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Markey Cancer Center

An NCI Comprehensive Cancer Center

Institutional Data and Safety Monitoring Plan

University of Kentucky
Markey Cancer Center
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Contents

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Date

I. 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 studying patients with cancer or those at risk for cancer conducted by MCC and MCC Research Network (MCCRN) 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 https://ukhealthcare.uky.edu/markey-cancer-center/research/clinical-research-organization/data-and-safety.

The MCC DSMP recognizes the NIH's definition of a clinical trial available at: https://grants.nih.gov/policy/clinical-trials/definition.htm.
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.

II. MONITORING THE PROGRESS OF TRIALS AND SAFETY OF PARTICIPANTS

1. 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 NCI CIRB Review C3.0400 SOP. Which can be located on the UK ORI IRB Policies and Guidance Page at https://www.research.uky.edu/office-research-integrity/policies-guidance

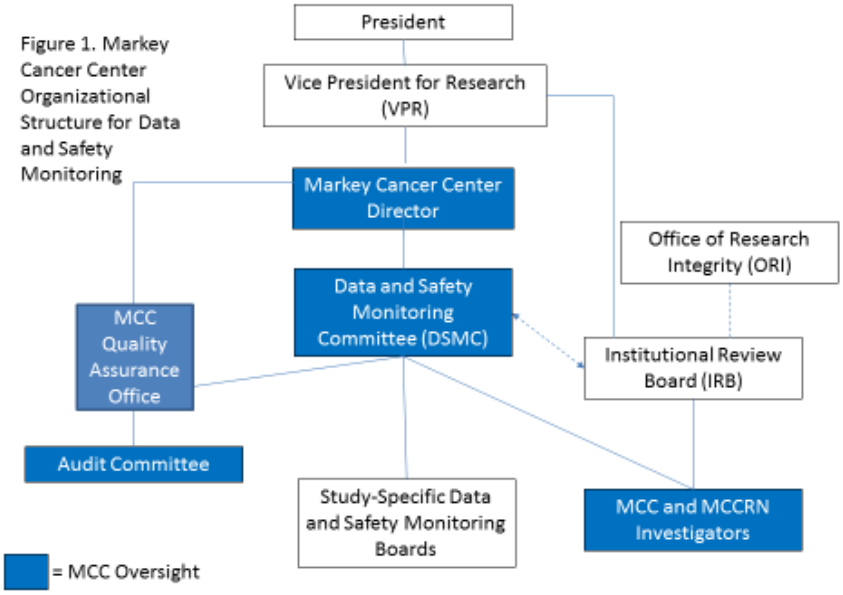
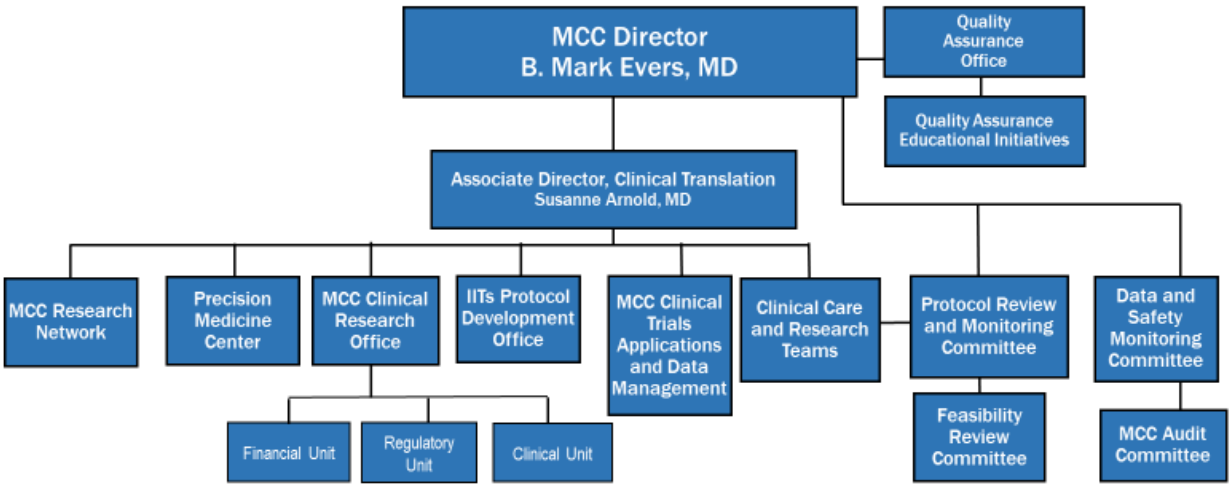


Figure 1. Markey Cancer Center Organizational Structure for Data and Safety Monitoring

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 MCCRN is a collaborative group of affiliate institutions committed to performing multicenter IITs that originate from the MCC, and who are committed to executing high quality research under the guidance of the MCC. The Director of the MCC holds overall responsibility for overseeing data and safety monitoring via the Data and Safety Monitoring Committee (DSCM) as well as scientific review functions of the Protocol Review and Monitoring System (PRMS) and its Protocol Review and Monitoring Committee (PRMC). The Director is assisted by the Associate Director (AD) of Clinical Translation, who oversees the function of the Clinical Protocol and Data Management (CPDM) system, the Clinical Trials Management System, the Precision Medicine Center, and the Clinical Care and Research Teams (CCARTs). The PRMC, Quality Assurance Program (QA), Audit Committee and Data and Safety Monitoring Committee report directly to the Director. The Associate Director for Clinical Translation reports directly to the MCC Director on all aspects of clinical research. In addition, the MCC Director and Associate Director for Clinical Translation are assisted by the Associate Director of Administration and the leaders of the Clinical Protocol and Data Management Program, which includes the Medical 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), CCARTs and the Investigator-Initiated Trials (IITs) Office (IITO) (**Figure 2**).

Figure 2. MCC Oversight of Clinical Research



2. MCC Trial Review and Monitoring Process

In accordance with MCC's clinical research mission and CCSG guidelines for NCI-designated Cancer Centers, MCC has established internal mechanisms for assuring the appropriate scientific scrutiny and oversight of the conduct of all cancer-relevant clinical trials of the Center. A Protocol Review and Monitoring System (PRMS) is required for all National Cancer Institute (NCI)-designated Cancer Centers. A PRMS is to review all cancer research studies in the areas of diagnosis, therapy, prevention and control of cancer that have not received traditional peer review for scientific merit.

The MCC Protocol Review and Monitoring System consists of four components: 1) the PRMS Administrative Office (including the PRMC Coordinator, FRC and CCART Coordinator), 2) Disease Working Groups (called Clinical Care and Research Teams or CCARTs), 3) the Feasibility Review Committee (FRC), and 4) the Protocol Review and Monitoring Committee (PRMC). Together, these components provide the oversight and infrastructure to ensure rigorous review of the scientific merit, feasibility, inclusiveness, and scientific prioritization of all cancer-relevant clinical trials of the MCC.

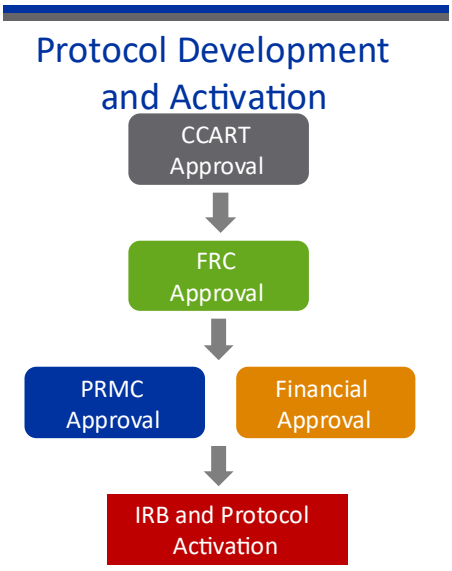


Figure 3. Clinical trial approval process.

