1. PURPOSE
   a. The purpose of this document is to describe the responsibilities and processes of the Protocol Review and Monitoring Committee (PRMC) at the University of Kentucky (UK) Markey Cancer Center (MCC).
   b. The purpose of the PRMC is to support the vision of the UK MCC by evaluating clinical trials to bring to our subjects and our community, thereby providing cancer patients from Kentucky and their families’ access to the latest research in cancer prevention, cancer control, and cancer treatment.

2. SCOPE
   a. This procedure applies to all UK MCC personnel.
   b. This procedure applies to all clinical trials being proposed at the UK MCC and the Markey Cancer Center Research Network (MCCRN).

3. RESPONSIBILITIES
   a. The PRMC has the authority of reviewing and approving new and continuing clinical cancer protocols for scientific merit prior to IRB submission, assigning a risk level, and approving amendments to open protocols. Open protocols initially approved by the PRMC will be submitted to the PRMC for continuing review prior to continuing review by the IRB to determine whether a study continues to have scientific merit and progress is being made through accruals. The PRMC also recommends amendments to protocols for scientific reasons and has the authority to terminate protocols for scientific reasons and poor progress and/or low accrual. Such reasons include the development of therapy which is superior to that proposed in the protocol or a change in the standard of care which is no longer reflected in the protocol. Clinical trials will be considered by the PRMC if they are Phase I, II, or Phase III National Cancer Institute (NCI)
cooperative group trials, industry-sponsored, or institutional investigator-initiated clinical trials focusing on cancer prevention, cancer control, or cancer treatment that have been approved by the appropriate Clinical Care and Research Team (CCART).

4. CROSS-REFERENCES
   a. University of Kentucky Markey Cancer Center Data and Safety Monitoring Plan
   b. Data Safety and Monitoring Committee Functional Overview – SOP No.: MCC-004.03
   c. Audit Committee SOP No.: MCC-006.02
   d. Markey Cancer Center/IRB/ORI Coordination SOP: IRB 06-0400

5. ACRONYMS AND ABBREVIATIONS
   a. CCART – Clinical Care and Research Team
   b. IIT – Investigator-Initiated Trial
   c. MCC – Markey Cancer Center
   d. MCC-CRO - Markey Cancer Center Clinical Research Office
   e. NCI – National Cancer Institute
   f. PRMC – Protocol Review and Monitoring Committee
   g. ePRMS- Electronic Protocol Review and Monitoring System

6. DEFINITIONS
   a. Clinical Trial – The MCC recognizes the NIH’s definition of a clinical trial available at: Clinical Trials | Office of Science Policy. 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.
   b. Protocol Review and Monitoring Committee – An interdisciplinary committee of senior physician scientists from medical oncology, surgical oncology, radiation oncology, pediatric oncology, radiology and pathology as well as pharmacists, statisticians, research nurses, and basic scientists, in addition to a patient representative.
   c. Conflict of interest - Any conflict or perceived conflict of interest a member might obtain should a protocol be implemented must be disclosed to the committee. All committee members must be in compliance with University COI policies.
   d. PRMC Administrative Research Assistant – The MCC-CRO staff person in charge of organizing and implementing the PRMC Meeting.

7. PROCEDURES
   a. Clinical trials will be considered by the PMRC if they are Phase I, II, or Phase III NCI cooperative group trials, industry-sponsored, or institutional investigator-initiated clinical trials focusing on cancer prevention, cancer
control, or cancer treatment that have been approved by the appropriate CCART.

b. The committee typically meets, at minimum, twice a month to review protocols.

c. Typically, no more than three new clinical trials will be slated for full committee evaluation and potential approval at any one PRMC meeting. The Chair of the PRMC makes the ultimate decision regarding trials accepted on the agenda.

   i. The Chair may call an ad-hoc committee meeting at any time to address issues of immediate concern.

d. Attendance by committee members is requested at all meetings, but it is understood and expected that other commitments will come up on occasion.

   i. If a committee member foresees that they will be unable to attend more than 50% of the meetings, that committee member has the responsibility of notifying the PRMC and should be considered for replacement.

   ii. Attendance will be taken at all scheduled meetings.

