipated problems/adverse events is available on the website: http://www.research.uky.edu/ori/SOPs_Policies/C2-0350-Unanticipated_Problems_Adverse_Events_SOP.pdf.

Reporting to other entities

The UK IRB has specific reporting requirements for external funding agencies that comply with the requirements of each specific agency, as outlined in the Mandated Reporting to External Agencies
SOP and available at: http://www.research.uky.edu/ori/SOPs_Policies/C4-0150-Mandated_Reporting_toExternal_Agencies_SOP.pdf. The MCC complies with UK IRB reporting requirements:

- **FDA:** For clinical trials conducted under IND held by MCC investigator, the PI reports SAEs in accordance with 21 CFR Part 312.32 Expedited Safety Reporting Requirements for Human Drug and Biological Products.
- **FDA:** For clinical trials conducted with a commercially available agent/device (no IND involved), the PI reports SAEs through FDA Form 3500 (MedWatch).
- **NIH Office for Biotechnology Activities:** For clinical trial involving recombinant DNA molecules (gene transfer), the PI follows the NIH Guidelines for Research Involving Recombinant DNA Molecules.

In addition the MCC has cancer-specific reporting requirements listed below:

- **MCC DSMC:** The PI reports all AEs for phase I and II IITs (CTCAE Grade 3, 4 and 5 AEs at a minimum) to the DSMC.
- **NCI CTEP and/or NCI sponsored NCTN or NCI cooperative group:** The PI reports all AEs and SAEs as required by the study protocol to CTEP and/or NCI NCTN/cooperative group.

Appendix I outlines the investigator’s responsibility in report serious adverse events to internal and external entities. In addition, if MCC is the coordinating center for multi-center clinical trials with other research entities, centralized reporting mechanisms and requirements will be instituted by the MCC as per defined SOPs and policies.

For trials involving behavioral or nutritional interventions that do not use an investigational agent: Since there are no standard grading scales for adverse events, defining suitable grades for AEs is the responsibility of individual investigators for each protocol. AEs of a psychological nature can occur with behavioral trials and should be specified for the particular intervention in question.

**ASSURING DATA ACCURACY, SECURITY, AND PROTOCOL COMPLIANCE**

The MCC has multiple mechanisms in place that cooperate to ensure data accuracy, security, and protocol compliance in clinical cancer research. These include complementary entities that strengthen the whole process including: 1) the MCC Quality Assurance Office, 2) the Audit Committee, 3) the BBSRF and the CRI SRF, 4) the Clinical Research Office (CRO), and 5) the investigators of the MCC. The integration of these entities is critical to high quality data acquisition and maintenance and relies on the key features of each entity, as described below.

**Quality Assurance Office**

The MCC Quality Assurance Office oversees the maintenance of quality standards in clinical cancer research through the following functions: 1) monitoring and audit of therapeutic and interventional cancer clinical trials at the center and at MCC Research Network (MCCRN) Affiliates, with a focus on IITs and cooperative group studies; 2) facilitate external audits (i.e. FDA, NCI etc.) by helping MCC study staff, MCCRN Affiliates study staff and PIs prepare for and respond to audits; 3) serve as a resource for education, maintenance of clinical research standards, and development of corrective action plans. The QA Program Manager and staff interact with the MCC Investigators, CRO, BBSRF, CRI SRF, and MCCRN Director, Project Coordinator, and Affiliates study staff and utilize data management platforms of the MCC, namely OnCore and internally developed systems to facilitate the work of the QA Office. The QA Program Manager reports directly to the MCC Director, with additional reporting to the ADCT and DSMC.
Internal Auditing

The MCC Audit Committee ensures the integrity of the data collected by MCC investigators and staff and is advisory to the DSMC and the MCC Director. The Audit Committee audits studies from initiation to IRB study closure. Every year, a minimum 10% of randomly selected patients accrued to adult therapeutic studies (excluding industry or pharmaceutical trials which have their own FDA-supervised monitoring processes) and a minimum of three different protocols per audit period will be audited. The focus of the Audit Committee is to ensure quality of all MCC IITs. IITs including all phase I IITs and all rapidly accruing IITs will be audited at least once during the lifetime of the study but may be audited more frequently at the discretion of the DSMC and/or the Audit Committee. The Audit Committee uses the definition of risk above to determine auditing frequency, as defined more specifically in the Auditing SOPs. Internal audits may occur at higher frequencies if requested by the MCC Director, MCC Associate Director for Clinical Translation or the DSMC.

