MARKEY CANCER CENTER QUALITY ASSURANCE OFFICE STANDARD OPERATING PROCEDURES		
SOP No.: MCCQA-002.00 *(previously MCC 006.04)* **Revision:** **Revision Date**: 4/3/17 Effective Date:	**Title:** MCC Audit Committee Functional and Administrative Overview	
Approval	**Signature**	**Date**
MCC Director		
MCC Associate Director of Clinical Translation		

1. PURPOSE

1. To describe the procedures for auditing all adult interventional cancer clinical trials conducted at the University of Kentucky's Markey Cancer Center (MCC).
2. To describe the methods used to verify compliance with the protocol and other requirements.
3. To describe the methods used to verify adherence to MCC Data and Safety Monitoring Plan.
4. To describe the methods used to provide information to the study staff regarding Good Clinical Practice (GCP) and data collection and to assure that:
    - The rights and well-being of human subjects are protected.
    - The reported trial data are accurate, complete, and verifiable from source documents.
    - The conduct of the trial complies with the currently approved protocol and amendment(s), with GCP, and with applicable regulatory requirement(s).

2. SCOPE

1. The Audit Committee facilitates the internal audit program of the MCC, reviews and approves MCCRN audit reports and reports findings to the Data Safety Monitoring Committee (DSMC), the MCC Director, and the MCC Associate Director for Clinical Translation (ADCT).
2. This procedure applies to all adult interventional cancer-related clinical trials operating under approval from the MCC Protocol Review Monitoring Committee (PRMC).
3. Unless otherwise required by the DSMC, IITs, early therapeutics (Phase I), and National Clinical Trials Network (NCTN) trials will be regularly audited by the audit program. The presumption that FDA-monitored studies (i.e., funded by corporate manufacturer of pharmaceuticals or devices) have adequate oversight can be overruled by the PRMC or DSMC.

3. RESPONSIBILITIES

1. The MCC Audit Committee is advisory to the DSMC, the MCC Director and the Associate Director for Clinical Translation. The Audit Committee members are comprised of the Audit Committee Chair, QA Program Manager, MCC Investigator(s), QA Auditor(s), and other ad-hoc members with particular expertise of benefit to the audit process as determined by the Audit Committee Chair and QA Program Manager. Section 2 of the Markey Cancer Center Internal Audit Manual outlines the responsibilities of:
    - Audit Committee
    - Audit Committee Chair

- QA Program Manager
- MCC Investigators
- QA Auditor(s)
- Data Safety Monitoring Committee

2. The ADCT is responsible for assuring compliance by the MCC staff and faculty.

4. PROCEDURE

1. Sections 3 through 6 of the Markey Cancer Center Internal Audit Manual outline the procedures for:
   - scheduling, preparing, and conducting audits
   - reporting audit findings and follow up
2. The Audit Committee meets monthly to ensure timely oversight of MCC internal and MCCRN audit reports.
3. The Audit Committee reviews external audit reports (NCTN, FDA, NCI…) to ensure that MCC is aware of audit activity and findings. The committee will determine if a for-cause internal audit is necessary.
4. The Quality Assurance Office provides administrative support to the Audit Committee. The audit reports are peer reviewed protected and are confidential and are not distributed or made public. Audit Committee Minutes are kept by the QA Program Manager and forwarded to the Committee Chair for review and approval. The minutes are approved and signed by the Audit Committee Chair. An original copy and scanned copy of the minutes will be housed in the Quality Assurance Office.

