PLAN FOR PROTOCOL REVIEW AND MONITORING SYSTEM

Ensuring the Scientific Merit and Progress of Clinical Research

Randall F. Holcombe, MD, MBA
Director, University of Hawai‘i Cancer Center

November 16, 2017
**Table of Contents**

<table>
<thead>
<tr>
<th>i</th>
<th>Table of Contents</th>
<th>Page 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>ii</td>
<td>Definitions and Abbreviations</td>
<td>Page 3</td>
</tr>
<tr>
<td>iii</td>
<td>Summary of Changes</td>
<td>Page 5</td>
</tr>
<tr>
<td>I</td>
<td>Introduction</td>
<td>Page 6</td>
</tr>
<tr>
<td>II</td>
<td>Purpose</td>
<td>Page 7</td>
</tr>
<tr>
<td>III</td>
<td>Protocol Review and Monitoring System Process</td>
<td>Page 7</td>
</tr>
<tr>
<td></td>
<td>A. Cancer Related Studies That Require PRMS Review</td>
<td>Page 10</td>
</tr>
<tr>
<td></td>
<td>B. New Protocol/Study Submission</td>
<td>Page 12</td>
</tr>
<tr>
<td>IV</td>
<td>PRMS Review Boards</td>
<td>Page 13</td>
</tr>
<tr>
<td></td>
<td>A. Board Membership</td>
<td>Page 13</td>
</tr>
<tr>
<td></td>
<td>B. Translational and Clinical Research Steering Committee</td>
<td>Page 14</td>
</tr>
<tr>
<td></td>
<td>C. Community Research Advocacy Board</td>
<td>Page 15</td>
</tr>
<tr>
<td></td>
<td>D. Data and Safety Monitoring Committee</td>
<td>Page 16</td>
</tr>
<tr>
<td></td>
<td>E. Protocol Review and Monitoring Committee</td>
<td>Page 17</td>
</tr>
<tr>
<td>V</td>
<td>Prioritizing Protocols</td>
<td>Page 17</td>
</tr>
<tr>
<td></td>
<td>A. Levels of PRMS Review</td>
<td>Page 17</td>
</tr>
<tr>
<td>VI</td>
<td>Protocol Monitoring</td>
<td>Page 22</td>
</tr>
<tr>
<td></td>
<td>A. Scientific Progress and Evaluation</td>
<td>Page 22</td>
</tr>
<tr>
<td></td>
<td>B. Protocol Suspension and Termination</td>
<td>Page 23</td>
</tr>
<tr>
<td>VII</td>
<td>Quality Assurance, Monitoring, Auditing and Risk Management</td>
<td>Page 24</td>
</tr>
<tr>
<td>VIII</td>
<td>Review and Approval of PRMS Plan</td>
<td>Page 25</td>
</tr>
<tr>
<td>Figure 1</td>
<td>PRMS Detailed Process</td>
<td>Page 9</td>
</tr>
<tr>
<td>Figure 2</td>
<td>PRMS Review Boards</td>
<td>Page 13</td>
</tr>
<tr>
<td>Table 1</td>
<td>Protocol Review Requirements</td>
<td>Page 19</td>
</tr>
<tr>
<td>Table 2</td>
<td>PRMC Decisions</td>
<td>Page 20</td>
</tr>
</tbody>
</table>
Definitions and Abbreviations

**Ancillary Study:** Studies that are stimulated by, but are not a required part of, a main clinical trial/study, and that utilize patient or other resources of the main trial/study to generate information relevant to it. Ancillary studies must be linked to an active clinical research study and should include only patients accrued to that clinical research study. Only studies that can be linked to individual patient or participant data should be reported.

**Behavioral Studies:** Often interventional can involve focus groups, surveys and cancer prevention.

**Correlative Study:** Laboratory-based studies using specimens to assess cancer risk, clinical outcomes, response to therapies, etc. Only studies that can be linked to individual patient or participant data should be reported.

**Epidemiological:** Studies among cancer patients and healthy populations that involve no intervention or alteration in the status of the participants, e.g. surveillance, risk assessment, outcome, and environmental.

**Externally Peer-Reviewed:** R01s, SPORES, U01s, U10s, P01s, CTEP, or any other clinical research study mechanism supported by the NIH or external organizations.

**Health services research:** Protocol designed to evaluate the delivery, processes, management, organization, or financing of health care.

**Hybrid Study:** Cooperative group and Investigator initiated protocol; Cooperative Group and Industry initiated protocol or other non-standard collaboration or unique design.

**Interventional Research:** Individuals are assigned prospectively by an investigator based on a protocol to receive specific interventions. The participants may receive diagnostic, treatment, behavioral, or other types of interventions. The assignment of the intervention may or may not be random. The participants are followed and biomedical and/or health outcomes are assessed.

**Interventional Treatment Trial:** Interventional treatment trials are protocols designed to evaluate one or more interventions for treating a disease, syndrome, or condition. The participants may receive diagnostic, treatment, behavioral, or other types of interventions.

**Investigators Initiated - Research conducted as a result of an investigator, on his or her own, developing, implementing and evaluating a research protocol. May be supported by institutional, industry or peer reviewed grant funding.

**Observational Research:** Studies that focus on cancer patients and healthy populations and involve no prospective intervention or alteration in the status of the participants. Biomedical and/or health outcome(s) are assessed in pre-defined groups of participants. The participants in the study may receive diagnostic, therapeutic, or
other interventions, but the investigator of the observational study is not responsible for assigning specific interventions to the participants of the study.