The primary goal of the MCC PRMS is to ensure that institutional, cooperative group, and industry-initiated cancer research studies involving human subjects conducted under the auspices of the MCC: (1) serve and support the mission of MCC; (2) have high scientific merit; (3) are statistically sound and appropriately designed; (4) are feasible for completion based on patient population and trials that are open and accruing the same population; (5) are inclusive of underserved populations (e.g., women, minorities, children); and (6) if applicable, are compliant with NIH guidelines for clinical trials, including monitoring for accrual and continued scientific relevance. 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 and non-IITs (**Figure 3**) 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, inclusiveness, biostatistical design, and relevance to the MCC mission.

3. Clinical Care and Research Teams: Initial Concept Review and Prioritization

MCC investigators conceive and develop trial concepts and full protocols or identify externally sponsored trials for potential participation and present these to disease-specific groups called Clinical Care and Research Teams (CCARTs). CCARTs provide the first stage review of protocols that will be presented for final scientific review by the PRMS. CCARTs are responsible for concept review and contributions to IIT protocol development, communication with the PRMS, as well as conduct and coordination of their disease group. CCARTs (disease teams) have operational responsibility for concept and protocol selection and endorsement, portfolio management, identification and resolution of gaps in the disease-specific trial portfolio including avoidance of overlap in trials. CCARTs are responsible for developing disease specific portfolios comprised of high-quality trials that match both the needs of patients and the scientific interests of faculty and are inclusive of special populations, minorities and the needs of the catchment area.

The CCART may approve a protocol or concept, reject the protocol or concept, or refer the investigator to the Investigator-Initiated Trials Office (IITO), which supports the development of high-quality investigator initiated clinical trials. The standard operating procedures (SOPs) of the MCC CCARTs are available at: https://ukhealthcare.uky.edu/markey-cancer-center/research/clinical-research-organization/data-and-safety.

4. Feasibility Review Committee (FRC)

The Feasibility Review Committee (FRC) is responsible for ensuring that adequate resources are available to safely and efficiently conduct clinical trials including staffing, financial and site feasibility assessment. Metrics reviewed include institutional feasibility, budget and contract feasibility, and site feasibility. The Cancer Research Informatics Shared Resource Facility (CRI SRF) provides the following metrics to both the FRC and the PRMC for their use in determining feasibility and scientific relevance of the proposed research: a) incidence of rare tumors for each disease site based on the NCI definition and b) current volume of patients seen at the MCC in each disease site. The FRC will provide an operational feasibility score to the PRMC at the time of protocol review. In addition, the FRC may deem a study not feasible and table it when there are substantive issues, such as: inadequate staff available for trial, significant institutional financial responsibility or risk, and lack of site capability to perform study-related procedures.

5. Protocol Review and Monitoring Committee (PRMC)

The MCC 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 (**Figure 2**). The PRMC is the body that focuses on, and is ultimately responsible for, independent review of scientific merit, feasibility, prioritization, and progress of cancer clinical research in the Center. The PRMC has the authority to open protocols that meet the scientific merit standards and scientific priorities of the center and to close or suspend protocols that do not demonstrate adequate scientific progress. To that end, the PRMC scientific review evaluates: background and rationale; scientific objectives; adequacy of the study design including primary endpoints, and statistical plan; presence of a data and safety monitoring plan of the protocol; inclusiveness of underserved populations; and the scientific priority in the context of the cancer center and feasibility of completion. The PRMC reviews NCI-sponsored cooperative group studies in an expedited manner in accordance with NCI guidelines. The review is conducted by the full committee or expedited (by the Chair or Vice-Chair). For multi-site institutional trials, the PRMS of the lead site is responsible for the full scientific review of the protocol. The other participating sites are responsible only for an expedited review focused on prioritization, competing studies, and feasibility. Per NCI

mandate, if the PRMS at the lead site is conditionally approved or disapproved, the full scientific review occurs at another participating NCI-designated cancer center with an approved PRMS. There is a collaborative agreement between MCC and the IRB so that all cancer related studies received by IRB without a PRMC approval memo are communicated to the PRMC coordinator prior to IRB review/approval. No cancer clinical trial is opened at MCC without PRMC and IRB review and approval.

PRMC reviews 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. There is a collaborative agreement between MCC and the IRB so that any study that is cancer related and first goes to the IRB is also sent to the PRMC. 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, the UK IRB provides an ongoing study listing of all cancer trials for which it is responsible to the PRMC coordinator and CTRP coordinator. If a researcher submits a clinical cancer research protocol to the IRB without having obtained PRMC review, the IRB notifies the investigator that PRMC review is required prior to study activation. The MCC will not activate any non-exempt (see PRMC definition below) cancer study without PRMC review and approval and IRB review and approval, which happens separately.

For this purpose, a clinical trial is defined as a prospective study involving human subjects that is designed to answer specific questions about the effects or impact of particular biomedical or behavioral interventions. Interventions may include drugs, treatments, devices, diagnostic (molecular or imaging), behavioral or nutritional strategies. Participants in these trials may be patients with cancer or people without a diagnosis of cancer but at risk for the disease. In addition to studies that would commonly fall under the PRMS, the MCC has also elected to oversee educationally focused research and observational studies. The PRMC Chair reviews a number of other studies because of the nature of the research being conducted, particularly in research being done in the catchment area served by the MCC. Examples include observational and educational studies that do not test interventions and are not considered clinical trials, but may qualify for review at the discretion of the Chair. The PRMC Chair serves as the scientific checkpoint to determine the scientific merit of research at the MCC and MCCRN, and in a rare instance will bring these studies forward to the full PRMC. This is used to elevate the quality of the science of studies that would otherwise not fall under a PRMC type structure.

The PRMC Chair and Vice-Chair are appointed for a three-year term by the MCC Director with the advice of the AD for Clinical Translation. The Director formally reviews the performance of the PRMC Chair and Vice-Chair at least annually and has full discretion to replace these positions, with the advice of MCC senior leadership. PRMC members are appointed by the MCC Director on the advice of the PRMC Chair and serve three-year terms. MCC's PRMC member roster comprise faculty representing diverse scientific and clinical disciplines, mirroring the kinds of protocols that are conducted at MCC and in concert with NCI expectations. Disciplines include the following specialties: adult and pediatric hematology/oncology, gynecologic oncology, radiation oncology, surgical oncology, pharmaceutical sciences, pathology, radiology, basic science, and population science. There must be at least one member from Biostatistics assigned to the PRMC, along with an alternate, since all protocols must be reviewed by a biostatistician. While faculty from all academic ranks should be on the PRMC, care will be taken to have an appropriate balance of senior and junior faculty. Attention to community outreach and engagement, as well as inclusivity of trials is emphasized by the PRMC. Non-faculty, non-voting PRMC members may include: PRMC Coordinator, Director of Operations of the CRO or designee, Quality Assurance Officer, and Investigator Initiated Trials Office Director (when applicable). PRMC members will serve a term of 3 years. Additional 3-year terms are approved by the PRMC Chair in order to assure diversity of membership and participation by members with multiple obligations.

PRMC required attendance and quorum rules are in accordance with NCI guidance. Attendance by committee members is requested at all meetings. If a committee member foresees that they will be unable to attend more than 65% of meetings, that committee member has the responsibility of notifying the PRMC and should be considered for replacement. In addition, to the quorum requirements, the PRMC Chair (or Vice-Chair), a biostatistician and one of the clinical reviewers may be physically present or present via telephone for a meeting to proceed. The quorum of $\geq$ 65% of the members with at least one biostatistician is required for PRMC to conduct a review of new protocols (with less than a quorum, there may be discussion of other matters, but not a voting matter). This is to ensure high-level scientific scrutiny by the PRMS process. To promote communication and timely resolution of issues, the PRMC encourages the PI of new protocols to be available in person or by phone at the time of review. PIs of IITs are required to be present; it is optional for other trials unless formally requested by the PRMC. 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). All members are asked to acknowledge any conflict of interest at the beginning of each meeting of the PRMC. Financial conflict of interest, PI or co-PI roles on the protocol reviews will signify automatic conflict and the member will recuse themselves from the review process of that protocol during the meeting. Members with conflicts will also recuse themselves from being a primary or secondary reviewer and will immediately notify the PRMC coordinator of such conflicts.