5. FORMS/ATTACHMENTS

1. Markey Cancer Center Internal Audit Manual

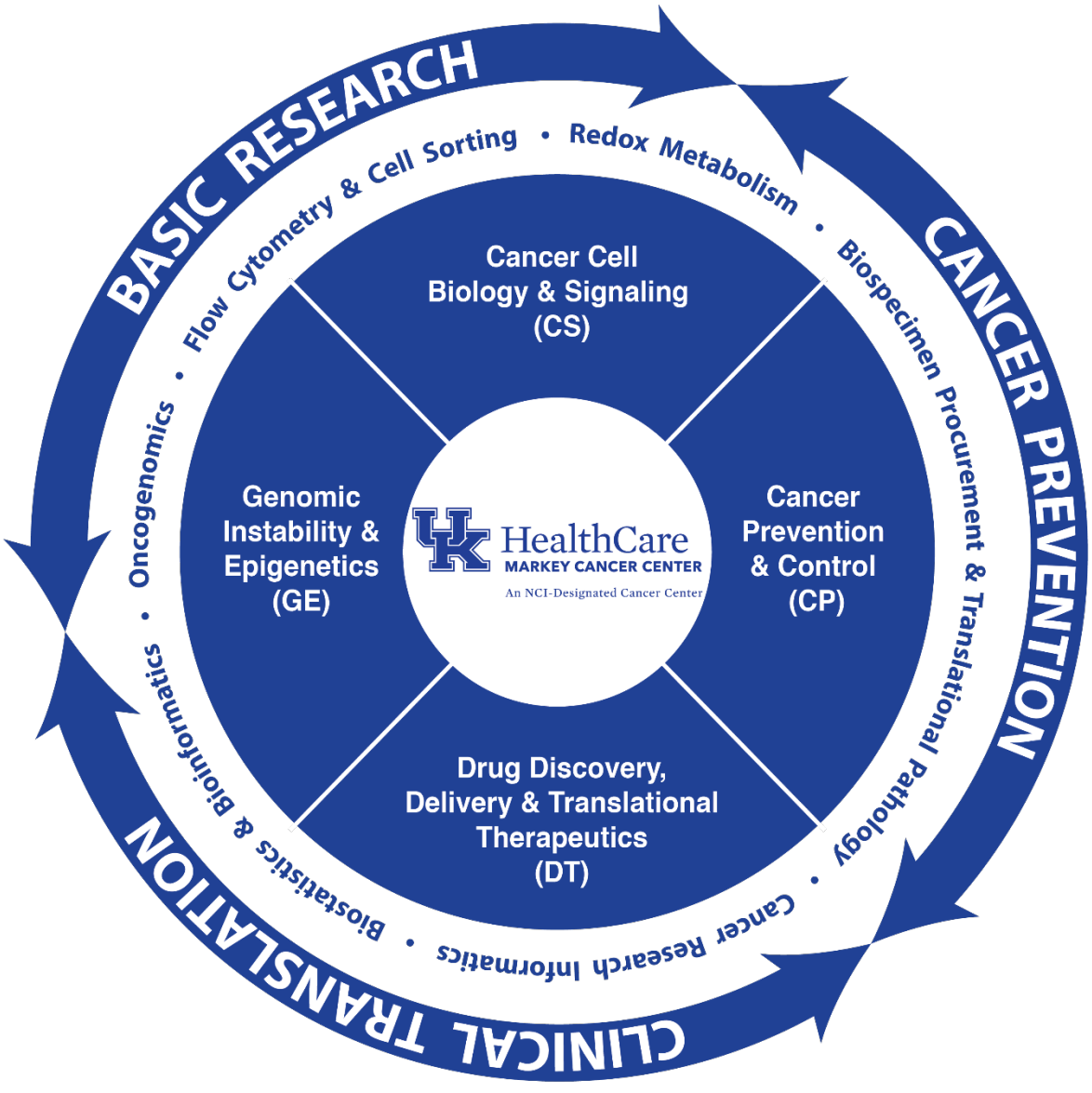
6. REFERENCES

1. Markey Cancer Center Internal Audit Manual-Section 8

7. REVISION HISTORY

Revision:
Date:
Description of change:

Markey Cancer Center
Internal Audit Manual



MCC INTERNAL AUDIT MANUAL

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SECTION 1: INTRODUCTION AND BACKGROUND

1.1 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 accuracy and quality of data obtained from clinical and translational research. Quality assurance is any method taken for the collection, processing, or analyzing study data aimed at preserving or further improve their reliability and validity. One of the functions of the MCC Quality Assurance (QA) Office is clinical trial auditing of MCC therapeutic and interventional cancer clinical trials. This document serves as a guideline for the Markey Cancer Center Internal Audit Program of therapeutic cancer clinical trials conducted by MCC investigators.

1.2 MCC Audit Committee

The MCC Audit Committee was formed in 2011 to conduct ongoing retrospective and focused audits of the MCC therapeutic clinical trials. The MCC Internal Audit Program is based on the audit guidelines prepared by CTMB, CTEP, DCTD, and NCI. The Audit Committee is advisory and reports directly to the Data Safety Monitoring Committee (DSMC), MCC Director and the Associate Director for Clinical Translation (ADCT) on the status of clinical research management.

1.3 Purpose and Goals

The purposes of the MCC Internal Audit Program are to:

- Ensure patient safety.
- Ensure investigator compliance with protocol, sponsor /MCC SOPs, GCP, and all federal regulatory requirements.
- Verify the accuracy of data submitted.
- Verify adherence to the handling of investigational/study drugs and devices.
- Provide educational support to the Markey Cancer Center staff and faculty.
- Track trends and deficiencies for education and training purposes.

The goals of the MCC Internal Audit Program are to:

- Prevent errors and detect possible problems.
- Recognize any non-compliance issues rapidly and take appropriate action(s) in a timely manner.
- Implement new processes or improve current processes, as needed.

SECTION 2: ROLES AND RESPONSIBILITIES

2.1 MCC Audit Committee

The MCC Audit Committee is advisory to the DSMC, the MCC Director and the ADCT. The Audit Committee members are comprised of the Audit Committee Chair, QA Principal Investigator (PI) Program Manager, MCC Investigator(s), QA Monitor(s), QA Education Specialist and other ad-hoc members with particular expertise of benefit to the audit process as determined by the Audit

Committee Chair and QA Program Manager. The Audit Committee meets monthly or at a minimum quarterly to ensure timely oversight of the internal and MCCRN audits. Minutes are kept and housed in the QA Office.

Members of the Audit team may not audit studies in which they are involved (i.e. PI or Co-PI). The roles and responsibilities of the MCC Audit Committee are:

- Conduct ongoing, retrospective and focused audits on selected protocols.
- Review all audit findings, reports and PI responses conducted internally and at MCCRN sites.
- Implement standard operating procedures to ensure consistency in internal audits conduct and management.
- Ensure the compliance and communication of MCC clinical trials audit guidelines.
- Provide education based on internal and external audit results.
- Provide final reports of auditing activity for review by the DSMC, as well as the MCC Director and ADCT.
- Complete any required training prior to conducting an audit.
- Participate as needed in the review of designated audit components for the audit.
- Attend all Audit Committee meetings or be available for questions and feedback.