**Patient-oriented research:** This type of research is conducted with human subjects (or on material of human origin such as tissues, specimens and cognitive phenomena) for which an investigator (or colleague) directly interacts with human subjects. Excluded from this definition are in vitro studies that utilize human tissues that cannot be linked to a living individual, tissue banking, and studies that do not require patient consent (e.g., retrospective chart reviews). Patient-oriented research includes: Studies of mechanisms of human disease, studies of therapies or interventions for disease, clinical trials and studies to develop new technology related to disease.

**Rare Cancer:** There is no universally adopted definition for rare cancers. The National Cancer Institute definition is fewer than 15 cases per 100,000 people per year. More recently, a consortium from the European Union (RARECARE) 2 defined rare cancers as those with fewer than 6 cases per 100,000 people per year, which is the definition UHCC subscribes to. (Cancer Facts and Figures 2017).
Summary of Changes

This revision of the current Protocol Review and Monitoring System (PRMS) Plan for the University Of Hawai'i Cancer Center (UHCC), a National Cancer Institute Designated Cancer Center, and member of the Hawai'i Cancer Consortium (HCC), is intended to reflect program review, progress made, and changes implemented to continue the ongoing growth and development of cancer research in the community.

The PRMS review process continues to clarify and develop work flows to be more transparent and easy to understand while supporting documented, robust scientific review. Process updates are reflected in new best practices, forms and attention to detail across integrated work flows, and to display changes in system processes and current practices.

The Early Phase Clinical Research Support (EPCRS) has been replaced with the Translational and Clinical Research Steering Committee (TCR Steering Committee) to comply with the change in funding structure requirements.
I. Introduction

The University Of Hawai‘i Cancer Center (UHCC) is a National Cancer Institute (NCI) designated clinical cancer center. NCI-designated Cancer Centers are a group of 69 cancer research institutions in the United States supported by the National Cancer Institute. This designation provides a unique and unprecedented opportunity to provide high quality, comprehensive cancer related care to the peoples of Hawai‘i in their home environment through access to clinical trials only available through a NCI designated center. Research conducted in the unique environment of the state of Hawai‘i has the potential to impact the treatment of cancer patients worldwide.

Research is supported through the University of Hawai‘i, the people of Hawai‘i, the National Institutes of Health and the creation of a rare and distinctive formal partnership between Hawai‘i health care institutions, providers and supporters. This unique partnership is formalized as the Hawai‘i Cancer Consortium (HCC). The HCC was established to put into action a vision by all stakeholders to substantially reduce the burden of cancer for the people of Hawai‘i and elsewhere through the support of clinical and translational cancer research. The vision is operationalized through the HCC mission to facilitate, support and assure the generation and conduct of high impact patient research with a focus on cancer diagnosis, prevention and treatment. Working in a formal partnership supports the most efficient and safe way possible to substantially reduce the burden of cancer for the people of Hawai‘i and elsewhere. Formal members include Hawai‘i Pacific Health (Includes Straub Medical Center, Pali Momi Medical Center and Kapi‘olani Medical Center for Women and Children.) The Queens Health System, Kuakini Medical Center, John A. Burns School of Medicine and the University of Hawai‘i Cancer Center. Additional affiliates include: Tripler Army Medical Center, Hawai‘i Cancer Care, Hawai‘i Oncology, Cancer Center of Hawai‘i and independent physician practices.

The objective of the Protocol Review and Monitoring System (PRMS) Plan is to ensure scientific merit and review, protocol prioritization, and scientific progress monitoring. To accomplish this objective multiple activities must be completed collaboratively, efficiently, and consistently. The effective utilization of resources is imperative to the conduct of research in a collaborative environment. Transparency of processes supports compliance with multiple regulatory, institutional and operational requirements.

Using distinct boards and Standard Operating Procedures, the PRMS plan fosters clinical research. Collaboration supports protocol evaluation and prioritization and provides the foundational structure of all research activities supported through the HCC. All participating HCC members, UHCC Faculty, and community affiliated investigators must participate in the PRMS plan to initiate any clinical or patient oriented research supported by the HCC or UHCC.
Studies conducted for the pediatric population at Kapi‘olani Medical Center for Women and Children (KMCWC) do not submit protocols for review to the UHCC. Selection and review of these protocols is conducted by a separate scientific review committee based at KMCWC.

The following sections detail the PRMS plan and required procedures.

II. Purpose

A functioning scientific review committee is a mandatory element of a National Cancer Institute (NCI) designation. Scientific review and ongoing monitoring is addressed through the Protocol Review and Monitoring System (PRMS). The PRMS is comprised of professional committees or boards with membership drawn from academia, community members and healthcare institutions in the community.

The PRMS oversees the scientific aspects of cancer related research involving human subjects conducted by members of the HCC. The PRMS facilitates development of innovative, collaborative, and scientifically sound studies that focus on the prevention, detection, diagnosis, support and the treatment of cancer and its long-term follow-up. The PRMS helps the community to prioritize studies to ensure optimal allocation of HCC and UHCC resources. The PRMS review process also mentors and guides inexperienced investigators in the development of research proposals that will result in meaningful community outcomes that are scientifically sound.

