1. PURPOSE

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 conducted at the University of Kentucky (UK) Markey Cancer Center (MCC) and Markey Cancer Center Research Network (MCCRN).

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. MEMBERSHIP

   a. The Chair of the DSMC is appointed for a three-year term by the MCC Director.
   b. Membership:

      Committee members are appointed by the Chair and approved by the Director and serve three year terms. Ad-hoc members may be appointed by the Chair, as needed. One of the voting members will serve as Vice Chair appointed by the Chair.

      i. Voting members:

         1. The committee Chair.
         2. Four (4) faculty members who are active investigators appointed for a three-year term.
         3. The Associate Director for Clinical Translation.
         4. A biostatistician from the BBSRF.
         5. A pharmacist from within the MCC and/or Investigational Drug Service.
         6. A clinical research nurse.
c. No communication, either written or oral, of the deliberations of the DSMB/DSMC will be made outside of the DSMB/DSMC.

5. ADMINISTRATIVE PROCEDURES
   a. All DSMC meetings are open during the discussion portion of all subject deviations, protocol deviations, and SAEs. The meeting enters a closed session status for all voting matters.
   b. In order for the meeting to take place, at minimum, the following must be present at the meeting:
      i. Committee chair or designee
      ii. Three clinical faculty members of the DSMC
      iii. A biostatistician from the MCC BBSRF
   c. The principal investigator (PI) or designee for each protocol to be reviewed is invited, but not required to be present.
   d. A clinical research associate (CRA) for each protocol to be reviewed is requested to be present and is excused prior to voting.
   e. For MCC Multi-Center Investigator Initiated Trials (IITs) 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 project coordinator 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. On each occasion that a MCC Multicenter IIT is selected for review by the DSMC, the MCC Lead Investigator and/or assigned Project Coordinator will attend and provide information for the overall study. If a protocol is not represented by the study CRA, Project Coordinator or the PI, the review may be deferred until the next DSMC meeting, if deemed necessary by the DSMC Chair.
   f. Abstention from monitoring review or voting by committee members will be accepted only if the committee member has a conflict of interest (COI) as defined by University of Kentucky’s COI policy. A committee member who is a PI or Co-principal investigator on a study will be asked to recuse themselves from the review process.
   g. All studies are required to be reviewed and the frequency of review is determined by the MCC PRMC.
   h. Studies with a status of ‘closed to accrual’ that have patients in follow up do not require review unless SAEs or deviations have been reported since the previous DSMC review.
   i. Review of Audit Reports.
      i. 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 Audit Committee Chair or designee for discussion with the DSMC. The Audit Committee Chair or designee will be excused at the time of DSMC deliberation. The DSMC will determine the appropriate action based on the audit report as follows: “Acceptable”, “Acceptable, needs follow-up” or “Unacceptable.”
      ii. A memo summarizing the nature of the audit findings and their resulting requirements will be sent to the PI, the Director of Clinical Research Operations, the MCC Director, and the Associate Director for Clinical Translation (ADCT), the Medical Director of Clinical Research Operations, the Audit Committee Chair, the Quality Assurance (QA) Program Manager, and the DSMC Chair. Additionally, if it is determined that the study
should be closed or suspended, all sponsoring agencies and relevant regulatory agencies will be notified.

iii. MCCRN site memos summarizing the nature of the audit findings and their resulting requirements will be sent to the PI, the lead CRA, MCC Director, ADCT, Director of MCCRN, MCCRN Clinical Trial Management Director, the MCCRN Project Coordinator, the Audit Committee Chair, and the QA Program Manager.

j. The DSMC is responsible for reviewing the adequacy of DSMPs of all protocols reviewed by the PRMC. Should a DSMP be found to be inadequate, the DSMC will query the PI for revisions.
   i. PRMC Coordinator reviews the protocol for the presence of a DSMP, based on the requirements of the NCI.
   ii. The DSMC reviews the adequacy of all DSMPs by review of the presence of the following:
       1. Plans for monitoring the progress of trials and the safety of subjects;
       2. Plans for assuring compliance with requirements regarding the reporting of adverse events;
       3. Plans for review or analysis of cumulative safety data to determine whether harm is occurring;
       4. Plans for assuring that any action resulting in a temporary or permanent suspension of a clinical trial is reported to the appropriate agencies, including the NCI;
       5. Plans for assuring data accuracy and protocol compliance;
       6. Plans for assuring communication among multi-center sites adequately protect the subjects (for multicenter studies where the lead PI is employed by UK or UK is the coordinating institution).

k. Post Meeting:
   i. Investigators will receive a DSMC memo indicating the committee determination as listed above with any requests for action.
   ii. In addition, copies of the DSMC Memo will be forwarded to the appropriate people based on the following DSMC decisions:
       1. Approved – Enrollment may continue
       2. Not Approved
       3. Approved with Caution
       4. Deferred
       5. Close to accrual – Close enrollment
       6. Suspend – delinquent progress report, need corrective action plan
   iii. Minutes of the meeting will be reviewed by the DSMC Chairperson and/or Vice Chair and final minutes will be signed and filed in the Clinical Research Office (CRO).