2.2 MCC Audit Committee Chair

The Audit Committee Chair will be designated by the MCC Director and the Associate Director for Clinical Translation and will server a three-year term. The responsibilities of the Audit Committee Chair are:

- Designate the quarterly MCC investigator auditors and ad-hoc members as internal auditors.
- Serve as an auditor as needed.
- Review all audit findings and PI responses, in conjunction with the Audit Committee.
- Review and approve the audit reports, in conjunction with the Audit Committee.
- Report final Audit findings to the DSMC.

Should the Audit Committee Chair be involved in any study that is audited, the audit findings and reports will be reviewed and approved by the ADCT or other Associate Directors as selected by the MCC Director.

2.3 Quality Assurance Program Manager- Audit Lead

The QA Office provides administrative support to the MCC Audit Committee. The QA Program Manager will function as or designate the Audit Lead and will be responsible as designated by the Audit Committee Chair for:

- Scheduling and coordinating all audits with the assigned auditors and study staff.
- Selecting patient cases to be audited using ONCORE.
- Notifying the appropriate PIs and appropriate study staff, of the upcoming audit with the list of protocols and patient charts selected for the audit.
- Coordinating the pharmacy audit/inspection when applicable.

- Coordinating any required training for the audit team members.
- Serving as an internal auditor.
- Compiling and preparing all audit reports and submitting them to the Audit Committee and Chair for review and approval.
- Facilitating the exit interview when applicable.
- Processing and submitting PI responses to the Audit Committee and Chair.
- Submitting the final audit reports to DSMC and the MCC Director.
- Coordinating and scheduling the Audit Committee Meetings.

2.4 MCC Principal Investigators

All MCC \Investigators are eligible to serve as auditors and are appointed by the Audit Committee Chair. The term they serve will be for one quarter and 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 MCC PI auditor responsibilities are:

- Serve as an internal auditor during the time appointed as MCC PI auditor.
- Be available for questions and correspondence regarding audit findings and responses.
- Review audit reports.
- Review all PI/ Study staff correspondence and responses.
- Provide input and feedback when requested in a timely manner.
- Lead the exit interview when applicable.

2.5 Internal Auditors

The internal audit team will consist of one or more QA Office auditors, at least one physician auditor, and other ad-hoc members as needed. The internal auditor(s) selected will be responsible as directed for:

- Reviewing conformance to Institutional Review Board and Informed Consent Content requirements.
- Reviewing shipping, storage, and use of investigational/study drugs and devices.
- Reviewing individual patient case elements (eligibility, consent, treatment, toxicity reporting, disease response, and data quality).
- Completing the IRB and ICC Audit Worksheet.
- Completing the Pharmacy Audit Worksheet.
- Completing the Patient Case Audit Worksheet.
- Submitting all completed audit worksheets to the Audit Lead for compilation of audit findings.

2.6 Data Safety Monitoring Committee

The Data Safety Monitoring Committee (DSMC) will review the final audit reports and will make the final determinations taking into account the Audit Committee's recommendations of each audit component. The assessment of Acceptable, Acceptable Needs Follow-Up, or Unacceptable will be determined. The DSMC will request further action and corrective and preventive action plans for

those components deemed Acceptable Needs Follow Up or Unacceptable. Each major deficiency will require a Corrective and Preventive Action Plan (CAPA) to be written and submitted back to the DSMC for review and approval. If the PI has previously addressed each major with a CAPA plan prior to the DSMC meeting or review, the DSMC will review and approve as is or may request additional information or action from the PI.

SECTION 3: MCC INTERNAL AUDITS

3.1 Audit

An audit is a systemic and independent examination of trial related activities and documents to determine whether the evaluated trial-related activities were conducted and the data were recorded, analyzed, and accurately reported according to the protocol, sponsor's SOPs, Good Clinical Practice, applicable regulatory requirement(s), and ethical standards of the MCC.

3.2 Frequency

MCC internal audits will be conducted quarterly or sooner if deemed by the DSMC and/or the Director of MCC and ADCT.

3.3 Types of Audits

There are two types of audits that may be conducted; a routine and a for-cause audit. The routine audit is a planned audit that will be conducted quarterly at MCC. A for-cause audit is an unplanned audit that can occur anytime the MCC Director, ADCT, or the DSMC determines that there is sufficient reason to audit without notice, such as reports of unexpected and/or unreported risks to subjects, failure to comply with federal and/or institutional requirements, or other significant concerns about the conduct of the study.

Routine and for-cause audits will be identically undertaken, with the following exceptions: for-cause audits may be scheduled at any time, without notice and the patient charts are not required to be chosen randomly. The number of charts audited will be based on the reason for the audit as determined by the DSMC and will not be limited.

3.4 Trials Audited

The MCC Audit Committee may audit studies from their initiation to IRB study closure, but mainly focuses on actively accruing studies. These will include those protocols sponsored by NCI, NCTN groups, and MCC investigator-initiated trials (IITs). Priority and importance will be given to the following protocols that are deemed High Risk by the PRMC:

- MCC phase I, I-II and II IIT's, or MCC IIT's 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 (industry or NCTN group sponsored) with agents that have never been used in humans.
- Gene therapies with agents that are not yet FDA approved.
- High dose studies (i.e., transplantation).