Kapi‘olani Medical Center for Women and Children (KMCWC) serves the unique needs of pediatric oncology patients. Due to this highly specialized environment, pediatric studies follow a separate PRMS process directed and driven by KMCWC selected members.

III. Protocol Review and Monitoring System Process

The PRMS process ensures that all research is scientifically sound and feasible within the HCC community by confirming studies have entry criteria that reflect the catchment population, a high probability of full accrual, do not compete with other studies, adequate resources available to answer the question being asked, and are consistent with the priorities of the UHCC. Ongoing monitoring assures continuance of scientific progress and best use of available resources to meet the needs of the community. The system contains two phases of review, Pre-PRMS and Post-PRMS, separated by the actual Protocol Review and Monitoring Committee (PRMC) discussion, evaluation and determination.

1). Pre-PRMS evaluations are completed by the TCR Steering Committee, the Community Research Advocacy Board (CRAB) and the Data Safety and Monitoring Committee (DSMC). The outcome from each of these evaluations is submitted to the PRMC for reference.
The PRMC review occurs after TCR Steering Committee, DSMC and CRAB and prior to the submission to the Institutional Review Board (IRB). PRMS functions are independent of the IRB, and do not duplicate or overlap with the responsibilities of the IRB. The PRMS has the authority to open protocols that meet the scientific merit and priorities of the UHCC and to terminate protocols that do not demonstrate scientific progress.

2.) Post-PRMS review and evaluations include IRB review, ongoing monitoring, auditing, and progress reporting.

**Figure 1** (page 9) illustrates the complete review and monitoring process for reviewing a protocol and **Figure 2** (page 13) provides a board level, concise overview.
Figure 1 PRMS Detailed Process

- **Clinical Trials are submitted to CTO Protocol Coordinator**
  - PC enters data into OnCore
  - PC provides documents to TCR Steering Committee
  - TCR Steering Committee reviews
    - Returns to PI for protocol refinement
    - CRAB recommends approval or non-approval to PRMC
      - PRMC votes for approval, disapproval or tabled for additional information
        - PI is notified of approval, disapproval or questions
          - PI chooses to manage own regulatory document submission (UH IRB only)
            - PI reports data and study updates to Compliance monthly for data entry in OnCore or enters into OnCore for required reporting.
  - Non-Exempt studies are sent to PC for distribution to TCR Steering Committee. PI is notified.
    - PI proceeds to Regulatory (IRB) review
      - PI contacts CTO Regulatory for Regulatory submission assistance
      - PRMC Chair notifies PRMC at next meeting of new study.

- **Non Clinical Trials are submitted to humansubjectsresearch@cc.hawaii.edu (Compliance)**
  - Compliance enters into OnCore
  - Compliance, with PRMC Chair oversight reviews for exemption from full PRMS review
    - Exempt studies are documented and PI and PRMS Chair notified.
      - PI proceeds to Regulatory (IRB) review
        - PI contacts CTO Regulatory for Regulatory submission assistance
          - PRMC Chair notifies PRMC at next meeting of new study.

- **PI submits protocol or research study**
  - PC enters data into OnCore
  - PC provides documents to TCR Steering Committee
    - TCR Steering Committee reviews
      - Notifies PC for placement on the next scheduled CRAB and PRMC and DSMC meeting
        - DSMC reviews DSMP and votes for approval or disapproval, or tables for additional information and provides recommendation to PRMC
          - CRAB recommends approval or non-approval to PRMC
            - PRMC votes for approval, disapproval or tabled for additional information
              - PI is notified of approval, disapproval or questions
                - PI may choose resubmission to PRMC
                  - PI reports data and study updates to Compliance monthly for data entry in OnCore or enters into OnCore for required reporting.

- II studies report quarterly and annually to DSMC. Local SAEs are reported as soon as identified to DSMC Chair
  - All interventional trials are audited at first subject in for QA. All II clinical trials are audited annually. 10% of National Group studies are audited annually.
    - Central Data Management System, Data Table 4 reporting, CTRP reporting, Monitoring and Auditing
A. Cancer Related Studies That Require PRMS Review

The NIH defines Clinical Research with human subjects as:

1) Patient-oriented research. Research conducted with human subjects (or on material of human origin such as tissues, specimens, and cognitive phenomena) for which an investigator (or colleague) directly interacts with human subjects. Excluded from this definition are in vitro studies that utilize human tissues that cannot be linked to a living individual. Research conducted with human subjects includes: (a) mechanisms of human disease, (b), therapeutic interventions, (c) clinical trials, or (d) development of new technologies.

2) Epidemiological and behavioral studies.

3) Outcomes research and health services research

The NIH defines a Clinical Trial as 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. (Common Rule definition of research at 45 CFR 46.102(d) and definition of human subject at 45 CFR 46.102(f))

The term "prospectively assigned" refers to a pre-defined process (e.g., randomization) specified in an approved protocol that stipulates the assignment of research subjects (individually or in clusters) to one or more arms (e.g., intervention, placebo or other control) of the clinical trial.

An intervention is defined as a manipulation of the subject or subject's environment for the purpose of modifying one or more health-related processes and/or endpoints. Examples include, but are not limited, to: drugs/small molecules/compounds, biologics, devices; procedures (e.g., surgical techniques); delivery systems (e.g., telemedicine, face-to-face); strategies to change health-related behavior (e.g., diet, cognitive therapy, exercise, development of new habits); and, treatment, prevention, and diagnostic strategies.