All studies that are under the purview of the NCI-Central Institutional Review Board (CIRB) will have a yearly administrative audit at the time of continuation review to confirm the following:

- The most current informed consent forms are being used in each study
- The most current UK-required HIPAA authorization forms are being used in each study.
- The current UK IRB-required format for clinical trials performed at UK and the UK IRB-required language regarding subject injury are retained in the consent document.

The ORI/UK IRB has defined processes for NCI-CIRB review by the MCC in its NCI-CIRB SOP, available at: [http://www.research.uky.edu/ori/SOPs_Policies/C3-0400-NCI_CIRB_SOP.doc](http://www.research.uky.edu/ori/SOPs_Policies/C3-0400-NCI_CIRB_SOP.doc).

Audits will be of two types: routine and for-cause audits. In a routine audit, the patient chart to be audited will be selected at random using OnCore. In a for-cause audit, the number of charts and required elements of the audit will be determined by the DSMC and/or the MCC Director and Associate Director for Clinical Translation. Routine and for-cause audits will be identically undertaken, except that for-cause audits may be scheduled at any time, the patient charts are not required to be chosen randomly, and the number of charts audited will be based on the reason for the audit, as determined by the DSMC, and will not be limited.

Internal Audit Committee

The MCC Audit Committee is advisory to the DSMC, the Director of the MCC, and the Associate Director of Clinical Translation. The Audit Committee Chair is appointed by the MCC Director and Associate Director of Clinical Translation for a three-year term. All faculty are eligible to serve as auditors for the Audit Committee and are appointed to perform audits by the Chair. Failure to comply with this requirement can result in termination of MCC membership and removal of the right to enroll patients on clinical trials. The Audit Committee will be comprised of the following:

- A MCC clinical investigator selected by the Associate Director for Clinical Translation
- Chair of the Audit Committee
- The MCC Quality Assurance Program Manager
- CRO/QA auditors as appropriate.
- Other ad-hoc members with particular expertise of benefit to the audit process as determined by the Audit Committee

Members of the current Audit Committee may not audit studies in which they are involved.
The Audit Committee will conduct ongoing retrospective and focused audits on selected protocols, coordinate internal audits, assist investigators with formal external audit responses to cooperative groups (if requested), review MCCRN external audit reports conducted by the MCC Quality Assurance Office, provide education based on audit results, and provide final reports of auditing activity for review by the DSMC, as well as the MCC Director and Associate Director for Clinical Translation. The MCC DSMC has ultimate authority for decisions regarding audits as outlined above in the DSMC section.

Internal and external Auditors review three main categories of information: conformance to IRB and informed consent content requirements; shipping, storage and use of investigational/study drugs, devices, and other agents; and individual subject elements (eligibility, consent, data quality, response assessment, compliance with study procedures, etc.). Any noted deficiencies will be accompanied by a brief explanatory comment. If an auditor notes a deficiency that requires urgent attention, he/she will address the issue immediately with the Audit Committee Chair and the ADCT, who will then determine if it should be reviewed by the Director, the DSMC as expeditiously as possible and/or reported to the IRB consistent with ORI/IRB/MCC Coordination SOP and the NCI CIRB Review SOP (http://www.research.uky.edu/ori/SOPs_Policies/C6-0400-Markey_SOP.pdf) and the NCI CIRB Review SOP (http://www.research.uky.edu/ori/SOPs_Policies/C3-0400-NCI_CIRB_SOP.pdf). Full processes for the Audit Committee are available at: http://ukhealthcare.uky.edu/markey/data-and-safety/