   iii. Each committee member may assign another individual within the practice group to attend a committee meeting and carry their vote in that meeting. Proxy assignments are to be sent to the attention of the committee Chair.

   iv. Guests are welcome at meetings. Principal Investigators (PIs) who are not committee members are required to attend meetings or send a proxy when their trial is being presented for consideration but may be asked to leave the room at any point during discussion.

e. Protocols to be reviewed by the PRMC will be evaluated by assigned reviewers.

f. The PRMC Administrative Research Assistant will notify reviewers that they have been chosen as a reviewer and will assist reviewers in accessing the ePRMS functions of OnCore. The reviewer must upload the completed review form to OnCore no later than the Wednesday before the scheduled meeting. If the reviewer is unable to perform the review, they are asked to notify the PRMC Administrative Research Assistant within 24 hours so that an alternate reviewer can be selected.

   i. The reviewers will access the protocol, the protocol submission information, including accrual estimates, and the standardized PRMC review form through the Oncore ePRMS system. The ePRMS review form collecting all the following elements is to be used by all reviewers. This form will include date, protocol title, phase of study, sponsor information, protocol number, and PI name. The specific major review criteria are:

      1. Scientific significance.

      2. Feasible accrual goals (at least 3 subjects annually, with exceptions of tumors defined as by the NCI, complementary and not competitive with current protocols).

      3. Programmatically relevant to the specific CCART goals.
4. Appropriate study design, including appropriate statistical analysis.
ii. The reviewer lists all major points for which they have a scientific criticism. The protocols can be rejected outright for major criteria flaws, requiring appeal and re-submission. The reviewer also describes any minor criticisms. Potential minor review criteria are: soundness of eligibility criteria, competing protocols, procedure and clinical assessment practicality, adequacy of appendices for reporting results, and drug accountability. The reviewer assigns a preliminary score based on the scoring rubric of the PRMC (Table D).
iii. Completed reviews and a copy of the protocol and abstract will be available to all committee members for discussion at the PRMC meeting.
iv. PRMC review forms will be accepted for discussion and be in lieu of attendance. All reviewers are asked to attend if their schedule can allow as a rich discussion helps PI's improve their studies.
g. All investigator-initiated trials undergo a two stage process. A concept must be approved or disapproved by the PRMC. When the protocol is final, the protocol must undergo a full committee review. Pharmaceutical company-sponsored trials must undergo a full review. A full review consists of two physician reviewers, an oncology pharmacist, and a statistician from the BBSRF. Exceptions to this two-stage review include those protocols that have had external peer-review and at the discretion of the PRMC chair for exceptional protocols.
h. Protocols derived from a national cooperative group will have an expedited review by the PRMC Chair or designee after the CCART has completed its review. The results of the expedited review will be presented at the next PRMC meeting.
i. Screening, supportive care, basic science, diagnostic, health services research may undergo expedited PRMC review by the PRMC Chair or designee.
j. A voting quorum is met by the presence of 51% of the current members of the PRMC, or their proxies.
k. PIs of studies under review are to recuse themselves during voting and will be asked to leave the room. However, they should be available for discussion of key questions during the discussion times.
l. The PRMC may make the following decisions regarding a clinical trial: Approve, Disapprove, Changes Required-Administrative Review, Changes Required-Full Review or Table. A final score is agreed upon by the full committee. For expedited reviews, a final score will be given by the PRMC Chair or designee (Table D).
i. If the committee decides that changes require administrative or full review, these revisions need to be submitted within 30 days. If longer than one month is required, a request for an extension must
be submitted in writing as well as a rationale for why the extension is needed to the PRMC Chair.

ii. If a trial is disapproved by the PRMC, the PI has the right to appeal the decision, provided each point of concern raised by the review process is addressed in the appeal.
   1. To appeal a decision by the PRMC, the PI notifies the PRMC Chair of their decision to appeal.
   2. The PI will receive a summary of the specific reasons the protocol was declined.
   3. The PI must provide written documentation addressing all the reasons why the study was declined.
   4. The appeal will be placed on the agenda for the next PRMC meeting.

iii. All substantive comments brought up during consensus voting by the committee will be addressed before final approval by the PRMC Chair.

