1. PURPOSE
   a. The purpose of this document is to describe the function of the Data and Safety Monitoring Committee (DSMC), an integral part of the Quality Assurance process for protocols being conducted at the University of Kentucky (UK) Markey Cancer Center (MCC) and Markey Cancer Center Research Network.

2. SCOPE
   a. This procedure applies to all MCC and MCCRN personnel.
   b. This procedure applies to all clinical trials approved by the MCC Protocol Review and Monitoring Committee (PRMC).

3. RESPONSIBILITIES
   a. The DSMC assures patient safety and protocol compliance.
   b. The DSMC Chair oversees the activities of the committee.

4. CROSS-REFERENCES
   a. University of Kentucky Markey Cancer Center Data and Safety Monitoring Plan
   b. Protocol Review and Monitoring Committee Functional Overview: SOP No.: MCC-002.03
   c. MCC Audit Committee Functional and Administrative SOP
   d. Markey Cancer Center Research Network Audit Overview SOP
   e. Markey Cancer Center/IRB/ORI Coordination SOP: IRB 06-0500
   f. IRB NCI/CIRB SOP: IRB C3-0400
   g. IRB Mandated Reporting to External Agencies: C4-0150
5. ACRONYMS AND ABBREVIATIONS
   a. BBSRF – Biostatistics and Bioinformatics Shared Resource Facility
   b. CRA – Clinical Research Associate
   c. MCC CRO – Markey Cancer Center Clinical Research Office
   d. DSMB – Data and Safety Monitoring Board
   e. DSMC – Data and Safety Monitoring Committee
   f. IRB – Institutional Review Board
   g. IIT – Investigator-Initiated Trial
   h. MCC – University of Kentucky Markey Cancer Center
   i. MCCRN- Markey Cancer Center Research Network
   j. MTD – Maximum Tolerated Dose
   k. PI – Principal Investigator
   l. RCO – Research Compliance Officer
   m. SAE – Serious Adverse Event
   n. SOP – Standard Operating Procedure

6. DEFINITIONS
   a. Maximum Tolerated Dose – The highest dose of a drug or treatment that does not cause unacceptable side effects. The maximum tolerated dose is determined in clinical trials by testing increasing doses on different groups of people until the highest dose with acceptable side effects is found.
   b. Greater than Minimal Risk Protocol – Any study not considered minimal risk.
   c. Minimal Risk Protocol – The probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests (45 CFR 46.102(h)(i)).
   d. Protocol Violation – Any exception or deviation from a protocol involving a single subject that is not approved by the Institutional Review Board (IRB) prior to its initiation or implementation. Protocol violations must be reported to the IRB following IRB reporting requirements.
   e. Protocol Exception – Any change in the inclusion/exclusion criteria provided for a single patient. A protocol exception requires IRB review and approval prior to implementation.
   f. Protocol Deviation – Any departure from the protocol for a single patient after the patient is enrolled in a protocol. A protocol deviation requires IRB review and approval prior to implementation.
g. Serious Adverse Event (SAE) or Serious Adverse Drug Reaction – Any untoward medical occurrence that at any dose:
   i. Results in death
   ii. Is life-threatening
   iii. Requires inpatient hospitalization or prolongation of existing hospitalization
   iv. Results in persistent or significant disability/incapacity or
   v. Is a congenital anomaly/birth defect
h. DSMC Coordinator – The MCC-CRO staff person in charge of organizing and implementing the DSMC meeting.