6. FUNCTIONAL PROCEDURES
   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, the NCI, 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) 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 recommend amendments 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 the Conflict of Interest Policy of the University of Kentucky and the MCC. No communication, either written or oral, of the deliberations of the DSMB/DSMC will be made outside of the DSMB/DSMC. 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.

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. Any DSMC 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 with the frequency determined by the PRMC. In addition, reviews may be requested 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, aggregate 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.
3. Subject deviations and violations.
5. Audit Committee reports, if applicable.
6. Previous DSMC reviews if appropriate.
7. Study-specific MCC DSMB reports, when applicable.
8. Suggested actions from other committees such as the IRB, Indemnification Committee, Conflict of Interest Committee, and Early Therapeutics CCART, if applicable.
9. DSMC and/or DSMB reports resulting in change or suspension of the trial from outside entities such as cooperative groups and industry sponsors of studies involving MCC subjects as determined by the chair.

10. The DSMC has oversight for MCC Multi-Center Investigator Initiated Trials (IITs) where MCC is the lead institution. The Lead Investigator or the Project Coordinator will be reporting AEs, SAEs, and deviations.

11. 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.

12. Suggested actions for any protocol (suspension, termination, or actions of significance) as determined by the Chair, if applicable.

iv. The DSMC will review the adequacy of DSMPs of all protocols reviewed by the PRMC. Should a DSMP be found to be inadequate, the DSMC Coordinator will query the PI to revise the DSMP.

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.

1. Review of Study Progress, Safety and Compliance:
   a. The DSMC Coordinator compiles the study elements for review and provides these elements 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 deferred to 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 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.

c. 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.

ii. Expedited Review: This may be performed for all trials deemed to be minimal risk.
   1. The DSMC Coordinator will compile the studies eligible for expedited review on a monthly basis for review by the Chair or Co-Chair.
   2. If no issues are found, the Chair will sign the Disposition Letter, approving the study and return it to the staff. Studies receiving an expedited review will be presented to the full committee at the next meeting.
   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. Not Approved
   iii. Approved with Caution
   iv. Deferred
   v. Close to accrual – Close enrollment
   vi. Suspended – delinquent progress report, need corrective cation plan

4. DSMC Decisions:
   i. A memo summarizing the nature of the committee findings 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 ADCT, 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.

h. The Chair reviews the committee decisions and signs the meeting minutes and memos. The DSMC Coordinator forwards the memo to the PI. The Regulatory Coordinator obtains a copy of the memo at the time of IRB renewal.
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 a corrective action.
   i. The DSMC reviews corrective and preventive actions taken as a result of the deviation.
   ii. The DSMC provides a decision regarding the need for further corrective or preventive action plans in a memo to the PI.
   iii. The DSMC Coordinator compiles the DSMC findings for the Chair.
   iv. Corrective action items are followed by the DSMC Coordinator and presented to the DSMC at the next meeting.
      1. Delinquent CAPAs are followed-up by the DSMC Coordinator, and delinquent CAPAs may result in suspension of an investigator, until satisfactory review by the DSMC occurs.
      2. 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 selected by the Chair or Co-Chair.
   i. Reviewers will complete their review prior to the next convened DSMC meeting and return comments to the DSMC Chair.
   ii. The DSMC Chair will present the reviews to the DSMC and final determination will be made by the DSMC. Results are provided 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 for all unacceptable audit reports 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.

7. 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.

8. FORMS
   a. None

9. REFERENCES
   c. University of Kentucky Markey Cancer Center Data and Safety Monitoring Plan
   d. Protocol Review and Monitoring Committee Functional and Administrative SOP
   e. MCC Audit Committee Functional and Administrative SOP
   f. Markey Cancer Center Research Network Audit Overview SOP
   g. Markey Cancer Center/IRB/ORI Coordination SOP: IRB C6.0400
   h. IRB NCI/CIRB SOP: IRB C3.0400
   i. IRB Mandated Reporting to External Agencies: C4.0150
   j. Examples of Major and Minor Protocol Deviations

10. REVISIONS HISTORY
    Revision: N1
    Date: May 24, 2018
    Description of change:
    4.b.ii: Removed non-voting members
    5.a: Added clarification concerning open and closed session matters.
    Other minor administrative changes.