iv. All correspondence must be kept in the Oncore ePRMS database and maintained in hard copy and electronic formats.

m. Abstention from protocol/amendment review or voting by committee members is accepted if the committee member has a conflict of interest and/or a lack of expertise in the scientific subject of the protocol.
   i. The UK Office of Sponsored Research Projects Administration have jurisdiction over the university’s conflict of interest and financial disclosure functions, and as such, shall have final say as to whether a PRMC member has a conflict of interest.
   ii. A committee member who is a PI on a study submitted to PRMC will be asked to recuse themselves from the review and voting process.

n. The PRMC will determine the level of safety monitoring required for each protocol on a case-by-case basis according to the Risk Definition (Table A).
   i. For investigator-initiated trials that are determined to be of high risk, the DSMC will monitor subject safety monthly.

o. The following monitoring activity is required by assigned level of risk (Table B).

p. Open protocols initially approved by the PRMC will be submitted to the PRMC for continuing review prior to continuing review by the IRB to determine if study continues to have scientific merit and progress is being made through accruals.
   i. The PRMC has authority to close a study and not submit it to the IRB for continuing review if accrual plan and/or scientific progress is not being achieved (Table C).

q. The Chair of the PRMC will review and approve scientific amendments, except those where there may be a conflict of interest; in that case, the amendments will be reviewed by the Vice Chair of the PRMC, or in their absence, the Associate Director of Clinical Translation. Administrative
amendments will be reviewed and approved by the Director of the Clinical Research Office or designee.

r. The PRMC recommends amendments to or termination of a protocol for scientific reasons. Such reasons include:
   i. The development of therapy which is superior to that proposed in the protocol.
   ii. A change in the standard of care which is no longer reflected in the protocol.

s. The PRMC has the authority to terminate protocols for lack of study progress including poor accrual.

t. Committee assignment is as follows:
   i. Physician members are chosen from the MCC and UK faculty.
   ii. The Chair is appointed by the Director of the MCC.
   iii. One of the voting members will serve as the Vice Chair appointed by the Chair. 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. There is no limit on the number terms a member may serve.

t. At least annually the PRMC will review its processes and receive training as needed from external sources, such as the cooperative groups or the NCI.

8. DOCUMENTS AND REQUIREMENTS
   a. PRMC memos and minutes will document committee discussion and decisions.
   b. Email communication may provide documentation of discussions.

9. ATTACHMENTS
   a. Table A: Risk Definition Table
   b. Table B: Study Risk Profile and Monitoring Requirements
   c. Table C: Accrual Criteria for review
   d. Table D: PRMC Scoring Rubric

10. REFERENCES
   a. NCI Dictionary of Cancer terms (NCI Dictionary of Cancer Terms - National Cancer Institute)

11. REVISION HISTORY
   a. Revision: 02
      i. Date: 27 November 2012
      ii. Description of change:
         1. References to the Affiliate Network removed
         2. Administrative changes
b. Revision: 03
   i. Date: 15 April 2015
   ii. Description of Changes
       1. Implementation of ePRMS
       2. Clerical and Administrative changes
       3. Description of two stage review process for IITs
       4. Addition of Table D: PRMC Scoring Rubric
Table A: Determination of Level of Risk in Clinical Trials

<table>
<thead>
<tr>
<th>Level of Risk</th>
<th>Explanation</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low Risk</td>
<td>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</td>
<td>• Behavioral Studies • Nutrition/food supplement Studies • Observation Studies • MRI or Ultrasound Studies • Survey/Questionnaire Studies • Correlative sample acquisition</td>
</tr>
<tr>
<td>Moderate Risk</td>
<td>Phase I, II, III, IV therapeutic, palliative or prevention trials that are sponsored by national cooperative groups or NCI/NIH that already include independent appropriate/approved data and safety monitoring plans</td>
<td>• Most cancer treatment studies • Cooperative group cancer treatment studies</td>
</tr>
<tr>
<td>Very High Risk</td>
<td>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 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” or “killed”</td>
<td>• First in human device and agent studies, and studies determining maximum tolerated dose • A gene therapy study or research involving recombinant DNA molecules (gene transfer) • Investigator-initiated multi-center trial • Study involving the manufacture of agents by UK facilities • Bone marrow support needed after chemotherapy</td>
</tr>
</tbody>
</table>
Table B: Study Risk Profile and Monitoring Requirements