Investigator Responsibilities

The PI of each study is ultimately responsible for every aspect of the design, conduct and final analysis of the protocol. As part of that scope, the PI is responsible for continuous monitoring of data and compliance with the protocol procedures, as well as ensuring adequate protocol description of procedures for protection of human subjects and accuracy of data and appropriate scientific endpoints. The BBSRF works with investigators to aid in monitoring of accrual, early stopping rules, interim analysis, and overall statistical progress. In addition, the BBSRF designs study-specific automated alerts and triggers at key points in the study (i.e., alerts to investigative team as dose level cohorts are filled or key toxicities are seen). This collaborative interaction ensures objective assessment of study progress and compliance with endpoints and study accrual goals. The CRI SRF supports investigators through development of informatics tools such as dissemination of results, aggregate and/or interim data reporting, and custom querying of study data and automated auditing functions to aid in data review and monitoring of required data elements.

In specific cases where an outside agency is the sponsor of the test agent, i.e., holder of the IND application, the PI submits individual AE reports to the funding agency (or agencies or sponsor) in accordance with agency and FDA regulations (Appendix I). The PI must also regularly submit reports to the DSMC and the relied upon IRB as designated and required by this plan. The PI is responsible for following all protocol-specific early stopping rules in conjunction with the biostatistician co-investigator. The DSMC will ensure that such guidelines are followed as part of its routine and ongoing review of clinical trials. It is the responsibility of the PI to lead his/her specific clinical research team according to Good Clinical Practice guidelines.

Institutional Training to Ensure Research Compliance

All research project personnel who work with research subjects, data, or samples must complete the IRB Training Program, accessed at: http://www.research.uky.edu/ori/human/Human_Research_Mandatory_Education.htm. HIPAA training is required, and accessed at: http://www.research.uky.edu/ori/HIPAA/main%20page.htm.
The MCC, UK IRB and the UK Center for Clinical Translational Science provide ongoing training in the proper conduct of research, including updates to federal and institutional requirements for human subjects research.

**Markey Cancer Center Clinical Protocol and Data Management Unit**

The Clinical Research Protocol and Data Management (CPDM) Unit is made up of the MCC Clinical Research Office (CRO), and is supported by the data management components of the BBSRF and the CRISRF.

**MCC Clinical Research Office**

MCC has within its Clinical Research Office (CRO) a robust and comprehensive infrastructure for clinical research support, including administrative/regulatory and scientific aspects of clinical protocol implementation and management. The CRO staff supports all clinical research and data management functions, the faculty, and administrative support of the DSMC and Audit Committees. The Director of the MCC CRO delegates the day-to-day operations to the Assistant Director of the MCC Clinical Research Operations. The MCC CRO supports all essential services necessary to perform clinical research in compliance with federal and state regulations.

- **MCC Clinical Research Office**
  - Hires and supports clinical staff responsible for coordinating and implementing studies
  - Reviews proposed protocols as part of CCARTs for procedural nursing issues
  - Coordinates clinical research activities in compliance with sponsor and regulatory requirements
  - Screens subjects for clinical studies at MCC
  - Assists with consenting subjects to clinical trials at MCC
  - Assesses subject safety at MCC
  - Coordinates study treatment administration at MCC
  - Tracks all protocol deviations
  - Conducts subject follow-ups
  - Collects research data
  - Resolves monitoring queries
  - Assists with external and internal audits
  - Tallies subject demographics and outcomes
  - Prepares study initiation meetings

- **MCC Clinical Research Office Regulatory Affairs**
  - Assembles all documents needed to open a study
  - Initiates confidentiality and Disclosure Agreements
  - Coordinates IRB applications and correspondence
  - Processes AEs
  - Tracks study contract
  - Coordinates protocol continuing review, amendments and reports
  - Implements study terminations
  - Retains training logs, Clinical Laboratory Improvement Amendments (CLIA)s and curriculum vitae
  - Retains document storage, conflict of interest records and communication with all MCC, cooperative groups, NCI, sponsors, and FDA regulatory committees or spokesperson
  - Arranges site initiation meetings
MCC Data Management System