7. PROCEDURE
   a. The DSMC will act as the Data and Safety Monitoring Board (DSMB) for studies approved by the PRMC unless otherwise specified by this plan or the IRB of record.
      i. The DSMC will review and monitor all study progress for MCC investigator-initiated trials, industry-sponsored trials, national group trials, or those designated by the PRMC.
      ii. In addition, the Early Therapeutics Clinical Care and Research Team reviews the progress of all phase I and complex phase II trials, as well as investigator-initiated trials IITs (IITs) on a monthly basis, reviewing all AEs and SAEs, study accrual and study progress.
      iii. If appropriate, the DSMC will designate and monitor corrective action(s) based on review outcome.
      iv. The DSMC will have the authority to amend and/or terminate protocols based upon issues of safety.
      v. The Chair may call an ad-hoc committee meeting at any time to solve ongoing problems.
   b. All DSMC members must abide by Confidentiality Agreements and Conflict of Interest Forms provided by the University of Kentucky and the MCC.
   c. 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.
      i. A committee member who is an investigator on a study will be asked to recuse themselves from the review process.
   d. The DSMC meets monthly to conduct monitoring reviews as outlined by the initial PRMC review and on an ad hoc basis at the discretion of the MCC director or Associate Director for Clinical Translation.
i. The DSMC will review study-specific reports regarding study status, safety and progress as designated by the risk assignment, and level of review. These reports will include protocol deviations, subject accruals, and analysis of SAEs, at a minimum. In addition, for all IITs, AEs will be included in the report.

ii. Reviews may occur monthly, quarterly, bi-annually or annually as outlined in PRMC and DSMC guidelines.

iii. The DSMC will monitor the following elements:
   1. AEs (at a minimum all Grade 3, 4 and 5 AEs) for IITs.
   2. SAEs for all studies.
   4. Audit Committee reports, if applicable.
   5. Previous DSMC reviews if appropriate.
   6. Study-specific MCC DSMB reports.
   7. Suggested actions from other committees such as the IRB, Indemnification Committee, Conflict of Interest Committee, and Early Therapeutics CCART, if applicable.
   8. DSMC and/or DSMB reports from outside entities such as cooperative groups and industry sponsors of studies involving MCC subjects.
   9. Analysis of primary and secondary efficacy parameters and outcomes if required (i.e., early stopping rules, interim monitoring, etc.)

10. Suggested actions, if applicable.

e. The DSMC will have an option of two levels of review: expedited and full, based on the following guide:
   i. Full Review: This will be performed for all trials deemed to be greater than minimal risk studies.

   1. Review of Study Progress, Safety and Compliance

      a. The DSMC Coordinator compiles the study elements for review and provides these elements in tabular form to the Chair of the DSMC.
      b. The Chair of the DSMC reviews each study in full committee with a review outcome determined at the meeting (see below). If there is insufficient data for a complete review, the study is re-reviewed at the next meeting.
2. Review of Audit Committee Activity
   a. Final audit reports will be provided to all attendees of the DSMC one week prior to the meeting with the expectation that all will review the report prior to the meeting. The report(s) will be presented by the Chair 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.”
   b. Audits are reviewed on a study-by-study basis, and components found to be unacceptable, require corrective and preventive action as defined by the DSMC. In addition, based on the findings, the DSMC may choose to suspend a study or an investigator until all deficiencies have been adequately addressed in writing to the DSMC Chair and approved by the DSMC. The principal investigator (PI) may present a formal appeal to the DSMC. The PI may request to be present at the DSMC 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.
   c. If the PI does not feel that the issues have been addressed in a satisfactory manner, the PI may appeal to the Associate Director for Clinical Translation and/or the Director of the MCC.

ii. Expedited Review: This may be performed for all trials not deemed to be greater than minimal risk trials.
   1. The DSMC Coordinator will compile the studies eligible for expedited review on a monthly basis for review by the Chair.
2. If no issues are found, the Chair will sign the Disposition Letter, approving the study and return it to the staff.

3. 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.

   iii. Studies which are non-interventional and therefore do not record SAEs or deviations in OnCore will require annual review.

1. Protocol staff will be required to provide IRB records of any SAEs or deviations reported during the review period.

f. Review Outcome: The DSMC will make the following recommendation for all trials reviewed during the DSMC meeting:

   i. Approved – Enrollment may continue
   ii. Close to accrual – Close enrollment
   iii. Temporarily Close to Accrual – Delinquent progress report, need for corrective action plan

   2. DSMC Decisions

   i. A cover letter summarizing the nature of the discrepancies and their resulting requirements and/or decisions by the DSMC will be sent to the PI, The Director of Clinical Research Operations, the MCC Director, the ADCR, 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 IRB and other relevant regulatory agencies will be notified.

   ii. Abstention from reviewing 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.

   iii. The DSMC Coordinator will compile the results of the member reviews and forward to the Chair of the committee.