Studies in human subjects where there is no intervention, such as observational studies, are not considered within the definition of a clinical trial and are not reviewed for potential subject participation, feasibility, logistics or scientific merit unless requested by the Principal Investigator (PI). These studies are exempt from community and scientific review. This does not exempt the research study from the protocol submission process or regulatory review process.

In order to encourage and support the research development process, peer mentoring and review in a collaborative environment are provided through the use of Concept review. For studies or trials that are not yet funded (interventional and non-interventional), unless funding is dependent on Institutional Review Board (IRB)
approval, the PI may request TCR Steering Committee concept review following the same Protocol/Concept submission and review process discussed throughout this document. The concept will be reviewed by the TCR Steering Committee only, not voted on, and feedback provided to the PI.

**Examples of Clinical Research Studies that may require review by the PRMS:**

- Studies that require consent of human subjects and/or involve human subjects;
- Treatment or therapeutic intervention studies involving agents or medical devices for cancer management;
- Laboratory studies of the mechanism of human disease that maintain identifiers or involve previously banked tissues;
- Studies that investigate cancer etiology, prevention or control;
- Studies that investigate secondary cancer prevention such as early diagnosis and screening, symptom management during and following treatment, and survivorship;
- Cancer care delivery;
- Studies that investigate cancer risk factors such as dietary studies that involve surrogate end points (e.g. precancerous lesions such as polyps for cancer, genetic markers, and interventions for cancer prevention);
- Prospective, hypothesis driven chart review studies.

**Examples of studies that may receive expedited review only:**

- Database infrastructure and tissue banking studies;
- Cancer control, Quality of Life (QOL), and prevention, screening, detection studies involving healthy subjects that do not have cancer as a disease endpoint or outcome;
- Studies that involve the promotion of a healthy lifestyle in healthy subjects without a cancer endpoint;
- In vitro studies utilizing human tissues that cannot be linked to a living individual;
- Studies that do not require human consent;
- Compassionate Use studies (one time approval to treat a specific cancer patient)

Studies that receive expedited review must always continue to the designated Institutional Review Board Review (e.g. IRB/CIRB/UH/Institutional) prior to initiating any human subject’s research activity.

All PRMS activity conducted through the UHCC is managed, reported, monitored, and tracked through the OnCore® Clinical Trial Management System (CTMS).
B. Protocol Submission Process

Application for Protocol Review and Approval

All clinical trials or research studies, excluding pediatric studies at KMCWC, that are conducted through the HCC or are supported by UHCC, complete the same scientific and safety review process that is sequential and step wise.

Completed Protocols or Draft Concepts may be reviewed. Applications may be submitted by Principal Investigators (PIs) or designees. PIs are responsible for the content of all submissions. Assistance is available in completing the protocol or the submission process by contacting Clinicaltrials@cc.hawaii.edu (Interventional Treatment Trials) or Regulatory@cc.hawaii.edu (Regulatory Assistance) or humansubjectsresearch@cc.hawaii.edu (other research studies/compliance) for further information. All applications must include a completed Protocol Submission Form (Appendix 8.3), informed consent form (if applicable), budget or draft budget or funding sheet as applicable/available and a Data and Safety Monitoring Plan if not included in the protocol/concept document.

All new clinical trial protocols for interventional clinical drug trials to be conducted through the HCC member hospitals and/or affiliates must be submitted to the UHCC Clinical Trials Office through Clinicaltrials@cc.hawaii.edu. All other research studies are submitted to humansubjectsresearch@cc.hawaii.edu.

New protocols or research studies should be submitted far enough in advance of the next scheduled review meeting to allow for appropriate review preparation. Meeting schedules are posted on the UHCC Web site at: http://www.uhcancercenter.org/.

Format for Protocol Submission

While not required, the NHLBI Sample Protocol Template may be used when preparing a protocol. The Template is available as Appendix 8.19 or may be retrieved from the NIH web site at www.nhlbi.nih.gov/files/docs/clinical-research-guide-protocol-template.doc. All protocols should be guided by A Handbook for Clinical InvestigatorsConducting Therapeutic Clinical Trials Supported by CTEP, DCTD, NCI Investigator’s Handbook 2014 (Version1.2) available at: http://ctep.cancer.gov/investigatorResources/docs/InvestigatorHandbook.pdf, or similar type reference appropriate to investigator discipline.
IV. PRMS Review Boards

Figure 2 illustrates the board level review process for new protocols:

A. Board Membership

The PRMC and DSMC Chair and committee members are appointed to annual renewable terms by the Associate Director for Translational and Clinical Research with the approval of the UHCC Director. Active participation is a condition of continued PRMC membership. It is expected that members attend at least 75% of all meetings. Member attendance is reported to both the PRMC Chair and UHCC Director and is incorporated into the members' yearly review. In order to ensure the necessary expertise so that it may provide critical scientific review of the entire spectrum of cancer clinical research at UHCC, the PRMC and DSMC are comprised of members from a broad array of subspecialties within medical, surgical, and radiation oncology, as well as basic and translational laboratory researchers, cancer prevention/control and population scientists and biostatisticians. Pharmacists are consulted as hoc as needed. Membership in the PRMC and DSMC are distinct with no overlap. Membership in the PRMC and DSMC are distinct with no overlap.