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.

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 and FRC have completed their reviews. 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, protocols involving 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 voting members of the PRMC. Protocols that require full review during a PRMC committee meeting include: 1) Institutional (investigator-initiated) interventional therapeutic clinical trials, 2) Institutional interventional behavioral or psychosocial clinical trials, 3) Institutional prospective molecular or imaging diagnostic clinical trials that use the information from the diagnostic test in a manner that affects medical decision-making or the study subject, 4) Non NCI-cooperative group consortium studies that meet the criteria of investigator-initiated studies above, 5) Industry (commercially-sponsored) clinical trials. The primary and secondary faculty reviewers, faculty oncology pharmacist, and a faculty statistician review the protocols and present their findings to the convened PRMC.

The PRMC is required to:1) review all protocol documents and reviewer evaluations, 2) assess accrual plan, 3) identify trials of rare tumors using a listing of rare tumor types as defined by the NCI, 4) consider CCART evaluations, 5) consider operational issues, presented by the Feasibility Review Committee (FRC), 6) conduct objective scientific merit, feasibility, and prioritization of protocol, 7) ensure subject inclusivity, 8) determine an overall PRMC review score, 9) ensure availability of DSM plan, and 10) assess need for external DSMB. The PRMC is responsible for ensuring that all review concerns are adequately addressed, and the protocol is appropriately revised prior to issuing Approval or Disapproving protocols that do not meet PRMC standards. Prior to approval, the PRMC will assure that all clinical trials that meet the NIH requirement for Data and Safety Monitoring Boards have an appropriate DSMB.

The PRMC is required to perform full committee review and approve all protocol amendments that significantly change the protocol design, analysis, and intended outcome as determined by the Chair. Minor protocol changes that do not impact study design and outcome may be reviewed and approved by the study Chair. Amendments to expedited protocols will be handled administratively at the Chair's discretion. Amendments not meeting the criteria for "significant change" or "minor changes" criteria will be handled at the Chair's discretion with selective input based on the amendment (e.g., addition of an interim analysis sent to a biostatistician).

The following describes the actions following PRMC review based on its voting/outcome determination.

- Approved, Administrative.
- Conditionally Approved, Administrative.
- Approved, Full.
- Conditionally Approved, Full.
- Scientifically Disapproved.

The PRMC is responsible for ongoing scientific review, including accrual monitoring. Responsibilities include:

- Assess the continued scientific relevance for all open and enrolling studies that are not PRMC exempt, in accordance with scientific review policy. Considerations include new findings that make the protocol no longer relevant and valuable to conduct.
- Assess accrual for all enrolling studies that are not PRMC exempt.
- Request (and approve) corrective action plans for poorly accruing studies, and close studies that do not meet accrual standards per accrual monitoring policy.

The PRMC has ultimate authority to close a study at the MCC <u>or</u> 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. CCARTs review all clinical trials for progress and performance, and engage the PIs of studies with poor progress or performance to improve trial performance or consider closing trials. PIs of studies at risk for closure are notified by PRMC Coordinator and/or Chair, and PIs of IITs are also notified by the IITO prior to PRMC closure review and urged to rectify the situation and to provide an explanation and a corrective action plan to improve accrual, which will be reviewed at the PRMC meeting. 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. For studies with no

accrual at 12 months, the PRMC will review for closure. 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. Protocols meeting accrual goals at 1 year will continue to be monitored to ensure that they continue to achieve their expected accrual goals.

6. Investigator-Initiated Trials Office

The IITs Office supports Markey clinical investigators who are in the process of protocol development and optimization of investigator-initiated interventional treatment trials (IITs), consistent with the goals of the PRMC and thus functions as an available complementary resource. The purpose of the IITs Office is to identify and promote high-quality, interventional treatment IITs, from early inception of a scientific concept thru to study close-out. The scope of the IITs Office comprises trial development and protocol writing, Letter of Intent submissions to external funding sources, liaison to statistical support and other salient institutional shared resources, and submission to the formal protocol review process at MCC as well as ongoing oversight of IIT's successful completion. Investigators may directly request support from the IITs Office, or receive a referral by their specific disease CCART, the PRMC or rarely, by UK IRB. The IITs Office provides assistance to clinical investigators in improving the potential of the IIT for successful launch and completion as well as meaningful scientific discovery.

The MCC IITs Office facilitates development via prioritization set by senior Markey leadership for new interventional treatment trials that request use of the Clinical Research Office and the MCC Data Management team. The IITs Office meets with senior Markey leadership on a regular basis to review active IITs within MCC's clinical trials portfolio and to facilitate development of new IITs. The IITs Office also coordinates the MCC IIT Executive Committee, an internal funding mechanism that contributes scientific review and supports development of new, meritorious impactful treatment IIT concepts. The IITs Office coordinates periodic meetings of the MCC IIT Executive Committee, comprised of senior Markey leadership, to conduct scientific review of new proposals by MCC clinical investigators.

7. Office of Research Integrity for the University of Kentucky

The UK ORI provides administrative support for six federally mandated review committees: four Medical and one Nonmedical IRBs, 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 and data ownership. The ORI reviews its policies and SOPs annually. The ORI reports directly to the UK Vice President for Research. Additional information is available on the ORI website: https://www.research.uky.edu/office-research-integrity.

8. Institutional Review Board for the University of Kentucky

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 either the Department of Health and Human Services' definition of both "research" and "human subjects" or the FDA definitions of both "clinical investigation" and "human subjects" 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 protocol 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, 5) protocol violations and deviations, and 6) final reviews for study closure. Types of IRB review 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. Consequently, the University has adopted the NCI required independent model for these trials.

The UK Vice President for Research appoints members to standing university research committees and, as authorized by the Provost and 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 as well as 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, 46.108(a)(2) 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 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 roles and responsibilities of the PRMS and IRB are complementary and not overlapping. PRMS focuses on scientific merit, whereas the IRB focuses on ethical issues, balancing the risk to the individual with the value of the research. The University of Kentucky ORI and MCC have developed shared guidance documents and collaborative SOP's available at https://www.research.uky.edu/uploads/ori-c30400-nci-cirb-sop-pdf (C6.0400-Markey_SOP and C3.0400-NCI_CIRB_SOP).

MCC has a parallel submission process for clinical trials, with sequential approval. There is a collaborative agreement between MCC and the IRB so that all cancer related studies received by IRB without a PRMC approval memo are communicated to the PRMC coordinator prior to IRB

review/approval. By agreement, the ORI staff screen IRB applications (broader than just clinical trials) to determine whether the study involves cancer research and if so, they communicate with the PRMC coordinator for clarification. Studies cannot open at MCC until they have IRB approval and PRMC approval. At the discretion of the PRMC Chair and CRO Director of Operations, parallel review is allowed for industry and cooperative group studies. There may be times when PRMC and IRB request review by the other body or together conduct complementary determinations regarding a protocol, particularly an open protocol in which there has been an occurrence of concern. Such matters are to be coordinated by the PRMC Chair and PRMC Coordinator along with the IRB Chair and ORI Research Compliance Officer (RCO). The ORI RCO provides the MCC PRMC Chair and the Associate Director for Clinical Translation with a copy of the final IRB deliberation and any reports generated during its review. The PRMC Chair disseminates the copy of the final deliberation and relevant information to PRMC members, thereby ensuring effective communication between these two bodies.

