Standard Operating Procedures for Protocol Submission and Review

1. Purpose

1.1. To define the process of protocol review for clinical research activity under the purview of the DLDCCC.
1.2. To assure that cancer related clinical research is undertaken in the most scientifically sound manner, consistent with the guidelines developed for NCI designated cancer centers.
1.3. Authority for DLDCCC review of clinical cancer related protocols, including initiation, monitoring and termination, has been delegated by the DLDCCC Director to reside with the PRMC. The DLDCCC Director is informed of all approval and termination actions. The PRMC Chair will inform the investigator of all PRMC decisions, including any relevant comments, in writing.

2. Scope

2.1. This policy applies to all cancer related clinical research within the institutions that comprise the DLDCCC.
2.2. All interventional clinical trials whose primary aim is cancer related, or whose primary target population is cancer patients, must receive approval from by the Protocol Review and Monitoring Committee (PRMC) before subject accrual may begin.

3. Definitions and Abbreviations

3.1.	PRMC	Protocol Review and Monitoring Committee
3.2.	BCM	Baylor College of Medicine
3.3.	BRAIN	Biomedical Research and Assurance Information Network
3.4.	DLDCCC	Dan L Duncan Comprehensive Cancer Center
3.5.	IRB	Institutional Review Board
3.6.	PI	Principal Investigator
3.7.	DWG	Disease Working Group
3.8.	PSO	Patient Safety Officer, who serves as the PRMC Coordinator
3.9.	NCI	National Cancer Institute
3.10.	IIT	Investigator-Initiated Trial
3.11.	CCGT	Center for Cell and Gene Therapy

4. Materials and Equipment None

5. Protocol Review

5.1. Overview of Review Process
  5.1.1. All DLDCCC interventional clinical trials whose primary aim is cancer related, or whose primary target population is cancer patients, must receive approval from the PRMC.
    5.1.1.1. Single-patient studies do not need PRMC review.
  5.1.2. Subject accrual may not begin until PRMC approval is obtained.

5.1.3. PRMC review prior to IRB submission is strongly preferred but not required.
5.1.4. PRMC review will take place after review by the appropriate Program or DWG; the Program/DWG recommendations will be included with the protocol submission to the PRMC.

5.2. First Stage: Program or DWG Review
5.2.1. The PI must submit the protocol to the appropriate Program or DWG for review.
5.2.2. The Program/DWG will discuss the study's priority, scientific merit, rationale, study design, prioritization, feasibility for completion within a reasonable time frame, and potential duplication of studies already in progress.
5.2.3. Studies will be reviewed by the appropriate Program or DWG.
5.2.3.1. Pediatric studies will be reviewed by the Pediatric Program
5.2.3.2. CCGT studies will be reviewed by the CCGT Program.
5.2.3.3. Breast cancer studies will be reviewed by the Breast Program.
5.2.3.4. Other adult studies will be reviewed by the appropriate DWG as determined by the DLDCCC Associate Director for Clinical Research.
5.2.4. The Program/DWG recommendations will be recorded on the Scientific Review Score Sheet (Appendix A); the PI will include the completed Score Sheet with the protocol submission to the PRMC.

5.3. Second Stage: PRMC Review
5.3.1. It is highly recommended that the PI submit the protocol to the PRMC before submitting to the IRB, especially for IITs.
5.3.1.1. At a minimum, the IRB protocol summary (in BRAIN ESP1) must be completed (in draft mode) before the protocol is submitted to the PRMC, as the PRMC module pulls the protocol information from the ESP1 IRB module.
5.3.2. The complete submission packet will be submitted to the PRMC via the BRAIN PRMC module. Detailed instructions can be found at the PRMC website (see Section 7.2). The submission must include each of these items:
5.3.2.1. PRMC Initial Review Coversheet, completed within BRAIN.
5.3.2.2. Protocol's BRAIN eSP-1 summary report, as submitted to the IRB (or as to be submitted).
5.3.2.3. Scientific Review Score Sheet, completed by the Program/DWG.
5.3.2.4. Full protocol, as submitted to the IRB (or as to be submitted). For PRMC review, interventional trials must have a separate protocol document, including (at a minimum) sections for background, procedures, statistics, and data safety monitoring.
5.3.3. The PSO will review the submission for completeness. Incomplete submissions will be returned to the PI.

5.4. Review Path Determination
5.4.1. The PRMC Chair or designee will review the submission to determine whether the protocol requires PRMC review or is exempt.

5.4.1.1. If a submitted protocol is determined to be exempt, the PSO will notify the PI that the protocol is exempt from both initial and continuing PRMC review.

5.4.2. If the protocol requires PRMC review, the PRMC Chair (or designee) and PSO will determine whether the protocol qualifies for expedited review (Section 5.5), or requires full review (Section 5.6).