A quorum is required for decision making. A quorum is defined as 50% of PRMC/DSMC membership, with the requirement that at least one attendee be a medical oncologist. Members may be present in person, or join the meeting via telephone or web conference. Attendance lists are maintained. If a quorum of committee members (or their alternates) is unavailable to meet on site, teleconference meetings may be scheduled. The PRMC/DSMC Chair can convene ad hoc meetings to ensure timely review of the clinical trials.
Members are selected based on their experience in designing or conducting research studies or special clinical expertise. Special consideration is given to incorporation of a significant number of senior faculty, though some junior members are included in order to enhance their level of expertise and career development. An alternate is assigned for each member and ad hoc members may be invited by the Chair to review protocols if specific expertise is required. The Medical Director of the CTO may be invited to attend PRMC meetings as a non-voting participant if needed to address questions related to protocol logistics.

All regular participants of the CRAB are required to complete a Confidentiality Agreement and Conflict of Interest Disclosure annually.

The list of designated reviewers and members for the PRMC and DSMC and is available at: [http://www.uhcancercenter.org](http://www.uhcancercenter.org).

**B. TCR Steering Committee.**

The TCR Steering Committee is comprised of experienced cancer investigators and meets bimonthly to review new interventional protocols that do not meet the IRB’s definition of minimal risk and are available through NCORP, industry or are new concepts for Investigator Initiated Trials (IITs). For NCORP and industry studies, the TCR Steering Committee considers how they support and align with the research missions of UHCC, whether they are appropriate for the catchment area target patient population, and whether there are existing, competing studies with equivalent eligibility criteria. The TCR Steering Committee is chaired by the Associate Director Translational and Clinical Research.

In addition to the previous criteria, IITs undergo careful consideration to address the following aspects of the protocol:

- Scientific value and rationale of the trial
- Expertise and effectiveness of the investigator
- Appropriateness of accrual goals
- Feasibility and quality of the study design and methodology

Investigators are encouraged to present the study concept in its early stages to the Steering Committee to facilitate development of a well-designed and pertinent protocol. At this stage, if not already identified, a biostatistician from the Biostatistics Shared Resource is assigned to work with the investigator on protocol development and address study design, sample size and statistical analysis issues. Once the protocol is developed, the investigator presents it again to the Steering Committee for additional input prior to presentation at CRAB. The Steering Committee will enlist the support of
ad hoc reviewers from other NCI cancer centers if specific expertise for review of an IIT is required. Additionally, the Steering Committee will identify a mentor for junior investigators to work with if felt necessary.

B. Community Research Advocacy Board

The Community Research Advocacy Board (CRAB) reviews all potential studies, except pediatric oncology trials, where a patient will be enrolled. Institutional and externally generated studies of cancer patients undergo this initial review. Community providers are key stakeholders in determining the need, applicability and potential success of research studies within their environment. To support community needs, a committee of interested clinicians, allied health professionals and community members give advice on the selection of studies in Hawai`i’s community practice setting. To support appropriate clinical trial selection for community requirements, needed resources and efficient clinical trial review, CRAB review takes place prior to the scientific review of the Protocol Review and Monitoring Committee (PRMC).

CRAB, reviews all potential PRMC studies received both externally generated (NCORP, other cooperative group and industry) studies and IITs. Minutes are maintained by the Clinical Trial Office (CTO) Manager for each meeting. CRAB discussions focus on whether community physicians are likely to enroll patients on a protocol by assessing:

1. Relevance of study questions to community practice patterns
2. Study design/methods and degree of difficulty conducting the protocol in Hawai`i’s community practice setting
3. Availability of patients for the protocol as determined by the Hawai`i Tumor Registry data and referral practice patterns to participating community investigators
4. Other feasibility considerations including financial and logistical considerations

CRAB provides a recommendation to the PRMC.

UHCC administrative reviews are completed by the CTO focusing on institutional feasibility, financial and other risks. Similar reviews are also conducted by the affiliated hospitals within the HCC. Results of these reviews are presented at the CRAB meeting for discussion.

The CRAB meets monthly on the second Thursday. The Manager of the Clinical Trials Office (CTOM) in conjunction with the Chair of the PRMC and Chair of the CRAB or designee sets the agenda for the CRAB and attends all meetings. Minutes, including participant attendance, are maintained for each meeting.

CTO Clinical Research Professionals (CRPs) provide an overview of each new protocol that are presented at each CRAB for consideration. Principal Investigators or designees
may also attend the meeting to provide information. All physician CRAB attendees have
the opportunity to participate in discussion of protocols and complete a written
evaluation. The CRAB Chair completes a written evaluation that summarizes the
members’ recommendation/non-recommendation for each protocol discussed. The
written summary of the recommendation/non-recommendation is provided by the CRAB
Chair to the PRMC Chair for use at the PRMC meeting.

CRAB membership is at will and a roster is not maintained. CRAB meetings are posted
annually on the UHCC Web Site. Administrative support and coordination is provided by
the UHCC CTO. The CTO Manager or designee is responsible for maintaining and
administering all support functions for the CRAB and the meeting schedule. Email
reminders to the participating community are sent out by CTO staff.

C. Data Safety Monitoring Committee
The Data Safety Monitoring Committee (DSMC) is the dedicated data and safety
monitoring committee for the UHCC. The DSMC communicates with the PRMC before,
during and after clinical trial completion to ensure subject safety and high quality data.