9. 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 Director. 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. 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 DSMC Chair. See Appendix C for DSMC Roster.

- **Voting members**
  - The Chair and Vice Chair
  - Six (6) members who are active investigators appointed for a three-year term.
  - Two biostatisticians from the BB SRF
  - Three pharmacists from within the MCC and/or Investigational Drug Service (IDS)
  - A clinical research nurse

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 non-conflicted voting members of the DSMC, a pharmacist and a biostatistician from the BB SRF. The MCC DSMC serves as the Data and Safety Monitoring Board (DSMB) for studies approved by the PRMC that meet the NCI's requirement for a DSMB 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 MCC DSMC reviews and monitors study progress for all MCC IITs. Concurrently, the Early Therapeutics CCART closely monitors the progress of all phase I and complex phase II trials, including all early phase MCC IITs on a weekly basis, and reviews all AEs and serious adverse events (SAEs), study accrual, and study progress at least monthly. 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), 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 DSMC Chair, the MCC Director or Associate Director for Clinical Translation. The DSMC reviews study-specific reports regarding study status, safety, and progress as designated by the risk assignment and level of review. These reports include protocol deviations, subject accruals, and analysis of SAEs, at a minimum. In addition, for all IITs, AEs are included in the review. The DSMC monitors the following elements:

- AEs (at a minimum all CTCAE Grade 3, 4 and 5 AEs) for IITs
- SAEs for all studies
- Subject deviations and violations for all studies
- Protocol deviations and violations for all studies
- 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 resulting in change or suspension of the trial from outside entities such as cooperative groups and industry of studies involving MCC subjects as determined by the Chair.
- Analysis of primary and secondary efficacy parameters and outcomes if required (i.e., early stopping rules, interim monitoring, etc.) for IITs and Phase I studies
- Suggested actions for any protocol (suspension, termination, or actions of significance as determined by the Chair), if applicable

Deaths on study that meet expedited reporting requirements require immediate notification of the MCC Director, the DSMC Chair or Vice-Chair and the IRB. Additionally, the ET CCART reviews all SAEs, dose escalations and deviations on its trials weekly. The DSMC coordinator also attends the ET CCART to monitor dose escalation and SAEs in these higher risk trials, and reports these to the DSMC.

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 has 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 recommendations for all trials reviewed during the DSMC meeting:

- Approved – Enrollment may continue
- Not approved
- Approved with caution
- Deferred
- Close to accrual – Close enrollment
- Suspend – delinquent progress report, need for corrective action plan

10. Multi-Institutional Investigator-Initiated Trials

For MCC Multi-Center Research Unit (MRU) Investigator Initiated Trials (IITs) and MCCRN trials where MCC is the lead institution/lead-investigator, the MCC lead investigator is responsible for reporting the data and safety monitoring of the overall study to the MCC DSMC. A Clinical Research Project Manager will be assigned to the trial and will be delegated tasks to assist the lead PI in obtaining and maintaining accurate and complete records for external participating sites. The MCC lead investigator and the assigned Clinical Project Manager are responsible for assuring that data for participating external sites are reported in accordance with established processes of the Markey Cancer Center. The MCC lead investigator and assigned Clinical Research Project Manager will manage and oversee external participating sites to assure data is entered into the OnCore® clinical

trials data management system. On each occasion that a MCC MRU IIT or MCCRN trial is selected for review by the DSMC, the MCC Lead Investigator and assigned Clinical Research Project Manager may attend and provide information for the overall study to the DSMC. In addition, when activities occurring at a participating MCCRN and/or MRU site are scheduled for review by the DSMC, the participating site investigator and coordinator may be asked to remotely attend these meetings to provide information and respond to questions by the DSMC.

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), MCC Lead Investigator, the external site investigator and the assigned MRU or MCCRN Clinical Research Project Manager. If the PI does not feel that the issues have been addressed in a satisfactory manner, the PI may appeal to Director of the MCC. If the Director has a conflict of interest, the Director will engage the assistance of the UK Vice President of Research to engage a reviewer or review committee for this appeal.

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, MCC Lead Investigator, the external site investigator(s), the assigned MRU or MCCRN Clinical Research Project Manager, the Medical Director of Clinical Research Office (CRO) and/or the Medical Director of Precision Medicine Center (PMC), 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 DSMC Chair for low risk studies. In addition, protocol and/or subject deviations/violations deemed minor in nature may be expeditiously reviewed. 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 to be entered in the MCC electronic clinical trials database, OnCore® or its partner Advarra EDC®, will require annual review by DSMC, with staff required to provide IRB records of any SAEs or deviations reported during the review period.

11. 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 if one has not been provided by the meeting date. 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 DSMC. The PI may request to be present at the DMSC meeting and must notify the DSMC Chair of the request to attend the DSMC meeting after the audit report is received. The PI should prepare and submit to the DSMC 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 DSMC members. In addition, the DSMC will have a closed session to review both the Audit Committee’s review and the issues presented by the PI followed by a determination. If the PI does not feel that the issues have been addressed in a satisfactory manner, the PI may appeal to the Director of the MCC. If the Director has

a conflict of interest, the Director will engage the assistance of the UK Vice President of Research to engage a reviewer or review committee for this appeal.

Temporary or permanent suspension of any NCI-sponsored clinical trial by either the DSMC 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 DSMC 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 DSMC that results in suspension of any NCI-CIRB monitored study, will follow the notification policies of the NCI CIRB Review SOP: https://www.research.uky.edu/office-research-integrity/policies-guidance (C3.0400 NCI CIRB Review SOP) and, if applicable, the MCC/IRB/ORI Coordination SOP: https://www.research.uky.edu/office-research-integrity/policies-guidance (C6.0400 MCC/IRB Coordination SOP)..

12. Adequacy of DSMP for Clinical Interventional Trials

The PRMC Coordinator reviews Industry and national cooperative group sponsored trials to ensure a data safety monitoring plan is available prior to PRMC review. The DSMC is responsible for reviewing the adequacy of DSMPs of MCC Investigator Initiated protocols reviewed by the PRMC. Should a DSMP be found to be inadequate, the DSMC Coordinator will work with the PI and the Quality Assurance Office to revise the DSMP.

All DSMC 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.

13. Investigational Drug Service (IDS) Oversight and Collaboration

The IDS supports all clinical drug-related research conducted by investigators at the UK HealthCare. The IDS reviews protocols for study drug concerns; receives and maintains investigational and/or study drugs; and stores, prepares, and verifies and dispenses study drugs. 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.

14. Radiopharmaceutical Services Oversight and Collaboration

The radiopharmaceutical services within Nuclear Medicine and Medical Oncology collaboratively support all clinical radiopharmaceutical-related research conducted by investigators at UK HealthCare. These teams and the Precision Medicine Team review protocols for study agent and radionuclide concerns; and the Nuclear Medicine team receives and maintains investigational and/or study radiopharmaceuticals; and stores, prepares, and verifies and dispenses study radiopharmaceuticals. Radiopharmaceuticals are managed by the Departments of Nuclear and Radiation Medicine and provides the support needed to assure safe and efficient conduct of clinical radiopharmaceutical trials including compliance with federal, state, and The Joint Commission (TJC) requirements regarding investigational agents. All inpatient radiopharmaceutical studies are required

by UK HealthCare policy to utilize Nuclear Medicine and supporting MCC teams as above. Any exceptions must be arranged in advance between Nuclear Medicine and the PI. The MCC utilizes Nuclear Medicine and Radiation Medicine for all outpatient radiopharmaceutical studies involving investigational agents. The MCC collaboratively works with Nuclear Medicine and Radiation Medicine regarding policy, performance metrics, and needs of the centers as they pertain to investigational radiopharmaceuticals.