The presumption is that Industry FDA-monitored studies (i.e., funded by corporate manufacturer of pharmaceuticals or devices) have adequate oversight and will not be included in the protocol and patient selection. However, this can be overruled by the PRMC and DSMC and when directed, will be included in the protocol and patient case selection.

While most patient cases will be selected from accruals since last audit, all patient cases accrued are subject to selection.

Attempts are made to distribute the audits evenly among the various disease sites and investigators. Subject selection is impartial. MCC IITs including all Phase I IITS and all rapidly accruing IITs will be audited at least once during the lifetime of the study but may be audited more frequently at the discretion of the DSMC.

Note: MCC IITs that are open, but have never been audited will be given top priority.

All studies that are under the purview of the National Cancer Institute-Central Institutional Research Board (NCI-CIRB) will have a yearly administrative audit at the time of continuation review by the MCC CRO Regulatory coordinator(s) and/or Audit Lead to confirm the following:

- The most current informed consent forms are being used in each study.
- The 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 is retained in the consent document.

SECTION 4: PREPARING FOR THE INTERNAL AUDIT

4.1 Scheduling the Audit

MCC internal audits of the MCC clinical trials will be conducted quarterly. The Audit Lead will coordinate the time and place the audit will take place. The Internal Auditor(s) will be selected during this time by the Audit Committee Chair and the Quality Assurance Program Manager. The date(s) of the audit will be approved by the Audit Committee Chair and PI auditor(s).

The Audit Lead will coordinate with Pharmacy research staff to schedule pharmacy reviews and inspection when applicable.

4.2 Selection of Protocols and Patient Cases

Every year a minimum number of 10% of participants accrued to adult therapeutic trials are selected for audits. A minimum of 25% of patients accrued to High Risk IITs and ETCTN trials will be selected for review. MCC internal audits will be conducted on a planned quarterly basis. A minimum of three protocols representing studies conducted at MCC will be selected when applicable. 10% of patient cases or a minimum of three patient cases accrued to MCC therapeutic trials will be randomly selected. While most subject cases will be selected from accruals since the last audit, all patients accrued are subject to selection.

In addition for training and educational purposes; any new CRA/CRN that enrolls a patient on a MCC therapeutic/interventional clinical trial for the first time will be audited. The audit component of the patient cases will include consenting and eligibility and the review of data quality and management. This may be done at any time with or prior to the planned audit date(s).The findings will be reported to the new CRA/CRN and supervisor to identify any additional education and training needs.

4.3 Notification Email to PI and Research Staff of Upcoming Audit

Once the protocols and patient cases have been selected, within two weeks of the scheduled audit an email notification will be sent by the Audit Lead notifying the following study staff of the upcoming audit date(s).

- Each protocol PI and designated CRA/Research Nurse
- Regulatory Coordinators
- Pharmacy Personnel if applicable
- MCC CRO Medical Director
- MCC CRO Clinical Trials Management Director

The email notification will list the selected protocols and patient cases that have been selected for the audit, along with what will be reviewed during the audit and the expectations required of the PI and all study staff prior to the audit.

4.4 Audit Preparation and Expectations

4.4.1 Principal Investigators and CRAs/Nurses

Prior to the audit it is the responsibility of each selected protocol PI and CRA/Research Nurse to provide all source documentation pertaining to the selected patient cases, including but not limited to the following:

- Original Informed Consent documents.
- Original eligibility checklist (if one was used by the protocol).
- Protocol and Clinic Flow sheets that are signed and dated.
- Inpatient and Outpatient medical records and charts.
- Physicians and CRA/ Research Nurses notes.
- Completed case report forms.
- Patient Diaries and Questionnaires.
- Chemotherapy IV infusion flow sheets.
- Radiation Therapy notes and flow sheets. (if applicable)
- Investigation/Study drug orders (IV, IM, SQ, and Oral) signed and dated by PI or sub PI.
- Diagnostic Radiology Imaging Reports.
- Histology, Pathology and Laboratory Reports.
- All Correspondences and any other relevant information.

Source Documentation: The ICH-GCP guidelines define source documents as "***original documents, data, and records***." Case report forms (paper or electronic) will not be accepted as source documentation. Certain cooperative groups will allow the use of the original eligibility checklist as source documentation provided it was signed and dated by the enrolling PI prior to enrollment/randomization. It is the responsibility of the study team to know which cooperative groups will allow this and to provide the policy if requested.

To help facilitate the review, it is requested that the selected patient cases be flagged and organized. Locate and mark for easy identification the following items:

- The original signed informed consent forms.
- Original Eligibility Checklist signed and dated by Physician.
- All reports from on study, during and follow up parameters. (Notes, labs, path, lab, radiology, etc.)
- Each Visit and/or Cycle notes.

When a discrepancy is noted that will require clarification, create a "note-to-file". These notes must be signed and dated and include how the information was obtained. Reminder: note-to-files do not replace the need for deviation and protocol violations submissions to IRB when applicable.

The patient case records are due the day before the scheduled audit date(s). In the event the study patient charts cannot be provided by the date(s) requested; it is the responsibility of the PI and or CRA/CRN to notify the Audit Lead, with reason and expected date the charts will be available. An extension may be granted, but ideally no longer than five working business days.

It will not be necessary for the PI or CRA/CRN to sit with the auditor(s) during the review, however a designated member of the study team should be available during this time to answer questions or locate missing source documents.