5.5. Expedited Review

5.5.1. A protocol is eligible for expedited review if it meets one of the following criteria:

5.5.1.1. Approved by the NCI Cancer Therapy Evaluation Program (CTEP) or Cancer Prevention and Control Protocol Review Committee.

5.5.1.2. Approved and supported by a Funding Organization with Approved Peer Review and Funding Systems, as defined by the NCI. (See Reference 7.3.)

5.5.1.3. Approved by the lead site's PRMC, for multi-site institutional trials. (See Reference 7.4.) The local PI must obtain a copy of the lead site's PRMC approval, and provide that to the DLDCCC PRMC with the submission.

5.5.1.4. The PRMC may designate a study as eligible for expedited review if it is determined that there has been a suitable external peer review process.

5.5.2. The Chair (or designee) will assign a PRMC member as the single Reviewer; the PSO will notify the Reviewer of this assignment. The Reviewer will review the study for:

5.5.2.1. Prioritization within the DLDCCC

5.5.2.2. Competing studies

5.5.3. The possible actions during expedited review are the same as for full review (see Section 5.6.7). The PI will be informed of the PRMC's decision in writing.

5.5.4. The protocol may be re-assigned to the full review path at the discretion of either the Reviewer or the PRMC Chair, if he/she feels that full review is warranted.

5.5.5. Protocols that are approved via the expedited pathway will be added to the agenda and minutes of the next Executive Committee meeting.

5.6. Full Review

5.6.1. Once the complete submission packet has been received and the protocol has been assigned to full review, the protocol will be assigned to a PRMC meeting based on the date the submission was received.

5.6.2. The Chair (or designee) will assign a primary reviewer, a secondary reviewer, and a statistical reviewer. The PSO will notify the assigned reviewers of their assignments.

5.6.3. The protocol will be distributed to all PRMC members for review prior to the meeting.

5.6.4. Quorum will consist of 50% of PRMC voting members, and final outcomes will be determined by a majority decision.

5.6.5. The PRMC will review the protocol and the Program/DWG recommendations.

5.6.6. The PI may be invited to the meeting at the committee's discretion; the PI, members of the study team, and any conflicted PRMC members will be excused before the final discussion and vote.

5.6.7. Possible determinations are:

5.6.7.1. Approved: Protocol is fully approved. Subject accrual may begin once all other appropriate regulatory approvals are obtained (e.g., IRB, FDA, etc.).

5.6.7.2. Approved with Modifications: Protocol requires minor clarifications or a response to concerns, but does not need to be re-reviewed by the full committee. The Chair or designee may approve the response, or may request that the committee review the response at the next meeting.

5.6.7.3. Tabled: Protocol requires significant modifications and/or the PRMC has significant concerns. The investigator must make the required modifications, and submit the revisions and/or a response. The response will be reviewed at the next PRMC meeting, and the committee will again vote on the appropriate action.

5.6.7.4. Disapproved: A protocol that is disapproved will not be reconsidered.

5.6.8. The PI will be informed in writing of the committee's decision, including any relevant comments and any required action or reply.

5.6.9. If the protocol is Approved with Modifications or Tabled, the PI must respond within 90 days. If no response has been received in that time, the protocol will be disapproved.

5.7. Exceptions for Pre-Approval Enrollments

5.7.1. Exception Condition A: Protocols under NCI CIRB Review:

5.7.1.1. As these protocols have undergone NCI CTEP review, they will be eligible for expedited PRMC review as outlined in Section 5.5.

5.7.1.2. If a protocol is being opened under the NCI CIRB as the IRB of record, limited local accrual may begin before PRMC approval once the protocol has met other institutional requirements for accrual.

5.7.1.3. The PI may accrue up to three (3) subjects before obtaining PRMC approval. A request for this exception is not required.

5.7.1.4. An exception is not final approval, and the protocol will continue the remainder of its course through the PRMC approval process.

5.7.2. Exception Condition B: Protocols under IRB Review other than NCI CIRB:

5.7.2.1. In rare instances where a protocol has been approved by the IRB of record and recommended by the Program/DWG, but the PRMC has not yet approved the protocol, the PI may request an exception to accrue up to three (3) subjects prior to final PRMC approval.

5.7.2.2. The request from the PI must include justification for the exception.

5.7.2.3. The enrollment exception will be granted by the PRMC Chair or designee.

5.7.2.4. The PI will be notified of the decision in writing.

5.7.2.5. An exception is not final approval, and the protocol will continue the remainder of its course through the PRMC approval process.

5.8. Study Prioritization
- 5.8.1. The PRMC will oversee the prioritization of competing protocols for use of DLDCCC resources (e.g., personnel and patients) from all sources, including cooperative group trials and industry trials, thereby ensuring optimal use of clinical resources for scientific purposes.
- 5.8.2. All approved studies under Full Review will be assigned two scores at the time of approval:
  - 5.8.2.1. Priority Score: High, Medium, or Low
  - 5.8.2.2. Scientific Merit Score: 1-Exceptional, 2-Outstanding, 3-Excellent, 4-Very Good, 5-Good, 6-Satisfactory, 7-Fair, 8-Marginal, 9-Poor
- 5.8.3. All approved studies under Expedited Review will be assigned a Priority Score; Merit score is not required.