<table>
<thead>
<tr>
<th>Task Owner</th>
<th>Task</th>
<th>Low Risk</th>
<th>Moderate Risk</th>
<th>High Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>PRMC</td>
<td>Subject Recruitment &amp; Retention</td>
<td>Required</td>
<td>Required</td>
<td>Required including drop out analysis</td>
</tr>
<tr>
<td>DSMC</td>
<td>Cumulative Adverse Events</td>
<td>Required</td>
<td>Required</td>
<td>Required</td>
</tr>
<tr>
<td>DSMC</td>
<td>Study specific DSMB</td>
<td>As Needed</td>
<td>As Required</td>
<td>As Required</td>
</tr>
<tr>
<td>DSMC</td>
<td>Records Audit</td>
<td>As Needed</td>
<td>As Required</td>
<td>Required</td>
</tr>
<tr>
<td>DSMC</td>
<td>Analysis of 1st and 2nd efficacy parameters, outcomes, if applicable</td>
<td>As Needed</td>
<td>As Required</td>
<td>As Required</td>
</tr>
<tr>
<td>DSMC</td>
<td>Protocol Deviations</td>
<td>Required</td>
<td>Required</td>
<td>Required</td>
</tr>
</tbody>
</table>

- Phase I, II, or III therapeutic, palliative, or prevention trials sponsored by industry or NCI-sponsored cooperative group that include appropriate and approved monitoring plans will be monitored annually.
Table C: Accrual Criteria for review

<table>
<thead>
<tr>
<th>Accrual</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>No accrual</td>
<td>Study may be required to be amended or considered for termination. The PRMC regards a situation of zero accrual as a potentially flawed study by the time of the first IRB annual renewal</td>
</tr>
<tr>
<td>&lt; 50% of projected accrual</td>
<td>Extenuating circumstances are considered first. The PI is then asked to justify continuing the study.</td>
</tr>
<tr>
<td></td>
<td>- Constructive suggestions to improve accrual will be considered such as:</td>
</tr>
<tr>
<td></td>
<td>- Altering the design or eligibility criteria</td>
</tr>
<tr>
<td></td>
<td>- Seeking extramural funding</td>
</tr>
<tr>
<td></td>
<td>- Activating the study at affiliate centers or through the outreach network, etc.</td>
</tr>
<tr>
<td>50%-100% of projected accrual</td>
<td>No Recommendation. Acceptable.</td>
</tr>
<tr>
<td>&gt; 25% of projected accrual</td>
<td>Recommendation by the committee in accordance with the level of over accrual.</td>
</tr>
</tbody>
</table>
Table D: PRMC Scoring Rubric

<table>
<thead>
<tr>
<th>Impact</th>
<th>Impact/Priority Score</th>
<th>Descriptor</th>
<th>Additional Guidance on Strengths/Weaknesses</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td>1</td>
<td>Exceptional</td>
<td>Exceptionally strong with essentially no weaknesses</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>Outstanding</td>
<td>Extremely strong with negligible weaknesses</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>Excellent</td>
<td>Very strong with only some minor weaknesses</td>
</tr>
<tr>
<td>Moderate</td>
<td>4</td>
<td>Very Good</td>
<td>Strong but with numerous minor weaknesses</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>Good</td>
<td>Strong but with at least one moderate weakness</td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>Satisfactory</td>
<td>Some strengths but also some moderate weaknesses</td>
</tr>
<tr>
<td>Low</td>
<td>7</td>
<td>Fair</td>
<td>Some strengths but with at least one major weakness</td>
</tr>
<tr>
<td></td>
<td>8</td>
<td>Marginal</td>
<td>A few strengths and a few major weaknesses</td>
</tr>
<tr>
<td></td>
<td>9</td>
<td>Poor</td>
<td>Very few strengths and numerous major weaknesses</td>
</tr>
</tbody>
</table>

Definitions

Minor: easily addressable weakness that does not substantially lessen the impact of the project.
Moderate: weakness that lessens the impact of the project.
Major: weakness that severely limits the impact of the project.