Externally coordinated studies (NIH, Industry and other national peer reviewed studies)
conduct a range of therapeutic and prevention clinical trials. These studies are
monitored by long standing and established systems for subject safety, data
submission, reporting, review, and monitoring. The UHCC will not place additional
review requirements on local Investigators supporting these studies, but will rely on
mandated reporting requirements (Protocol specific requirements and regulatory
reports). Local deviations, audit findings, monitoring visit letters and serious adverse
events are reviewed for all studies conducted through the UHCC.

All Investigator Initiated trials or studies with intervention based human contact are
reviewed by the DSMC beginning in January 2018, prior to this date, only therapeutic
IITs had mandatory DSMC review. The PI of each study is ultimately responsible for
every aspect of the design, conduct and final analysis of the protocol.

The DSMC meets every two months to review Investigator Initiated (II) protocols and
studies.

At the protocol or concept initial submission stage for local, investigator generated
clinical trials the PI is required to submit a copy of the proposed Data and Safety
Monitoring Plan (DSMP) for review. The DSMC chair reviews the protocol specific
DSMP for local investigator initiated clinical trials and provides approval to the PI and
PRMC Chair. If the DSMC Chair is unable to approve a local investigator initiated
DSMP, the DSMC communicates with the PI to obtain resolution. A list of DSMC
members and scheduled meetings is posted annually on the UHCC Web Site. Administrative support and coordination is provided by UHCC Compliance.

E. Protocol Review Monitoring Committee

The Protocol Review Monitoring Committee (PRMC) is a standing committee of the UHCC. The PRMC is charged with the review of all new cancer-related clinical research protocols to assess their scientific merit and statistical validity and to prioritize them relative to the missions of the UHCC. It is also responsible for ongoing monitoring of research protocols to ensure continued scientific and statistical appropriateness and satisfactory progress toward accrual goals. The multidisciplinary membership of the PRMC Scientific Review committee is drawn from senior clinical investigators at UHCC and within the HCC.

V. Prioritizing Protocols

In general, protocols are prioritized for activation to ensure that Center investigator-initiated studies of the highest scientific quality will be completed. For example, proposed new protocols that would compromise the timely completion of ongoing Center investigator-initiated NCI, R01 or other national peer review-funded studies would not be approved. Similarly new protocols would not be approved if resource/patient competition would compromise the completion of ongoing protocols supported by NCI P30 developmental funds. For competing new protocols priority is given to Center studies initiated by Center investigators over imported studies, and to the level of scientific quality as determined by type of previous peer review.

Patient accruals are prioritized to achieve adequate accrual as per the above criteria, by the following mechanisms:

- Not approving competing trials for similar patient populations
- Provider education of Center priorities and accrual progress in high priority studies

The PRMC prioritizes studies for review and approval. In general, protocols are prioritized for activation to ensure that Center investigator-initiated studies of the highest scientific quality will be completed. For example, proposed new protocols that would compromise the timely completion of ongoing Center investigator-initiated NCI, R01 or other national peer review-funded studies would not be approved. Similarly new protocols would not be approved if resource/patient competition would compromise the completion of ongoing protocols supported by NCI P30 developmental funds. For competing new protocols priority is given to Center studies initiated by Center investigators over imported studies, and to the level of scientific quality as determined by type of previous peer review.
Patient accruals are also prioritized to achieve adequate accrual as per the above criteria, by the following mechanisms:

- Not approving competing trials for similar patient populations
- Completing accurate feasibility assessments including: Estimating available patient population(s) and verifying available resources (i.e. qualified scanners/lab availability).
- Monitoring trial accrual on similar studies/pilot studies
- Highlighting Investigator Initiated Studies in UHCC meetings and communications
- Sharing information gained through attendance at national conferences, media, ongoing education etc.
- Encouraging intradepartmental and institutional collaboration

A. Levels of PRMS Review

The PRMS has two levels of board review: Full PRMC review and expedited PRMC review.

PRMC administrative review is required for all Cancer-related protocols (e.g., epidemiologic, observational, outcome, ancillary, companion, and correlative) that include either cancer patients or healthy populations for which informed consent is required but involve no intervention or alteration in the status of the participants. An administrative review may receive an exemption from PRMC board review if the study does not involve an intervention with human subjects (non-interventional) or meets the IRB definition of minimal risk and compassionate use.

PRMC Full Board Review

Full board review is required for all interventional protocols - treatment, supportive, prevention and diagnostic - that have not undergone peer review at the NIH, a cooperative group, or an entity approved by the NCI as a peer review funding system. This specifically includes pharmaceutical protocols that have not undergone national level peer review.

The PRMC Chair assigns reviews to appropriate members. Reviewer’s complete written documentation for each protocol reviewed.

Study sponsorship and previous level of review determines the type and number of written reviews required. All studies in the current review cycle are discussed at PRMC meetings. The PRMC Chair documents approval in a memorandum or letter to the
investigator and notifies the PRMC membership of approval of a compassionate use protocol, during the PRMC scheduled meeting.

**PRMC Expedited Board Review**

PRMC expedited board review is required for clinical trials which have received funding on the basis of peer review from a national body (e.g., National Institutes of Health, American Cancer Society), will be given expedited review. This includes specific protocols developed by national clinical trial cooperative groups.

Table 1 summarizes board review requirements by sponsor type.