4.4.2 Regulatory Coordinators

The responsibility of the Regulatory Coordinator for each protocol selected will be to provide the Regulatory Binder for review. The Regulatory Binder should contain the following documents:

- IRB initial approvals (Initial, Continuing Reviews and Amendments)
- Current and past versions of the protocol.
- Current version of the consent document.
- Reported adverse events and serious adverse events.
- Safety reports and memos with appropriate IRB correspondence.
- Copy of Federal Wide Assurance.
- FDA 1572 Form and curriculum vitae for each investigator.
- Laboratory and Pharmacy Certifications.
- Financial Disclosure Forms and Conflict of Interest Forms.
- Delegation and training logs with certifications (if applicable).

These documents are due within one day of the audit(s) date scheduled. In the event the Regulatory Binder cannot be provided by the date(s) requested; the Regulatory Coordinators are required to

notify the Audit Lead, with reason and expected date the Binder will be provided. An extension will be granted, but ideally no longer than five working business days.

It will not be necessary for the any Regulatory Coordinators to sit with the auditors during the review, however a member from the team should be available during this time to answer questions or locate missing source documents.

4.4.3 Pharmacy

The Pharmacist or assistant will be responsible for providing copies of the Drug Accountability Record Forms (DARFs) for each patient case selected for audit. The DARFs will be due within one day of the audit date(s) scheduled.

A pharmacy inspection will be conducted at every other planned quarterly audit. A pharmacist or pharmacist assistant must be available for the inspection and for any questions that arise. There will be at least three INDs reviewed when applicable. A cross check of the balances recorded on the DARFs will be compared to shelf inventory. For each patient case selected for audit, all pharmacy records associated with the investigational/study drugs will be reviewed. The following records are required for review at the inspection:

- Drug orders, receipts, and transfers.
- NCI DARFs
- Satellite records if applicable
- Destruction of drug policy and destruction records
- Return of drug receipts

In addition to review of records, the pharmacy will also be inspected for adequate security measures and adequate storage of investigational/study drugs.

SECTION 5: CONDUCTING THE AUDIT

5.1 Audit Assessments

The MCC internal audit will be conducted utilizing the guidelines prepared by the CTMB, CTEP, DCTD, and NCI. http://ctep.cancer.gov/branches/ctmb/clinicalTrials/docs/ctmb_audit_guidelines.pdf

There are three components that will be reviewed and evaluated:

- Conformance to IRB and Informed Consent Content (ICC) requirements.
- Drug accountability and pharmacy compliance.
- Patient case report forms review.

Each of the three components will be assigned an assessment of Acceptable, Acceptable Needs Follow-up, or Unacceptable based on findings at the time of the audit. Although it is difficult to precisely define what constitutes an unacceptable audit, we will use a common set of terms or examples of major and minor or lesser deficiencies to assess each component of an audit.

5.1.1 Major Deficiency

A major deficiency is defined as a variance from protocol-specific procedures that makes the resulting data questionable or places patients at risk for morbidity.

5.1.2 Lesser Deficiency

A lesser deficiency is defined as a deficiency that is not judged to have a significant impact on the outcome or interpretation of the study and is not described as a major deficiency. An unacceptable frequency of a minor deficiency is treated as a major deficiency in determining the final rating of a component.

5.1.3 Acceptable Assessment

An "Acceptable" assessment will be assigned to any component when:

- No deficiencies are identified.
- Few or lesser deficiencies are identified.
- Any major deficiency that is identified during the audit, that was addressed and corrected prior to the audit, wherein a written and dated corrective and preventive action plan (CAPA) exist and no further action is required by the MCC PI and no similar deficiency has occurred since the corrective action plan was implemented. **Note:** If the major is associated with a safety concern and it is determined by the Audit Committee or DSMC that further action is necessary, this approach may not apply.

5.1.4 Acceptable Needs Follow-Up Assessment

An "Acceptable Needs Follow-Up" will be assigned to any component when:

- Multiple Lesser Deficiencies have occurred
- Any Major deficiency that is identified during the audit not addressed and or corrected prior to the audit.

5.1.5 Unacceptable Assessment

An "Unacceptable" will be assigned to any component when:

- There are multiple major deficiencies identified.
- A single major flagrant deficiency has been identified.
- Multiple lesser deficiencies of a recurring nature have been found in most of the patient cases reviewed.

5.2 IRB and Informed Consent Content Review

The auditor(s) will complete the IRB and ICC Audit Worksheet For each protocol that is selected for audit, the following documentation will be the minimum source documents that are reviewed:

- Full initial IRB approval of protocol and consent form.
- Full IRB continuing review re-approvals.
- Protocol amendments approvals or disapprovals that affect more than minimal risk.
- IRB approval or re-approvals prior to patient registration.
- FDA 1572 forms and curriculum vitae for each investigator.

- Copy of Federal Wide Assurance
- Financial Disclosure forms and Conflict of Interest if applicable.
- Laboratory and Pharmacy Certifications.
- All reported safety reports and IRB correspondence.
- Reported deviations and protocol violations.

Consent:

- All required elements required by the federal regulations are listed.
- All risks and alternatives are listed as in the model consent form.