   3. The Chair reviews the committee decisions and signs the meeting minutes and memos. The DSMC Coordinator forwards the memo to the PI, Research Nurse and Regulatory Coordinator.

   i. The DSMC has authority to request additional information to be provided to the committee, an internal audit of subject record(s) and regulatory information or protocol amendment(s). Additional requested items may be:

      i. Best response to treatment for each subject, for phase II and III studies.
      ii. Treatment arm for each subject, for phase III studies, if unblinded.
      iii. Study and survival status of each subject.
      iv. Results of any interim analyses required by the protocol.
v. Copies of abstracts or papers written using study data.

j. The PI will be required to provide any additional information within a specific time frame as determined by the committee. The DSMC Coordinator will follow up and provide the Chair with the required information. The Chair will review the information and uphold the review outcome or make further recommendations.

k. All DSMC decisions are conveyed in writing to the PI.
   i. The DSMC will state specific reason(s) for the decision.
   ii. PIs may appeal DSMC decisions in writing to the DSMC Chair within fourteen (14) working days.
   iii. The PI must respond to each reason(s) in the decision.

l. Corrective action item(s) may be requested based on review findings. Any review finding that results in a protocol deviation requires correction action.
   i. The reviewer provides a recommendation for corrective action on the DSMC Reviewer Form.
   ii. The DSMC Coordinator compiles the reviewer findings for the Chair.
   iii. The Chair reviews and approves requested corrective action.
   iv. The key members of the research team receive a copy of the DSMC disposition with the required corrective action.
   v. Corrective action items are classified as “administrative” or “scientific” based on the following criteria:

Corrective Action Criteria for Investigator-Initiated Trials

<table>
<thead>
<tr>
<th>Administrative – issues reflecting:</th>
<th>Scientific – items reflecting:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low Risk Trials</td>
<td>Research Objectives</td>
</tr>
<tr>
<td>Nominal Changes to Protocols</td>
<td>Consent/Eligibility</td>
</tr>
<tr>
<td>Data Quality</td>
<td>Treatment/Response</td>
</tr>
<tr>
<td>Accrual Targets</td>
<td>Adverse Events</td>
</tr>
</tbody>
</table>

Entity Responsible for Review of Corrective Action

| DSMC Chair | Full DSMC |

vi. Corrective action items are followed by the DSMC Coordinator
   1. A follow-up disposition is completed when a corrective action item(s) is completed or delinquent and reviewed by the appropriate individual per the above criteria.
   2. The disposition is forwarded to the key members of the research team.
3. Documentation is maintained in both the MCC Clinical Research Office files of DSMC and in the study regulatory manual.

m. Appeals will be electronically distributed to two (2) members of the DSMC who were not involved with the original review.
   i. Reviewers will have five (5) working days to complete their review and return comments to the DSMC Chair.
   ii. The DSMC Chair will convey the results in writing to the PI. All appeal decisions will be final.

n. 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. The MCC follows the guidance of the IRB in terms of reporting to external sponsors, in their SOP “Mandated Reporting to External Agencies”. If Clinical 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.

o. The DSMC Chair forwards a copy of the final audit report to the ORI Research Compliance Officer (RCO). The RCO forwards the report to the IRB and/or ORI Director in accord with standard ORI operating procedures.

p. The DSMC Chair and the Associate Director for Clinical Translation will meet at least annually to review the DSMC SOP.

8. DOCUMENTATION REQUIREMENTS
   a. DSMC minutes and approval letters will document DSMC decisions as well as meeting attendance details.
   b. Attendance logs, meeting minutes, meeting memos and meeting materials will be maintained in the MCC CRO.

9. ATTACHMENTS
   a. None

10. REFERENCES
    b. 45 CFR 46.102(h)(i)

11. REVISION HISTORY
    a. Revision: 02
b. Date: 27 November 2012

c. Description of change:
   i. Administrative changes
   ii. Change membership to voting and non-voting members

d. Revision: 03

e. Date: 15 Apr 2015

f. Description of change:
   i. Administrative changes
   ii. Clarified non-voting membership
   iii. Addition of DSMC monitoring element to correspond with DSMP
   iv. Clarified Audit Committee final assessments
   v. Addition of MCCRN