The data from all investigator-initiated clinical trials or NCI-sponsored clinical trials that do not have sponsor-required data management systems are housed in the OnCore Clinical Trials Data Management system of the MCC. MCC investigator-initiated therapeutic trials are required to have all clinical data contained in OnCore. Non-therapeutic trials have defined minimum data sets required for accrual summary in OnCore. The OnCore data management specialist manages the development of electronic case report forms (eCRFs), study-specific OnCore specifications, protocol-specific data elements and entry requirements and reports utilized by the investigators and committees of the MCC. Account access to OnCore is maintained by the Data Management Specialist and requires an application, approval, and training in order to access or utilize the data management system. The OnCore database captures all features of the clinical research enterprise of the MCC including: 1) PRMC process and review details for each protocol, 2) DSMC timeline, determined by the PRMC at initial review, 3) DSMC process, and 4) protocol-specific information portals.

The OnCore Data Management Specialist performs periodic quality checks of OnCore data to ensure timeliness and accuracy of data, using a variety of discrepancy reports found in OnCore and on the report server. For IITs, the OnCore Data Management Specialist will create OnCore Specifications, an OnCore Calendar, and eCRFs in collaboration with the PI and study team. Any data fields or data capture forms needed to automate notifications will be created based on the specific protocol needs. A Data Management Plan (distinct from this Data and Safety Monitoring Plan) to document the data monitoring type and frequency and to document the process of validating, locking, and unlocking the database, as well as instructions for data entry will be created by the OnCore Data Management Specialist. Specifications, Calendar, and eCRFs are validated by a study team including a biostatistician, a CRA, Quality Assurance Manager, and the PI and approved by the PI and biostatistician. In addition, for all therapeutic IITs, the OnCore Data Management Specialist will review and query data using the OnCore Data Monitoring Console. The MCC Quality Assurance Monitor will verify source data as indicated in the protocol-specific Data Management Plan. The BBSRF and the CRI SRF staff will have access to data in all IITs in order to perform interim safety and efficacy assessments, which will be automated through OnCore wherever possible. For IITs, once enrollment is complete and all forms have been monitored following the protocol-specific Data Management Plan, the eCRFs will be locked to prevent further data entry and allow for analysis per the OnCore SOP outlining this process.

Data Management Delineation of Duties

MCC Quality Assurance Office Responsibilities

The Quality Assurance Office will assist the PI, Biostatisticians and OnCore Data Management Specialist in creating data monitoring and quality assurance specifics in the Data Management Plans. The frequency and timelines will depend on the risk of the study. The Quality Assurance Monitor(s) are responsible for performing all source data verification based on the Data Management Plan. The Quality Assurance Monitor will communicate and collaborate directly with the OnCore Data Management Specialist for creation and submission of queries as needed and report directly to the PI and Quality Assurance Manager with all monitoring related activities and reports. The Quality Assurance Program Manager is responsible for reporting to the MCC Director, ADCT, and DSMC of all internal and external monitoring activities and reports.
OnCore Data Management Specialist Responsibilities

The OnCore Data Management Specialist validates all study forms, monitors individual data fields, and develops a timeline for source data verification, submits queries, and is responsible for locking of all forms once all the data is clean and finalized.

BBSRF Responsibilities

The MCC BBSRF statisticians are responsible for checking the consistency, quality and completion of study endpoints, interim analyses endpoints (if appropriate), and other important data elements, including the consistency of dates and important data variables across the course of the study by performing range and logic checks. Form sequence is verified along with individual form data. For Phase I and II studies, BBSRF verifies that dose limiting toxicities and all toxicities are appropriately captured. BBSRF staff develop and monitor trigger e-mails requested by PIs for interim analyses, safety alerts and data management timelines. In addition, they monitor and check linkage between OnCore and any correlative databases for inconsistencies and errors.

CRI SRF Responsibilities

CRI SRF staff maintains the servers that host the OnCore Oracle database, manage all upgrades to the OnCore system and maintain linkage between the OnCore Oracle database and the SAS server. They also develop ancillary databases (LabKey, etc.) for any IITs with correlative data not collected in OnCore with input from the PI and CRO and BBSRF study staff.