15. 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. If the PRMC determines that a DSMB is required on an investigator-initiated protocol, the PRMC will request that the PI convene a study-specific DSMB and will notify the MCC DSMC of this request. The DSMC will work with the investigator to draft a charter and provide advice regarding potential Board membership. Details on what types of trials require external DSMBs and how they are convened are found in the UK IRB's C3-0350-Data and Safety Monitoring Plan (https://www.research.uky.edu/office-research-integrity/policies-guidance). 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). In general, interim analysis, outcome data, and blinded information should not be made available to individuals outside the DSMB/DSMC until accrual has been completed and subjects have completed their randomized treatment. Interim reports only contain aggregate/summarized data and no patient identifier information are presented. For interim reports of randomized studies, Closed and Open session reports are generated with treatment assignment presented as coded information. Any special release of this data should be approved by the DSMB/DSMC (for manuscript preparation or planning of future studies). Exceptions may also be made in circumstances where there are special requests for release of information regarding toxicity findings. 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. No communication, either written or oral, of the deliberations of the DSMB/DSMC will be made outside of the DSMB/DSMC. 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: https://www.research.uky.edu/uploads/ori-c30350-data-and-safety-monitoring-sop-pdf

16. Conflict of Interest

As a public land-grant institution, the University has an obligation to the citizens of the Commonwealth and the 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 be non-compliant 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 Regulation 7:2 Financial Conflicts of Interest in Research,* available at: https://www.uky.edu/regs/ar7-2.

To summarize, an individual investigator shall complete at least annually a Financial Interests Disclosure Statement (Disclosure Statement) whether 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 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: https://www.uky.edu/regs/ar7-9.

17. 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

Level of Risk	Explanation	Examples
Low Risk	Non-intervention trials (epidemiologic, outcome, observational, QOL, correlative lab/ancillary) Interventional Trials that are behavioral, nutritional, psychosocial or pose no more risk than expected in daily life DSMC reviews at least annually.	• Behavioral Studies • Nutrition/food supplement Studies • Observational Studies • Survey / questionnaire studies • Correlative sample acquisition
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 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 DSMC reviews all SAEs and deviations in an ongoing manner, and every 3-6 months as determined by the PRMC if no SAEs or deviations occur.	• Most cancer treatment studies • Cooperative group cancer treatment studies
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" DSMC reviews these trials monthly and all SAEs and deviations in an ongoing manner. All investigational radiopharmaceutical agents	• 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 • CAR-T cell therapy

18. 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 Interventional 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 or Lead-Institution

The University of Kentucky's Office of Research Integrity has a reliance agreement process for studies sharing oversight of research with another organization. https://www.research.uky.edu/uploads/ori-c10350-irb-reliance-sop-pdf. 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. The MCC DSMC will have oversight over multicenter IITs per the guidelines of the MCC DSMP. The MCC will require IRB approval for all participating sites from the central IRB of record for the study or their local IRB if the study does not require use of a central IRB, under which each site will conduct its research. For many multicenter trials, participating sites will defer to a central IRB for the specific study. This process will be facilitated by the assigned project manager.

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 or multicenter 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.

III. ASSURING COMPLIANCE WITH REQUIREMENTS FOR UNANTICIPATED PROBLEMS/ADVERSE EVENT REPORTING

1. 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: https://www.research.uky.edu/uploads/ori-c60400-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 (CR) Reporting
CR includes a written summary of both unanticipated problems and available information regarding adverse events since the last IRB review. The summary must include the PI's assessment of whether the problems/adverse events warrant changes to the protocol, consent process, or risk/benefit ratio.
For multisite studies, the written summary should describe external events determined to be unanticipated problems involving risks to subjects.

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: https://www.research.uky.edu/uploads/ori-c20350-unanticipatedanticipated-problemadverse-event-reporting-uk-sop-pdf. .

2. 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: https://www.research.uky.edu/uploads/ori-c40150-mandated-reporting-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)
- For clinical trials conducted under and IDE held by MCC investigator, the PI reports SAEs in accordance with 21 CFR Part 812.150
- 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. **Appendix A**
- 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 B**

Appendices A and B outline the investigator's responsibility in reporting serious adverse events to internal and external entities. In addition, if MCC is the coordinating center for multicenter 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.

IV. 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 BB SRF and the Data Management Team, 4) the Clinical Research Office (CRO) and Precision Medicine Center, 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.

1. Quality Assurance Office

The MCC Quality Assurance Office oversees the maintenance of quality standards in clinical cancer research through the following functions: 1) facilitates and conducts audits of adult therapeutic and interventional cancer clinical trials at the MCC center and at MCC Research Network (MCCRN) Affiliates, with a focus on IITs and cooperative group studies; 2) facilitates 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) clinical data monitoring of MCC IITs; 4) serve as a resource for education, maintenance

of clinical research standards, and development of corrective action plans; 5) provides administrative support to the DSMC and Audit Committee. The QA Program Manager and staff interact with the MCC Investigators, CRO, PMC, BB SRF, IIT Office, Data Management Team, MCCRN Director, Project Coordinator, and Affiliates study staff. The QA Office utilizes data management platforms of the MCC, namely OnCore® and internally developed systems to facilitate their work. The QA Program Manager reports directly to the MCC Director, with additional reporting to the ADCT and DSMC.

2. 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 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 according to the monitoring plan and at the discretion of the DSMC and/or the Audit Committee. A minimum of 25% of patients accrued to High Risk IITs and ETCTN trials will be selected for review. 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 review 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: https://www.research.uky.edu/office-research-integrity/policies-guidance. (C3.0400 NCI CIRB Review SOP).

MCC Research Network sites participating in MCC IITs or NCTN trials where MCC is the parent institution will be subject to routine audits by the MCC QA office. Every year a minimum 10% of patients accrued to adult therapeutic and interventional studies and a minimum of three different protocols will be selected for audit. The focus of these audits is to ensure quality of MCC IITs. NCTN trials may be included in these audits, however MCC IITs will be given priority. The MCC QA office will coordinate and facilitate these audits and will report findings to the MCC Audit Committee and the MCCRN executive committee and MCC Director.

Audits will be of two types: routine and for-cause audits. The routine audit is a planned audit. In a routine audit, when applicable, the patient chart to be audited may 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.

3. MCC 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:

- An MCC clinical investigator selected by the Audit Committee Chair
- Chair of the Audit Committee
- The MCC Quality Assurance Program Manager
- QA Monitor/Auditor(s)
- 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 Auditors, 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.

Auditors may 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 at: https://www.research.uky.edu/office-research-integrity/policies-guidance.
Full processes for the Audit Committee are available at https://ukhealthcare.uky.edu/markey-cancer-center/research/clinical-research-organization/data-and-safety.

4. Investigator Responsibilities

The PI of each study is ultimately responsible for every aspect of the design, conduct and final analysis of the protocol. All protocols must include a description of the procedure that will be utilized to ensure data integrity and protocol adherence, as well as a procedure for independent monitoring of trial safety. All protocols must include a DSMP, and where applicable, per federal guidelines, a DSMB. The PI is responsible for providing a human subjects consent form and describe procedures for protection of human subjects. All protocols must have a description of adverse event determination and reporting, including a schedule for reporting serious adverse events and unanticipated problems that follows the requirements of the University of Kentucky's Institutional Review Boards and/or the NIH/FDA. For multi-institutional studies, the overall study PI is responsible for submitting outside safety reports and data and safety monitoring reports to the MCC DSMC. All blinded studies should describe a randomization scheme and specific criteria and procedures for unblinding. The application should also designate individuals with access to unblinded data. All amendments or modifications should be submitted to the MCC PRMC, the UK IRB and other regulatory bodies for review and approval before altering the trial procedure.