For protocols that utilize the NCI Central IRB (CIRB) as the IRB of record, the following source documents must be available for review:

- Approval letter from the CIRB to the PI for the specific study.
- Documentation that IRB approval was obtained prior to patient registration.
- Reporting of any unanticipated problems per OHRP/FDA policy.
- Any other correspondence with the CIRB
- CIRB approval of Institution Worksheet About Local Context (ICF)

5.2.1 IRB and Informed Consent Content Deficiency Examples

CTMB guidelines will be utilized when assessing IRB and ICC compliance and assigning a major or lesser when a deficiency is identified. The Auditors will refer to the CTMB-Audit Tool Checklist (Tables A and B) for examples of IRB and ICC majors as a guideline and to document any deficiencies identified and observations that are noted. This is not an all-inclusive list.

5.2.2 Assessing IRB and Informed Consent Content Findings

The guidelines used in assigning of Acceptable, and Acceptable needs follow-up and Unacceptable will be:

Acceptable:

- There were no or few lesser deficiencies identified
- Any major deficiency that is identified during the audit, that was addressed and corrected prior to the audit, wherein a written and dated corrective and preventive action plan (CAPA) exist and no further action is required by the MCC PI and no similar deficiency has occurred since the corrective action plan was implemented. **Note:** If the major is associated with a safety concern and it is determined by the Audit Committee or DSMC that further action is necessary, this approach may not apply.

Acceptable Needs Follow:

- Any major deficiency that is identified during the audit not addressed and or corrected prior to the audit.
- Multiple lesser deficiencies have occurred.

Unacceptable:

- Multiple major deficiencies have been identified.
- A single major flagrant deficiency has been identified.
- An excessive number of lesser deficiencies have been identified.

5.3 Pharmacy Review

Drug Accountability Record Forms (DARFs) are required to be maintained by all institutions conducting clinical trials with NCI-supplied investigational agents. The FDA requires institutions to maintain records of receipt, use and disposition of all drugs that are deemed investigational for the purposes of any protocol.
http://ctep.cancer.gov/protocolDevelopment/agents_drugs.htm

For each protocol and patient case that is selected for audit, the DARF(s) will be reviewed for accuracy. The auditors will complete the Pharmacy Audit Worksheet.
The following items will be reviewed but not limited to:

- DARFS are completely and correctly filled out.
- DARFs are protocol and drug Specific.
- NCI DARFs are kept as Primary transaction Record.
- Prescriptions were signed by Authorized personnel.

Each protocol that uses investigational drugs and or commercially available drugs for an investigational purpose when designated by the protocol must have a specific drug supply for use with that protocol only. When different protocols are using the same investigational agent, the agents used must be separated by protocol and a separate DARF maintain. Protocols that are multi-agent must have a separate DARF for each agent. Each different dose of strength of an investigational agent must each have separate DARFs. DARFs are not to be patient specific, unless the drug is being compared with a placebo in a double-blind study where the agent is supplied per patient by NCI. Refer to the
http://ctep.cancer.gov/investigatorResources/docs/InvestigatorHandbook.pdf

A pharmacy inspection will take place every other audit. The auditor(s) will complete the Pharmacy Audit Worksheet. During this inspection the pharmacy will be reviewed for:

- Adequate security of investigational/study drugs.
- Appropriate storage of investigational/study drugs.
- Inventory of investigational/study drug. The balance on each DARF reviewed will be compared to shelf balances.
- Drug orders, receipt of drug, Return receipts, transfer forms and authorized local destruction of investigational/study drugs.
- Records from treating affiliates if applicable.

5.3.1 Pharmacy Deficiencies: Non-Compliance

Categorizing major and lesser deficiencies related to investigational/study drug accountability and storage can be difficult. Therefore, the auditors will determine the ratings based on compliance to the required procedures for drug accountability and storage. The guidelines adopted form the CTMB will be used for assessing compliance and non-compliance with proper use of NCI DARFs, drug accountability and storage regulations. The Auditor(s) will refer to the CTMB-Audit Tool/Checklist (Table C) for examples of and assessing Pharmacy non-compliance.

5.3.2 Assessing Pharmacy Findings

The guidelines used in assigning of Acceptable, and Acceptable needs follow-up and Unacceptable will be:

Acceptable: Compliant in all areas and/or any non-compliant item that was identified during the audit had been addressed or corrected prior to the audit with a signed and dated corrective preventative action plan and no further action is warranted. And no similar non-compliance issue has occurred since then.

Acceptable Needs Follow: Non-compliant item was found during the audit which had not been addressed or corrected prior to the audit.

Unacceptable: Unable able to track the disposition of Investigational/Study Drugs, agents or devices, and/or multiple non-compliant items.

5.4 Patient Case Review

During each quarter audit, a minimum of three patient case charts will be reviewed. The auditors will complete the Patient Case Audit Worksheet for each patient case. The following minimum components of each case will be reviewed and compared to source documents:

- Original signed and dated informed consent document(s)
- Eligibility
- Treatment Parameters
    - Correct treatment and sequence was given.
- Disease and Tumor Response
- Adverse Events/ SAE Reporting
- Data Quality and Management

5.4.1 Patient Case Deficiency Examples

CTMB guidelines will be utilized when assessing patient case review findings and assigning major or lesser when a deficiency is identified in either one of the patient review categories. The Auditors will refer to the CTMB-Audit Tool/Checklist (Table D) for examples of majors and lessors of each patient review category. This will provide as a guidance and is not an all- inclusive list.