Database Oversight, Security, and Data Entry Requirements

In addition to the above, the CRO and the CRI SRF ensure quality data and protocol compliance with additional requirements of MCC studies and investigators:

• All protocol participants must be registered in the OnCore database.
• For NCI-sponsored and all other MCC studies, if any answer indicates the participant does not completely meet eligibility, the subject will not be enrolled in the clinical trial.
• The date in the current informed consent document is displayed on the upper right hand corner of the first page of the consent to ensure only the most current IRB-approved version is used.
• A case report form must be filled to collect data required by the protocol to meet protocol objectives. Consent date, registration date, off study date, and eligibility data are required for all registrants. The current electronic data capture system of the MCC must be used for all IITs. An accession log will be maintained allowing subject identification by study personnel only. All case report forms to be reviewed by outside personnel will be anonymous. For pharmaceutical trials, the company case report form will be used, as needed. For cooperative group trials, the case reporting system of the cooperative group will be used. HIPAA rules are implemented per MCC and university regulations.
• Protocol deviations for IITs will be reviewed by the DSMC at intervals determined by the PRMC and all appropriate actions taken as listed above.
• The OnCore Data Management Specialist provides regular data verification and protocol compliance checks of all IITs of the MCC.
• To ensure timely monitoring of dose-limiting toxicities (DLTs) for phase I trials, The BBSRF has developed an automated system for real-time access of AEs and DLTs. Specifically, CRAs enter adverse events into eCRFs in OnCore and specify whether or not a particular AE is due to a DLT. An SAS program scheduled at least daily will run on an SAS Server and access an Oracle view via SAS Access in the OnCore Oracle database. The view will
query the data stored in the database from the AE eCRF. The SAS program is written such that it monitors the current data in the AE view and based on protocol specified monitoring rules for DLTs will send via an SMTP email server appropriate e-mail notifications and reports to a distribution list (PIs, CRAs, and statistician) defined within the SAS program.

In addition, the support of the CRI SRF ensures accurate, timely, and secure data acquisition and dissemination, as well as the interoperability of informatics systems in compliance with evolving data standards.

**REPORTING TEMPORARY OR PERMANENT SUSPENSION OF AN NCI-FUNDED CLINICAL TRIAL TO THE NCI**

Any NCI- sponsored trial suspended temporarily or permanently by the IRB and/or MCC DSMC will be reported by the IRB to the FDA & OHRP. The UK IRB requires the PI to report to their funding agency providing IRB with documentation that incident has been reported. The IRB and the MCC DSMC coordinate internal dissemination of this information between the two bodies in an ongoing manner and as documented in the SOP of collaboration. The MCC DSMC will also ensure prompt reporting to the NCI Grant Program Director responsible for the grant as outlined by the agency sponsoring the research. If CTEP drugs are used in the study, the suspension will also be reported immediately to CTEP. If the suspension is temporary, the NCI and CTEP will also be notified in a timely manner by the PI regarding the resolution of the issues that caused the suspension, and the date that the suspension was lifted. Documentation of the notification of the NCI (and CTEP, if applicable) should be filed in the study-specific regulatory binder. Any action taken by the UK IRB will follow the IRB’s policy and will be reported to the NCI. These steps are described in the ORI’s SOPs [http://www.research.uky.edu/ori/human/SOPs_&_Policies.htm](http://www.research.uky.edu/ori/human/SOPs_&_Policies.htm) and in the coordination SOP between MCC and IRB and ORI: [http://www.research.uky.edu/ori/SOPs_Policies/C6-0400-Markey_SOP.pdf](http://www.research.uky.edu/ori/SOPs_Policies/C6-0400-Markey_SOP.pdf).
APPENDICES
Appendix I: Flow Diagram of Serious Adverse Event Reporting by Investigators
Fig. 1. Adverse event and Serious Adverse Event Reporting in Oncore
Appendix II: Adverse Event Reporting for Trials for which NCI is also the IND sponsor

For details, see the NCI Investigator Handbook, available online at http://ctep.cancer.gov/investigatorResources/investigators_handbook.htm