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 A**). IND requirements are described in 21 CFR Part 312. If the IND pertains to an investigational medical device or biologic product (virus, therapeutic serum, vaccine, etc.), the investigator must adhere to FDA regulations 21 CFR Part 812 (Investigational Device Exemptions) and 21 CFR Part 600 (Biological Products). For those clinical trials funded by the NCI, the PI is required to notify the NCI grant program director of any temporary or permanent suspension of the trial. This includes actions by the FDA, IRB, or commercial sponsor or by the PI him/herself. 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.

Investigators need to be aware of:

- NIH policy "Guidance on Reporting Adverse Events to Institutional Review Boards for NIH-Supported Multicenter Clinical Trials" (NIH Guide for Grants and Contracts, June 11, 1999)
- "NIH Policy for Data and Safety Monitoring" (NIH Guide for Grants and Contracts, June 10, 1998)
- "Further Guidance on a Data and Safety Monitoring for Phase I and Phase II Trials" (NIH Guide for Grants and Contracts, June 5, 2000)
- “Essential Elements of a Data Safety and Monitoring Plan for Clinical Trials Funded by the NCI”

The PI must ensure that cancer clinical trials are conducted in accordance with federal, state, and institutional regulations. The PI must maintain ongoing quality oversight of clinical research protocols to ensure protocol compliance and data accuracy and participate in MCC Quality Assurance Office audits and monitoring as per its SOPs. The PI must train investigators and clinical trial staff in the development and conduct of clinical trials. The PI must supervise the collection, maintenance and oversight of data on patients enrolled in clinical trials, including data on accrual, adverse events and unanticipated problems. The PI must maintain on file current FDA forms 1571 and 1572 when applicable, ensure that INDs and up-to-date correspondence pertaining to INDs.

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, and providing a DSMP that is appropriate to the level of risk and scope of work required by the specific protocol. The BB SRF works with investigators to aid in monitoring of accrual, early stopping rules, interim analysis, and overall statistical progress. Protocol-specific interim safety and efficacy reports are generated by protocol statisticians from the BB SRF and forwarded to the study PI and study team. In addition, the BB SRF 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 Data Management Team supports investigators through development of informatics tools such as electronic case report forms, data reporting, 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. The BB SRF, Data Management Team, CRI SRF and MCC Quality Assurance Office have developed collaborative standard operation procedure (SOPs) to ensure an integrated and comprehensive data management process during development and implementation of MCC IITs.

5. 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: https://www.research.uky.edu/office-research-integrity/human-subject-protection-hsp-training-faqs

HIPAA training is required and accessed through the University of Kentucky online web-based training platform.

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.

6. 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, the Precision Medicine Unit, the IITs Office, the CCARTs, OnCore and Clinical Data Management Support Units, the Data and Safety Monitoring Committee (outlined above) and the MCC Quality Assurance Program (outlined above). The CPDM is supported by the Clinical Research Office, as well as the BB SRF.

7. 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 and the faculty. . 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 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
    - Tracks study contract
    - Coordinates protocol continuing review, amendments and reports

- Implements study terminations
- Retains training logs, Clinical Laboratory Improvement Amendments (CLIAs) 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 Clinical Research Office Finance Affairs
- Responsible for budget development and negotiations
- Coordinates pre- and post-award grant management
- Manages the budget/finances of the clinical research units
- Coordinates Medicare Coverage Analyses submissions and financial calendar development with University of Kentucky Clinical Research Support Office (CRSO)

8. MCC Clinical 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, or the UK REDCap database. 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®. As indicated above, the data management components of the BB SRF and the Clinical Data Management Team works with the MCC CRO to ensure an integrated process for all aspects of clinical data management for MCC clinical trials.

The OnCore® CTMS Manager is primarily responsible for managing and maintaining the OnCore® CTMS (clinical trial data management system). The OnCore® CTMS Team employs a team of Informatics (IT) and training personnel. The Data Management Team oversees development and maintenance of electronic case report forms (eCRFs) for each treatment interventional IIT, study-specific OnCore® and Advarra® EDC specifications, protocol-specific data elements and entry requirements and reports utilized by the investigators and committees of the MCC. Account access to OnCore® and Advarra® EDC are maintained by the OnCore® CTMS Team and requires an application, approval, and training in order to access or utilize the clinical trial management system. The OnCore® database and Advarra® EDC capture 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 Clinical Data Management Team along with biostatisticians from the BB SRF perform periodic quality checks of OnCore® data to ensure timeliness and accuracy of data, using a variety of discrepancy reports found in OnCore® and ad hoc reports created from SAS r. For IITs, the Clinical Data Management Team will create OnCore® Specifications, an OnCore® Calendar, and eCRFs in collaboration with the PI, the UK Clinical Research Support Office and study team. Any data fields or data capture forms needed to automate notifications will be created based on the specific protocol needs. A Clinical Data Management Plan (distinct from this Data and Safety Monitoring Plan) and Clinical Data Monitoring Plan are created to document the data monitoring type and frequency and to document the process of go live, validation, and locking of the study database. In addition, data entry review and guidelines are created by the Clinical Data Management Team to assure timely and accurate data capture. 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 interventional IITs, the Clinical Data Management Team and the QA Monitor will review and query data using the OnCore® Data Monitoring Console. The MCC QA Monitor will verify source data as indicated in the protocol-specific Clinical Data Monitoring Plan. The BB SRF and the Clinical Data Management Team will have access to data in all IITs to

perform interim safety and efficacy assessments, which will be automated through OnCore® wherever possible. For interventional therapeutic IITs, once study enrollment is complete and all forms have been monitored following the protocol-specific Clinical Data Management Plan, the eCRFs will be validated and locked in order to a) prevent further data entry and b) allow for final data analysis, per standard operating procedure.

9. Data Management Delineation of Duties

MCC Quality Assurance Office Responsibilities
The Quality Assurance Office will assist the PI, Biostatisticians and Clinical Data Manager in creating Clinical Data Monitoring Plans and quality assurance specifics in the Clinical Data Management Plans. The frequency and timelines will depend on the risk of the study. The QA Auditor/Monitor(s) are responsible for performing routine monitoring of MCC IITs, based on a study-specific Clinical Data Monitoring and Audit Plan, including source data verification and frequency of monitoring events. The QA Auditor/Monitor, in conjunction with the Clinical Data Management Manager, is responsible for the creation and submission of queries and as applicable, will communicate and collaborate with the Biostatistician or other members of the project team on the preparation and issuance of queries. The QA Auditor/Monitor will submit monitoring reports of all monitoring related activities and reports to the Quality Assurance Manager and the PI or as applicable for multicenter studies MCC Lead Investigator and the MCCRN Director. 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.

Data Management

OnCore® Clinical Trials Management System Responsibilities
The MCC employs a Clinical Trials Management System Database Administrator to manage all cancer-related support for the deployment of the OnCore® system and to maintain communication with the university-wide OnCore® database and the Advarra Cloud-based hosting of the platform. The Applications Manager is assisted by systems analysts, OnCore® trainer and other staff, and is supervised by the AD for Clinical Translation and the AD for Administration.