5.4.2 Assessing the Patient Case Review Findings

The guidelines used in assigning of Acceptable, and Acceptable needs follow-up and Unacceptable will be:

Acceptable:

- There were no or few lesser deficiencies identified
- Any major deficiency that is identified during the audit, that was addressed and corrected prior to the audit, wherein a written and dated corrective and preventive action plan (CAPA) exist and no further action is required by the MCC PI and no similar deficiency has occurred since the corrective action plan was implemented. **Note:** If the major is associated with a safety concern and it is determined by the Audit Committee or DSMC that further action is necessary, this approach may not apply.

Acceptable Needs Follow:

- Any major deficiency that is identified during the audit not addressed and or corrected prior to the audit.
- Multiple lesser deficiencies have occurred.
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Unacceptable:

- Multiple major deficiencies are identified.
- A single major flagrant deficiency has been identified.
- An excessive number of minor or lesser deficiencies identified.

5.5 Exit Interview

Protocols and patient cases that are found to have no or few lesser deficiencies and no majors, a formal in person exit interview will not be required. The PI and study team will be notified via email of the findings and that no further action is required at this time. However, if the PI and or study staff would like a meeting, one will be arranged.

In protocols and patient cases where majors are identified, an exit interview will be required to discuss preliminary audit findings and to provide opportunity for questions, clarifications and recommendations. The Auditor(s) will meet with the lead study coordinator, regulatory coordinators, research pharmacist and the study Investigator (if available) to discuss the audit findings. The lead study coordinator will also be asked to provide answers to any questions that the auditor may have.

Those audit findings found to be inaccurate or resolvable by updating the study records at the exit interview will not be included in the initial audit report. This can be done in person or by a telephone conference. Ideally, the exit interview will be held within one week of the completed audit. The PI and appropriate study staff will be notified that an exit interview will be arranged.

SECTION 6: AUDIT FINDINGS AND REPORTING

6.1 Preliminary Audit Findings, Reporting and PI Response

The preliminary audit findings and report will be due within –four weeks of the completion of the audit. The report will include the date(s) of the audit, IRB, ICC, Pharmacy, and Patient Case review findings and a detailed list of lesser and majors, along with recommendations when applicable. The Audit Lead will compile the reports and submit to the Audit Committee Chair and Audit Committee for review and approval. Once approved, the preliminary report(s) will be sent out via email to the:

- Protocol PI and Research Nurse/CRAs
- Research Pharmacist when applicable
- Regulatory Coordinators
- MCC CRO Medical Director
- MCC CRO Clinical Trials Management Director

The PI will have fourteen days to respond to all queries and deficiencies noted in the preliminary report and submit any missing documentation. The PI will be required to submit a written and signed response to the Audit Committee Chair and Audit Committee for review and approval.

6.1.1 Deficiencies Requiring Immediate Attention and Actions

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.

A complete review of the violations and action plan will be determined within 24-48 hours. Examples of deficiencies that require urgent attention would be:

- Evidence of scientific misconduct.
- Evidence of research Fraud.
- Research subjects have been placed at significant risk of harm or the welfare of subjects has been jeopardized, and that the findings have not previously been reported to the IRB.
- Evidence of continuing non-compliance by an investigator.
- Audit with numerous deficiencies identified.

When applicable, within 24-48 hours of notification, the DSMC will vote to determine an Unacceptable audit rating, and the immediate action to be taken if needed for patient safety or study status. The DSMC may choose to temporarily or permanently suspend a study or investigator to accrual until all deficiencies have been adequately addressed in writing to the DSMC Chair and approved by the DSMC. In addition a for-cause audit may be conducted on remaining patients accrued to the study.

The DSMC Chair and or ADCT would notify the protocol PI within 24 hours by phone of audit findings and the immediate actions that will need to take place. A final audit report with the rating

will be sent to the PI electronically with a request for a written and signed corrective and preventive plan (CAPA) addressing each major violation within five working days.

The DSMC will review the PI responses and either accept or require clarification of responses if they are found to be inadequate. Once the responses from the PI have been accepted, the DSMC will vote on whether to lift the suspension on the study or investigator, or keep the suspension until further action or recommendations have taken place. A follow up will be required.

6.2 Final Reporting of Audit Findings and PI Response

Once the PI has responded to the preliminary audit report, the responses will be reviewed by the Audit Committee Chair and Audit Committee. If the responses are acceptable and approved a final report will be compiled by the Audit Lead with recommendations given by the Audit Committee. The Audit Lead will forward the complete final audit report electronically to the DSMC for review. The final audit report will contain the following:

- PI and study title. Date(s) of the audit and prior audit if applicable.
- A summary of any major or lesser deficiencies related to regulatory, pharmacy, and patient case review.
- PI responses and CAPA plans when applicable.
- Items required to be reported to the IRB.
- Recommendations.

6.3 DSMC Review

The DSMC receives and reviews final audit reports and recommendations from the Audit Committee and renders decisions based on these reports. Final Audit 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”.

Audits are reviewed on a study-by-study basis, and for ratings that are found Acceptable Needs Follow Up or Unacceptable, the PI will be required to address each major deficiency and respond with a corrective action and or preventive plan (CAPA) with in five working days to the DSMC for review and acceptance. If the PI has previously addressed each major with a CAPA plan prior to the DSMC meeting or review, the DSMC will review and approve as is or may request additional information or action from the PI.