**TABLE A: Expedited Reporting for Phase I Studies (including hospitalization*)**

<table>
<thead>
<tr>
<th>UNEXPECTED EVENT</th>
<th>EXPECTED EVENT</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>GRADES 2 - 3</strong></td>
<td><strong>GRADES 4 - 5</strong></td>
</tr>
<tr>
<td>Attribution of Possible, Probable or Definite</td>
<td>Regardless of Attribution</td>
</tr>
<tr>
<td><strong>Grade 2 - Exempted report within 10 working days Grade 3 - Report by phone to IDB within 24 hrs. Expedited report to follow within 10 working days. (Grade 1 - Adverse Event Expedited Reporting NOT required.)</strong></td>
<td>Report by phone to IDB within 24 hrs. Expedited report to follow within 10 working days. This includes all deaths within 30 days of the last dose of treatment with an investigational agent regardless of attribution. Any late death attributed to the agent (possible, probable, or definite) should be reported within 10 working days.</td>
</tr>
</tbody>
</table>

**Table B: Expedited Reporting for Phase II and III Studies**

<table>
<thead>
<tr>
<th>UNEXPECTED EVENT</th>
<th>EXPECTED EVENT</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>GRADES 2 - 3</strong></td>
<td><strong>GRADES 4 - 5</strong></td>
</tr>
<tr>
<td>Attribution of Possible, Probable or Definite</td>
<td>Regardless of Attribution</td>
</tr>
<tr>
<td>Expedited report within 10 working days (Grade 1 - Adverse Event Expedited Reporting NOT required.)</td>
<td>Report by phone to IDB within 24 hrs. Expedited report to follow within 10 working days. This includes all deaths within 30 days of the last dose of treatment with an investigational agent regardless of attribution. Any late death attributed to the agent (possible, probable, or definite) should be reported</td>
</tr>
</tbody>
</table>
within 10 working days. Grade 4 Myelosuppression or other Grade 4 events that do not require expedited reporting will be specified in the protocol.

*For Hospitalization Only* – Any medical event equivalent to CTC Grade 3, 4, 5 which precipitated hospitalization (or prolongation of existing hospitalization) must be reported regardless of requirements for Phase of study, expected or unexpected and attribution. Expedited reporting may not be appropriate for specific expected adverse events for certain later Phase II and Phase III protocols. In those situations the adverse events that will not have expedited reporting must be specified in the text of the approved protocol. An expected Grade 3 event that is definitely related to the investigational agent is only to be reported if the patient is hospitalized using the generic reporting criteria, for instance. In a trial of an investigational agent where Grade 3 diarrhea requiring hospitalization is expected, only diarrhea requiring ICU care (Grade 4) might be designated for expedited reporting.

B. Trials of an investigational agent for which NCI is not the IND holder

The controlling regulations are those of the Food and Drug Administration (21 CFR, Part 312.32: Expedited Safety Reporting Requirements for Human Drug and Biological Products) and are available at http://www.fda.gov/cder/aers/fr07oc97.htm. They describe the responsibilities of the investigator and the IND holder. Additional sponsor or institutional requirements may be appropriate for specific agents and included in the pertinent protocol sections.

C. Trials involving commercially available agents only (no INDs involved)

Serious adverse events that occur with commercially available agents/devices are reported through Food and Drug Administration Medwatch (http://www.fda.gov/medwatch/index.html).

D. Trials involving recombinant DNA molecules (gene transfer)

In addition to the reporting requirements for investigational agents (see A or B above, as appropriate), investigators should adhere to NIH Guidelines for Research Involving Recombinant DNA Molecules (Gene Transfer) (http://www4.od.nih.gov/oba/guidelines.html).

E. Food and Drug Administration reporting requirements of serious adverse events for postmarketing trials of vaccines (no cancer vaccines yet in this category)

Serious adverse events must be reported according to applicable FDA regulations (http://www.fda.gov/cber/vaers/vaers.htm).

F. Trials involving behavioral or nutritional interventions that do not use an investigational agent

Since there are no standard grading scales for adverse events, defining suitable grades for adverse events is the responsibility of individual investigators for each protocol. Adverse events of a
psychological nature can occur with behavioral trials and should be specified for the particular intervention in question.