The Cancer Research Informatics Shared Resource Facility (CRI SRF) develops ancillary databases (LabKey, REDCap, etc.) for any IITs with correlative data not collected in OnCore® CTMS with input from the PI, the MCC CRO and BB SRF biostatisticians. OnCore® and Advarra® EDC, are an indispensable tools for MCC clinical research. This robust clinical trial management system supports the essential functions of CPDM, including: 1) protocol review and accrual monitoring; 2) regulatory flow process tracking; 3) adverse event monitoring; 4) eCRF development; 5) updated protocol access for all MCC clinical investigators on the main campus and at remote sites; 6) statistical review and analysis by Biostatistics and Bioinformatics (BB) SRF personnel; 7) QA and internal auditing; 8) required reporting procedures of the NCI, CTRP and clintrials.gov; and 9) data and safety monitoring functions. This secure, encrypted, web-based system meets all federal and state requirements for clinical research data and data storage and integrates all clinical trials management into one system. The Markey provides support for the technical administration of OnCore® through a CTMS database manager, research database analysts, and other CTMS data managers and support personnel. These personnel ensure timely and consistent data transmission into OnCore®, as well as the NCI's Clinical Trials Reporting Program, and assistance with Medidata Rave. Support data managers assist with data editing, timely resolution of queries from CTMS, quality control, and verification of submitted data into the OnCore® data platform. In conjunction with the Markey Clinical Research Office. Markey maintains high-quality clinical data management using an effective quality assurance (QA)/quality control (QC) process, with a QA Manager, internal monitors and auditors, who perform routine internal

audits and oversight of data submission, preparation for external audits, and assistance with Corrective Action and Preventive Action (CAPA) plans and audit reports.

The Clinical Research Office and Precision Medicine Center managers supervise clinical research nurses, clinical research coordinators and data entry staff and oversee the daily operations of the clinical teams. Markey's data entry staff co-locate with the research staff to assure team-based structure emphasizing timely and accurate communication. All data entry coordinators, clinical research coordinators and clinical research nurses have received training in reporting of trial participant data to OnCore®, Advarra® EDC, industry, federal agencies, CDUS, CTMS, Medidata RAVE, and other EDC platforms as appropriate. In addition, the Markey Quality Assurance Office employs educators, auditors and monitors whose responsibilities include training and education of staff regarding data reporting and management as well as assuring quality control benchmarks are being met within the early phase clinical trials team.

All cancer interventional trials include statistical analysis plans for clinical and biomarker endpoints, and are supported by the Markey Biostatistics and Bioinformatics Shared Resource Facility (BB SRF). Statistical analysis related to outcome, design, conduct and implementation of Phase I and Phase II clinical trials entail comprehensive application of several statistical principles and methods including operational definition of appropriate study endpoints, estimation of sample size and statistical power, statistical analysis of primary and secondary safety, efficacy and correlative endpoints as well as interim monitoring. The BB SRF is well versed in standard and novel statistical methods and models for analysis of preclinical and translational studies; clinical and correlative endpoints for early phase IITs; and interim analyses implemented in the conduct of IITs.

Data Formats
Following successful completion of protocol development, Markey-led protocols are created in OnCore® and sent in parallel to the CIRB or appropriate IRB of record. If approved by the CIRB, Markey manages protocol status (Open/Expand/Close) via the IWRS system at Theradex. When the protocol is available for accrual, Markey will register patients using the Oncology Patient Enrollment Network (OPEN) system. The IWRS system interacts with the OPEN to ensure cohort slot availability and if available/successful sends subject enrollment to Rave. Markey research staff interact with Rave directly to provide electronic Case Reporting Form (eCRF) data as required by the protocol. AE's and SAE's are recorded in Rave and flow through the Safety Gateway and onto CAEPRS and CTEP-AERS. Markey research staff concurrently enter data, demographics and AEs, SAEs into OnCore® for reporting, auditing and operations.

Data compatibility plans. To ensure the compatibility and transportability of data, software, and algorithms generated by the Markey research team (*e.g.*, the ability of external collaborators, monitors, and other appropriate entities to access and utilize data or software components generated during studies), our data compatibility plan relies on the integrated platforms of the NCI (OPEN, IWRS, and Rave systems), thus assuring wide scope compatibility as well as utilization of the OnCore® CTMS which assures excellent interoperability. The design, implementation, and maintenance of information management and analysis tools, including databases, intermediary ETL, translation, and analytical services, are provided by the OnCore® Administrator with assistance from the Cancer Research Informatics Shared Resource Facility.

Markey Clinical Trials Data Management
In addition, Markey employs an OnCore® Data Management Team, including a Clinical Trials Data Manager who oversees the DM Team and works with BB SRF statisticians and the MCC CRO and PMC protocol personnel to perform data management of all MCC IITs. Specifically, this team implements the study-specific Data Management Plan which defines the roles and processes for critical data variables, validation, database lock and exports. The assigned OnCore® Data

Management Specialist in conjunction with the QA Auditor/Monitor validates all study forms, as applicable, submits data management related queries, and is responsible for locking of all forms once all the data is clean and validated. The Clinical Trials Data Manager is supervised by the AD for Clinical Translation and the AD for Administration.

BB SRF Responsibilities
The MCC BB SRF 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, BB SRF verifies that dose limiting toxicities and all toxicities are appropriately captured. BB SRF staff develop automated trigger programs and send 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. As indicated above, BB SRF statisticians are involved in all aspects of clinical data management from eCRF design, development of Data Management Plan, study interim monitoring and final data clean-up and database lock for generation of final statistical reports and analysis.

10. Database Oversight, Security, and Data Entry Requirements

In addition to the above, the CRO, Data Management Team, and as applicable for multicenter trials, the assigned Project Coordinator ensure quality data and protocol compliance with additional requirements of MCC trials 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 and Phase II trials, The BB SRF has developed automated system for real-time access of enrollment and AE data. Specifically, the study team needs review AE/SAE/DLT data and made decisions as the study progress. An SAS program scheduled weekly 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. The SAS program is written such that it monitors the current enrollment progress and 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. For studies that requires prompt actions to specific events (such as change of study treatment, AE of special interests), a customized SAS program will be developed

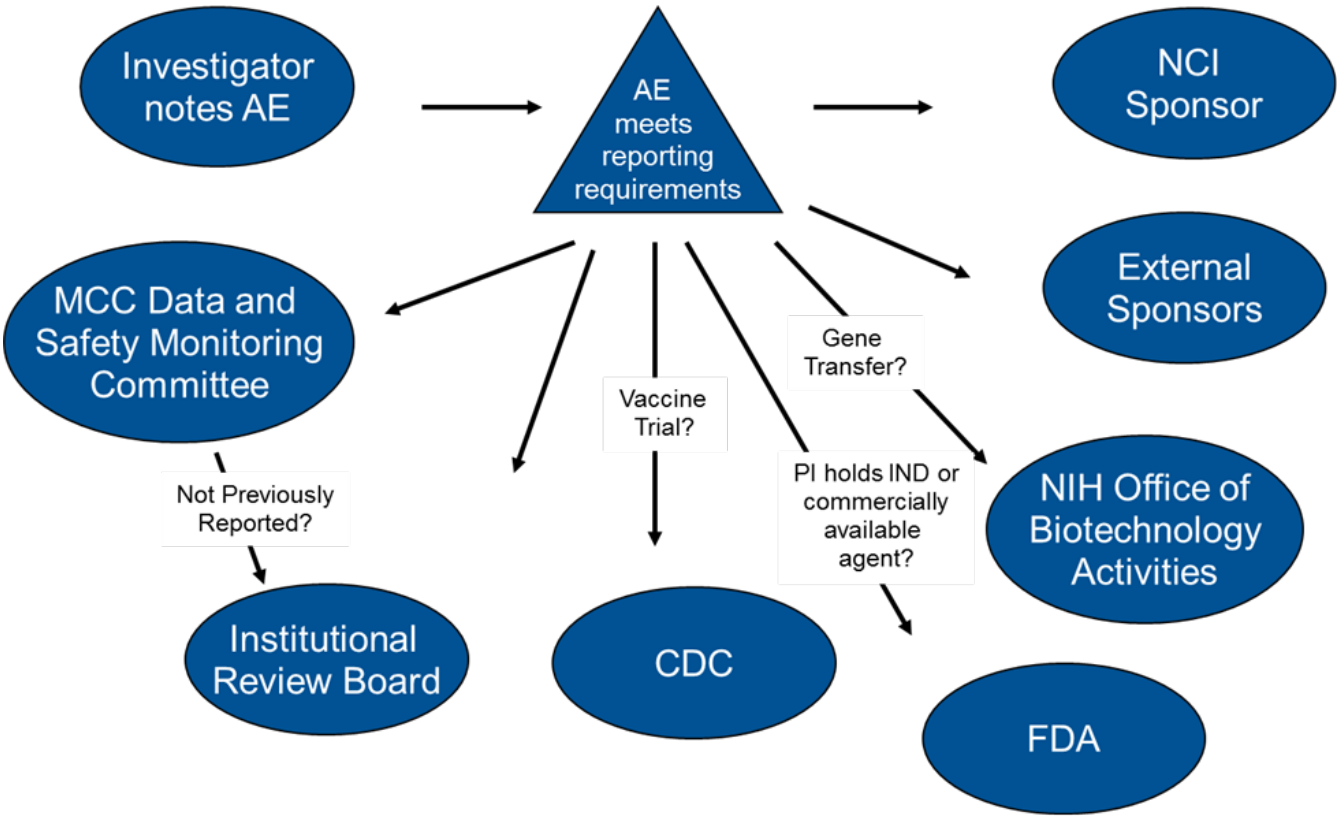
to monitor the current data in AE as well as other relevant data, and distribute email notifications to the relevant study team members..