<table>
<thead>
<tr>
<th>Sponsor</th>
<th>PRMC Required Minimum Reviews</th>
</tr>
</thead>
<tbody>
<tr>
<td>National peer reviewed investigator-initiated study “Externally Peer Reviewed”</td>
<td>PRMC review; 1 medical oncologist.</td>
</tr>
<tr>
<td>Nationally reviewed group study</td>
<td>PRMC review; 1 medical oncologist.</td>
</tr>
<tr>
<td>No National Peer Review/Other (e.g., industry studies, Investigator Initiated)</td>
<td>PRMC review, 1 medical oncologist, full statistical and pharmacology or other specialty as indicated. (with reviews by primary and secondary reviewer plus pharmacist and statistician)</td>
</tr>
</tbody>
</table>

Concepts and protocols will be evaluated using the following criteria:

1. **Protocol (Clinical Trial) Review Criteria (Scientific Merit)**
   - Importance/potential impact of objectives on reducing cancer mortality, morbidity or incidence
   - Scientific rationale for the proposed research
   - Study design and methodology
   - Bio-statistical considerations, such as sample size and analysis
   - Plans for data and safety monitoring and quality control
   - Feasibility for completion within a reasonable timeframe

2. **Expedited Review Criteria**
   - The PRMC should not duplicate traditional peer review, which includes peer-
reviewed protocols supported by the various NIH and NCI-approved peer review mechanisms, other approved funding agencies, and clinical research protocols approved by NCI’s Cooperative Groups or Cancer Therapy Evaluation Program (CTEP). These protocols receive an expedited review for the purpose of prioritization only.

- Scientific review is completed by the PRMC Chair (or a designee, typically a medical oncologist for NCORP and other cooperative group studies) and are discussed and approved at the next PRMC meeting. If any concerns are raised, a decision is made by the chair to have the protocol undergo full PRMC review.

- All Cancer-related protocols (e.g., epidemiologic, observational, outcome, ancillary, companion, and correlative) that include either cancer patients or healthy populations for which informed consent is required but involve no physical/medical intervention or alteration in the status of the participants or meets the IRB definition of minimal risk and compassionate use.

3. **Compassionate Use Criteria**

- Specific to a single patient. Reviewed by the Human Subjects Research Compliance (HSRC) Director in consultation with the PRMC Chair using expedited review criteria. Review outcome is documented in a letter to the PI. Reviews are announced to the PRMS membership at the next meeting by the PRMC Chair.

Table 2 shows PRMC decisions, with consequent action.
Table 2 PRMC Decisions

<table>
<thead>
<tr>
<th>DECISION</th>
<th>ACTION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Approved as submitted</td>
<td>Investigator may send to the designated IRB</td>
</tr>
<tr>
<td>Approved with recommendations</td>
<td>Return to investigator, who is asked to make suggested changes and submit to the designated IRB, copying the PRMC coordinator the final version of the protocol</td>
</tr>
<tr>
<td>Approved pending revisions</td>
<td>Return to investigator for revision and reconsideration by the PRMC</td>
</tr>
<tr>
<td>Disapproved</td>
<td>Return to investigator</td>
</tr>
</tbody>
</table>

The PRMC meets monthly on the third Thursday. A list of members and scheduled meetings is posted annually on the UHCC Web Site at: [http://www.uhcancercenter.org](http://www.uhcancercenter.org). Administrative support and coordination is provided by the UHCC CTO.

All reviews and votes are documented in the HCC OnCore® Clinical Trial Management System.

PRMC decision results are sent out to the HCC community. Additionally, the PRMC Chair sends a PI decision letter to the Principal Investigator (PI), UHCC Regulatory Staff, and the UHCC Office of Compliance.

**Exemption Review**

The Human Subjects Research Compliance Director reviews all non-interventional, observational, behavioral, or other minimal risk social studies received to determine possible exemption from full CRAB/PRMC review status or potential compassionate use only status. If the study does not involve an intervention with human subjects (non-interventional), Compliance documents the exemption from additional CRAB/PRMC review in an email memo to the PI and/or designee with instructions to proceed with the appropriate Institutional Review Board. The email memo is sent to the PI and/or designee with a copy to Regulatory Staff, PRMS Administrator and the PRMC Chair.
The exempt study is reported to the PRMC at the next meeting and documented in the minutes. The PRMC retains the ability to request additional information from the PI.

The HSRC Director reviews all protocols upon receipt. The HSRC Director consults with the PRMC Chair as needed if questions exist or clarification is needed before granting an exemption from PRMC review. The HSRC Director provides a letter of exemption to the PI, regulatory staff, the protocol coordinator and the PRMC Chair, usually within 24 hours of receipt. The PRMC Chair has the authority to request a biostatistical review or request that the protocol be submitted to the committee for a full board review.

Examples of studies that may receive expedited review only:
- Database infrastructure and tissue banking studies
- Cancer control, Quality of Life (QOL), and prevention, screening, detection studies involving healthy subjects that do not have cancer as a disease endpoint or outcome
- Studies that involve the promotion of a healthy lifestyle in healthy subjects without a cancer endpoint
- In vitro studies utilizing human tissues that cannot be linked to a living individual
- Studies that do not require human consent
- Compassionate Use studies (one time approval to treat a specific cancer patient)

VI. Protocol Monitoring

A. Scientific Progress Evaluation

All active, interventional, and therapeutic clinical trials reviewed by the PRMC that have been open to accrual of subjects for at least one year will be monitored for scientific progress on an annual basis. The Clinical Trials Office (CTO) at UHCC will complete annual reviews of non-pediatric studies.