When an audit component is determined to be unacceptable, the DSMC may recommend that the study or investigator be suspended from accrual until all deficiencies have been adequately addressed in writing to the DSMC Chair and approved by the DSMC. This will depend on the components and nature of the findings.

Note: If a protocol amendment is proposed as a result of the audit findings, the PI will be required to submit the proposed amendment with the signed final audit report for review and approval by the DSMC before submission to the UK IRB. The DSMC will review the proposed amendment with the final audit report and corrective action plan, if applicable. In some cases, the PI may be

required to submit the proposed amendments to the PRMC, prior to final submission to the UK IRB.

The DSMC will be responsible for reporting all final determinations, decisions and recommendations for each study to the PI and MCC Director.

6.3.1 PI Formal Appeal Process

In the event that the PI disagrees with the DSMC decisions, he/she 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 and make a determination.

If the PI does not feel that the issues have been addressed in a satisfactory manner, the PI may appeal to the 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.

6.3.2 NCI-CTEP Trials Suspensions

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 final audit report to the ORI Quality Improvement Program coordinator, who forwards the report to the IRB and/or ORI Director and UK research compliance officer in accord with standard ORI/IRB operating procedures.

SECTION 7: DOCUMENTATION REQUIREMENTS

7.1 Documents

The following audit documentation will be filed appropriately under each audit:

- Patient Case Audit Worksheet.
- IRB and ICC Audit Worksheet.
- Pharmacy Audit Worksheet.
- Preliminary and Final Audit Reports.
- PI responses, CAPAs and correspondences.
- Audit Committee meeting minutes and email correspondences.
- DSMC final determinations and reports.
- Any other important or relevant email communications.

7.2 Quality Assurance Office

The Quality Assurance Office will maintain the electronic databases that will house all audit reports, documentations and correspondences. All documentation associated with each audit will be kept on the MCC Quality Assurance Share filed under the appropriate quarterly audit. All audit reports are peer reviewed, confidential internal documents, and are not distributed or made public.

7.3 Contact Information

For further information concerning the Markey Cancer Center Audit Program or the activities described herein, please contact:

Tosia E. Courtney, RN, BSN, CCRP
Quality Assurance PI Program Manager
University of Kentucky/Markey Cancer Center
800 Rose Street-CC424 Roach Building
Lexington, Kentucky 40536
Telephone: (859)-218-2995
tosia.jordan@uky.edu

SECTION 8: ACRONYMS AND ABBREVIATIONS

UK -University of Kentucky

MCC - Markey Cancer Center

MCCRN-Markey Cancer Center Research Network

QA- Quality Assurance

CTMB- Clinical Trials Management Branch

CTEP- Cancer Therapy Evaluation Program

DCTD-Division of Cancer Treatment and Diagnosis

NCI-National Cancer Institute

NCTN-National Clinical Trials Network

DSMC- Data and Safety Monitoring Committee

ADCT- Associate Director for Clinical Translation

SOP-Standard Operating Procedure

GCP-Good Clinical Practice

CRO-Clinical Research Office

PI-Principal Investigator

ICC- Informed Consent Content

PRMC- Protocol Review and Monitoring Committee

IIT-Investigator Initiated Trial

IND-Investigational New Drug

IDE-Investigational Device Exemption

FDA- Food and Drug Administration

CRA- Clinical Research Associate

SAE- Serious Adverse Event

IRB-Institutional Review Board

NCI-CIRB- National Cancer Institute-Central Institutional Review Board

HIPAA- Health Insurance Portability and Accountability Act: Privacy Authorization Form

DARF- Drug Accountability Review Form

CAPA- Corrective and Preventive Action

REFERENCES:

1. CTMB, CTEP, DCTD, and NCI Audit Guidelines:

   http://ctep.cancer.gov/branches/ctmb/clinicalTrials/docs/ctmb_audit_guidelines.pdf

2. ICH Website: http://www.ich.org/

3. CTMB Audit Tool/Checklist:

   http://ctep.cancer.gov/branches/ctmb/clinicalTrials/docs/Appendix_2.pdf

4. Protocol Review and Monitoring Committee Functional Overview: MCC SOP

5. Unanticipated/Anticipated Problem/Adverse Event Reporting: UK ORI and IRB SOP C2.0350

6. NCI CIRB Review Form: UK ORI and IRB SOP C3.0400

7. Markey Cancer Center/IRB/ORI Coordination SOP: IRB 06-0400

8. UK MCC Data and Safety Monitoring Plan

9. Data and Safety Monitoring Committee Functional Overview-MCC SOP-

10. OHRP: https://www.hhs.gov/ohrp/

    http://www.hhs.gov/ohrp/policy/advevntguid.pdf

11. Protocol Agents/Drugs: http://ctep.cancer.gov/protocolDevelopment/agents_drugs.htm

12. Investigators Handbook:

    http://ctep.cancer.gov/investigatorResources/investigators_handbook.htm

Revision: 03
Date: 30May2018

a. Description of Change:
    i. Administrative and Clerical changes
    ii. Clarification of processes

Revision: 02
Date: 03April2017

a. Description of Change:
    i. Administrative and Clerical changes
    ii. Clarification of processes

Revision: 01
Date: 29May2015

a. Description of Change:
    i. Administrative and Clerical changes
    ii. Clarification of processes
    iii. Addition of MCCRN