V. 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 the 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 SOP (C4.0150 Mandated Reporting to External Agencies) and in the coordination SOP between MCC and IRB and ORI (C6.0400): https://www.research.uky.edu/office-research-integrity/policies-guidance

APPENDICES

Appendix A: Flow Diagram of Serious Adverse Event Reporting by Investigators



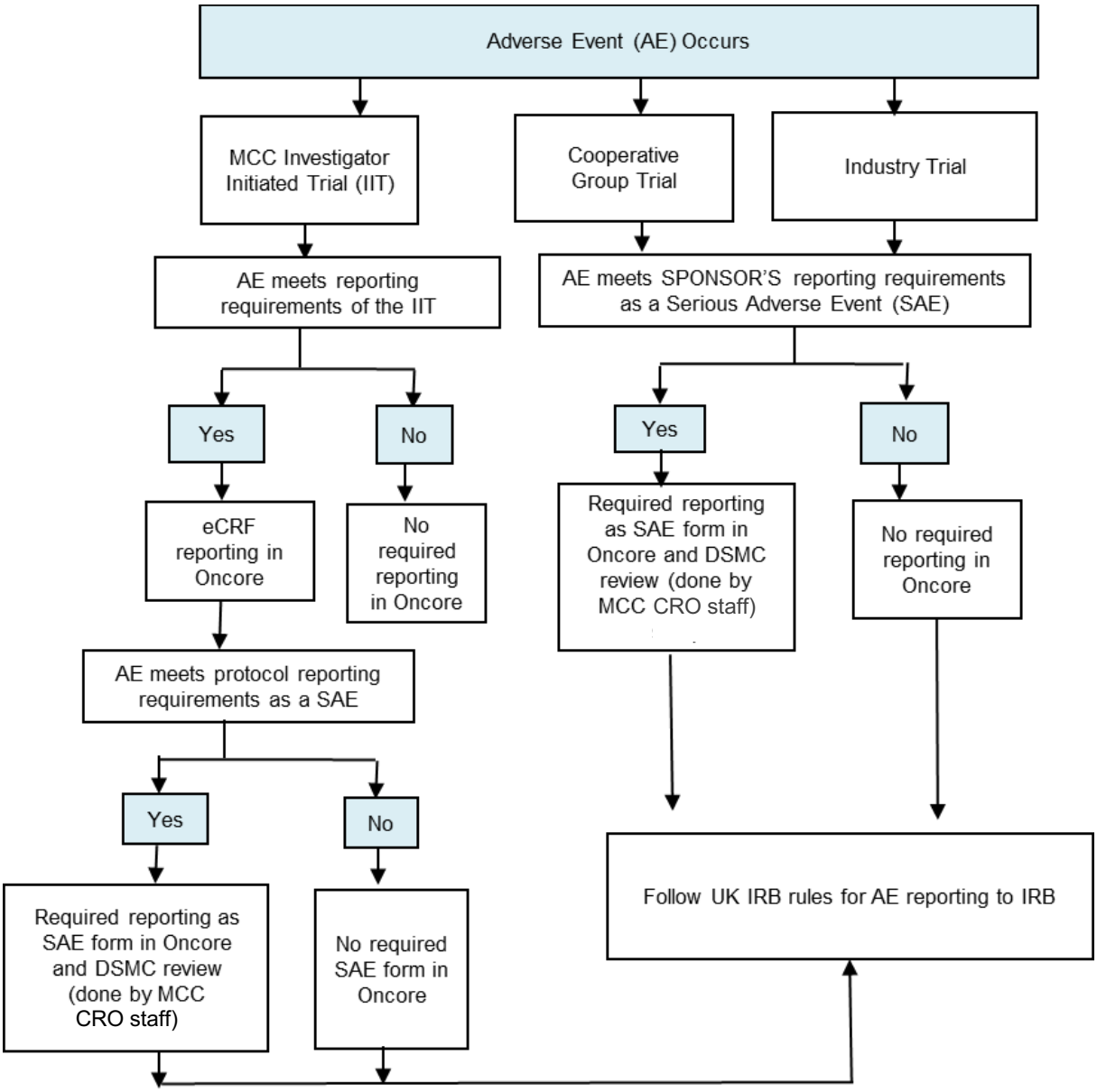


Fig. 1. Adverse event and Serious Adverse Event Reporting in Oncore

Appendix B: Adverse Event Reporting for Trials for which NCI is also the IND Sponsor

A. 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

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 https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfCFR/CFRSearch.cfm?fr=312.32 and http://www.fda.gov/ScienceResearch/SpecialTopics/RunningClinicalTrials/ucm120262.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 which are unexpected that occur with commercially available agents/devices are reported through Food and Drug Administration Medwatch. (https://www.fda.gov/safety/medwatch-fda-safety-information-and-adverse-event-reporting-program).

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) (https://grants.nih.gov/grants/guide/notice-files/NOT-OD-02-052.html and https://osp.od.nih.gov/biotechnology/nih-guidelines/).

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

Serious adverse events must be reported according to applicable FDA regulations (Food and Drug Administration reporting requirements of serious adverse events for post-marketing trials of vaccines).

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.

Appendix C: Data and Safety Monitoring Committee Roster

Data & Safety Monitoring Committee	
Voting Member Name	**Expertise**
Susanne Arnold, MD	Vice Chair, Clinical Investigator, Oncology, Associate Director for Clinical Translation
Tom Badgett, MD	Clinical Investigator, Pediatric Oncology
Allison Butts, PharmD	Pharmacist, MCC
Kyle Dawson, PharmD	Pharmacist, MCC
Charles Dietrich, MD	Clinical Investigator, Gynecologic Oncology
Denise Fabian, MD	Clinical Investigator, Radiation Oncology Medicine
Chaitanya Iragavarapu, MD	Clinical Investigator, Hematology & BMT
Rani Jayswal, MS	Biostatistician, BBSRF
Seth Larkin, PharmD	Pharmacist, Investigational Drug Service
Ronald McGarry, MD	**Chair, Clinical Investigator, Radiation Oncology Medicine**
Reema Patel, MD	Clinical Investigator, Medical Oncology
Brent Shelton, PhD	Biostatistician, BBSRF
Yvonne Taul, RN, CCRC	Research Nurse, MCC, CRO
Joseph Valentino, MD	Clinical Investigator, Surgery