Scientific progress is evaluated through the annual assessment of study accruals.

A PI whose clinical trial does not meet established accrual standards will be sent a Scientific Progress Evaluation Notification from the PRMC Chair via the CTO. PI's must submit a written request for a 6-month extension that includes an accrual action plan for enrollment prior to the next scheduled PRMC meeting. The formal request should provide an explanation for the low accrual rate and a detailed action plan that outlines the plan to increase accrual in the future. The PI may also choose to close the study at this time.
Trials given approval for a 6-month extension will be tracked to ensure they are
reevaluated by the designated committee at the end of their probationary period.
Notification of final probationary review will be sent to the PI one month in advance of
the meeting. Studies that show adequate accruals at the end of the 6-month period will
be removed from probation and will continue to be monitored for scientific progress on
an annual basis.

If the PRMC Chair does not receive a written response prior to the next PRMC meeting,
the PI will be notified that the trial will be closed.
All studies that receive a Scientific Progress Evaluation will be placed on the
appropriate PRMC meeting agenda. The PRMC will evaluate each study as well as any
extension requests received and vote to either grant a 6-month extension or to close the
study.

Although there may be mitigating circumstances for any individual protocol; the PI’s of
trials that do not meet at least one of the following criteria at the scheduled time of
review will be sent Scientific Progress Evaluation notifications:

i. Total accrual to date $\geq$ 50% of expected accrual to date
ii. Average annual accrual $\geq$ 50% of expected annual accrual rate
iii. Last 12 month accrual $\geq$ 50% of expected annual accrual rate

Where:
- Expected accrual to date = target accrual goal x Duration study is open
  Expected study duration
- Expected annual accrual rate = Target accrual goal
  Expected study duration in years

B. **Protocol Suspension and Termination**

Protocols not meeting annual review requirements or for which extension requests are
not approved are expected to close to *new enrollment* immediately after notification from
the PRMC Chair. Notification of suspension or termination is communicated to the
Principal Investigator, the Associate Director of Translational and Clinical Research, the
DSMC Chair, UHCC Compliance Director and the UHCC Regulatory Office.

The DSMC also provides annual and ongoing review of Investigator Initiated Studies
involving human subject contact, external monitoring visits of all studies, all serious
adverse events experienced by local subjects, deviations and all external data safety
monitoring committee reports. The DSMC may recommend suspension or termination of
any trial. DSMC recommendations will be provided directly to the PRMC Chair for review and action. The DSMC Chair may suspend accrual immediately to any trial for patient safety concerns and will follow up with the PRMC Chair and PI for additional actions.

Patients/Research Subjects who are in the screening process at the time of notification by the PRMC Chair to the PI of protocol suspension or termination will be reviewed by the PRMC Chair upon request by the PI. A subject in the screening process at the time of notification of suspension or termination may be enrolled if approved by the PRMC Chair; however, the study should be closed immediately to additional new screening and enrollment as soon as the first notice is received after the individual PRMC review is complete.

The PI has the right to appeal any closure of a clinical trial to the UHCC Director via the Associate Director of Translational and Clinical Research Services. All appeals should include supporting information and be made in writing. Final determinations will be made by the Center Director within two business days of receipt of the appeal and be communicated in writing to the Associate Director of Translational and Clinical Research Services, the PI, the PRMC Chair and UHCC Compliance.

VII. Quality Assurance, Monitoring and Auditing and Risk Management

The UHCC Compliance Director is the administrator of the Quality Assurance Committee (QAC) for the HCC. Meetings are quarterly. Membership is open to all members of the HCC. Meetings are conducted via webinar. The purpose of the committee is to provide oversight and monitoring of clinical trial activity and collaborate on issue identification and facilitation of resolution. Members receive monitoring information on study status, identified issues and corrective action plans. Members are expected to return information to their institution for additional dissemination as appropriate and issue awareness. QAC minutes are provided to the DSMC for additional review and evaluation.

UHCC Compliance Director monitors all deviations, serious adverse events, regulatory, or Good Clinical Practice issues for compliance and quality assurance and reports out to QAC, DSMC and Senior Leadership as appropriate.

All Center-generated or supported protocols approved by the PRMC that have been activated to subject accrual are subject to audit by the UHCC Compliance Director as part of the UHCC Data and Safety Monitoring Plan. All external audits are reviewed. Follow up and reporting up is completed by the UHCC Compliance Director with appropriate staff, managers or supervisors. UHCC Compliance provides education and training in areas identified as appropriate or requested.

The intent of all audits is to function in the role of quality assurance to protect human subjects, assess protocol, research and regulatory compliance and evaluate staff
training and process needs. Audits are never retaliatory or punitive and are to be used as a guide for quality, process or safety improvements.

VIII. Review and Approval of PRMS Plan

The Plan for the PRMS will be reviewed at a minimum of every two years by the UHCC Human Subjects Research Compliance Director, Associate Director of Translational and Clinical Research Services, HCC Leadership and the PRMC. This review of the current process and procedures will be conducted at HCC and PRMC meetings in the fourth quarter of the year. Recommendations for changes in the Plan or processes will be discussed and voted on by the consortium members. If revised, the PRMS Plan will be released no later than the first quarter of the following year.