5.9. Continuing Review
- 5.9.1. Once a protocol is approved, it will be reviewed by the PRMC on a periodic basis to monitor study progress.
- 5.9.2. The review will occur at least annually; the PRMC may also decide to conduct review more frequently, e.g., after a certain number of months, or after a certain number of enrollments.
- 5.9.3. The PI should submit the protocol for PRMC continuing review at the same time as the IRB renewal, or as required by the PRMC.
- 5.9.4. If the protocol has permanently closed to accrual since its last review, that should be noted on the submission to the PRMC, including the date of closure and the reason.
  - 5.9.4.1. Once a protocol has closed to accrual, and has been submitted to the PRMC as closed to accrual, future PRMC reviews are no longer required, even if the study remains open with the IRB for ongoing study activities.
- 5.9.5. Possible outcomes are the same as for initial review (Section 5.6.7).
  - 5.9.5.1. If the PRMC determines that accrual or other aspects of scientific progress are insufficient, the PRMC may take action that it deems appropriate, up to and including requiring that the protocol be permanently closed to subject accrual.
  - 5.9.5.2. The PRMC may also determine that continuing review is no longer necessary.
- 5.9.6. Continuing reviews will be discussed at the PRMC meetings, and the discussion and vote will be part of the meeting minutes.
- 5.9.7. The PI will be notified the committee's decision in writing, including any required action or reply.

5.10. Amendment Review
- 5.10.1. The PRMC will review all amendments that involve a significant scientific change in the protocol. This includes, but is not limited to:
  - 5.10.1.1. Change in BCM Principal Investigator.

5.10.1.2. Change in or addition of a primary objective of the study.
5.10.1.3. Change in a BCM IIT to become multicenter or if BCM becomes the coordinating center.
5.10.1.4. Addition or deletion of a study arm.
5.10.1.5. Major change in eligibility criteria.
5.10.1.6. Addition or deletion of a therapeutic or supportive agent, or major change in administration schedule if the change is due to a change in scientific or safety design.
5.10.1.7. Change in the number of subjects to be accrued if it is due to a change, addition, or deletion of an objective, or due to the results of an interim analysis.
5.10.1.8. Non-administrative changes (such as above) required by an IRB or DSMC/DRC/DSMB.

5.10.2. The following amendments do not require PRMC review:
5.10.2.1. Amendments to protocols that qualify for Expedited Review as defined in Section 5.5.1.
5.10.2.2. Administrative amendments.

5.11. Documentation
5.11.1. The DLDCCC will maintain central PRMC files for:
5.11.1.1. Minutes from Working Group meetings.
5.11.1.2. All correspondence related to the protocol's initial and ongoing reviews, including protocol submissions, correspondence to and from the PI, and PRMC approval letters.
5.11.1.3. Minutes from PRMC meetings.
5.11.1.3.1. Minutes will include a brief description of the discussion, any issues of concern, any abstentions or recusals, assigned Merit and Priority Scores, and the determination/action of the committee.
5.11.1.3.2. The PRMC minutes will be forwarded to the DLDCCC Director.
5.11.2. Administrative and expedited approvals that occur between meetings will be added to the agenda and minutes of the next meeting, as documentation of the action.
5.11.3. PRMC actions and determinations will be captured in the DLDCCC database.

6. Conflicts of Interest
6.1. Any PRMC members who are in conflict with a study under review cannot serve as a reviewer, and must abstain/recuse from the final discussion and vote of that study.

7. References
7.1. These procedures were developed in accordance with the NCI CCSG guidelines for protocol review and monitoring, as required for all NCI cancer centers.
7.2. DLDCCC PRMC Website: https://www.bcm.edu/centers/cancer-center/research/clinical-research/protocol-review-and-monitoring-committee

7.3. NCI Funding Organizations with Approved Peer Review Funding Systems: https://cancercenters.cancer.gov/documents/PeerReviewFundingOrganizations508C.pdf
7.4. Cancer Center Support Grants (CCSGs) for NCI-Designated Cancer Centers (P30)
7.5. NIH Definition of clinical trial: https://grants.nih.gov/faqs#/clinical-trial-definition.htm

8. Appendices

Appendix A: Program/DWG Score Sheet

Appendix B: What is a clinical trial?

The following questions should be used to determine whether a study meets the NIH clinical trial definition:

- Does the study involve human participants?
- Are the participants prospectively assigned to an intervention?
- Is the study designed to evaluate the effect of the intervention on the participants?
- Is the effect being evaluated a health-related biomedical or behavioral outcome?

If the answers are all “yes,” the study is a clinical trial.
If any answers are “no,” the study is not a clinical trial