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.	DLDCCC	Dan L Duncan Comprehensive Cancer Center
3.4.	IRB	Institutional Review Board
3.5.	PI	Principal Investigator
3.6.	DWG	Disease Working Group
3.7.	PSO	Patient Safety Officer, who serves as the PRMC Coordinator
3.8.	NCI	National Cancer Institute
3.9.	IIT	Investigator-Initiated Trial
3.10.	CCGT	Center for Cell and Gene Therapy
3.11.	ePRMS	ePRMS module in OnCore

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 and other expanded access studies do not need PRMC review. Expanded access studies should be presented to the appropriate Disease Working Group.

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 Disease Working Group (PWG or DWG) Review

5.2.1. Each WG is composed of individuals involved in the development or conduct of clinical trials in the specific program or disease area, including clinical investigators, research coordinators, and clinical research operations and regulatory staff. Additional members, such as pharmacists and biostatisticians, may be recruited as appropriate. Of note, for investigator-initiated trials a biostatistician is required to be involved at the PWG/DWG stage during protocol development, prior to PRMC submission. PWG/DWG leaders are appointed by the Associate Director of Clinical Research. Working group meetings are coordinated and supported by a Review Group Coordinator provided by the CTSU, who maintains the documentation generated during this first phase of review.

5.2.2. The PI must submit the protocol to the appropriate Program or DWG for review.

5.2.3. 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.

5.2.4. Studies will be reviewed by the appropriate Program or DWG.

5.2.4.1. Breast Cancer Program: Clinical trials that are targeted to non-pediatric breast cancer patients, excluding those that utilize cell and gene therapy products.

5.2.4.2. DWG: Clinical trials that are targeted to non-pediatric patients with diseases other than breast cancer, excluding those that utilize cell and gene therapy products.

5.2.4.3. Pediatric Cancer Program: Clinical trials that are targeted to pediatric patients, excluding those that utilize cell and gene therapy products.

5.2.4.4. Cell and Gene Therapy (CCGT) Program: Adult and pediatric clinical trials that utilize cell and gene therapy, defined as those which involve the infusion of whole cells or vectors designed to modify the existing genetic structure of cells in subjects, target hematopoietic stem cell transplant patients, or are ancillary to cell or gene therapy studies.

5.2.5. 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. The PRMC co-Chairs are appointed by and report to the Director of the Cancer Center. Members are appointed by the PRMC co-chairs in consultation with the Director. PRMC members comprise a broad range of both clinical and basic scientists, with expertise in adult hematology and oncology, pediatric hematology and oncology, cell and gene therapy, biostatistics, pathology, surgical oncology, and regulatory affairs. Individuals are selected based on their scientific and clinical research expertise. In addition, more junior members are appointed for their individual expertise and are mentored by the PRMC co-chairs to develop a cohort of experienced members for the future. Initial appointments to the PRMC are for 2 years with the possibility of re-appointment. If additional expertise is necessary to conduct a thorough scientific review, an ad hoc reviewer may be solicited from another Working Group or the wider DLDCCC membership. At least one member of the COE, with expertise in issues related to underrepresented populations in research, must be a member of the PRMC. Moreover, the PRMC must include at least one individual serving as a patient advocate. Care is taken to ensure that Committee membership does not duplicate the Data Review Committee (DRC) Committee roster.
Additional PRMC members include the Director of the Clinical Trials Support Unit (CTSU; ex officio), the administrative coordinators of each working group (ex officio), the Associate Director of Clinical Research of the Cancer Center or his/her designee (ex officio), and other at large members that may be appointed. The PRMC is supported by CTSU, who provides a Patient Safety Officer, who is responsible for the administrative management of submitted clinical trials, coordination of meetings, and recording of review outcomes.

5.3.2. It is highly recommended that the PI submit the protocol to the PRMC before submitting it to the IRB, especially for IITs. The latter are also encouraged to be presented at the IIT incubator.

5.3.3. The complete submission packet will be submitted to the PRMC via ePRMS in OnCore. Detailed instructions can be found at the PRMC website (see Section 7.2). The submission must include each of these items:

- 5.3.3.1. As described in the ePRMS Submitter instructions, the minimum fields must be completed in ePRMS.
- 5.3.3.2. DWG/Program Clinical Trial Score Sheet, completed by the Program/DWG.
- 5.3.3.3. 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 and safety monitoring.
- 5.3.3.4. Data and safety monitoring plan: If the protocol document does not contain a DSMP, a separate DSMP must be submitted.
- 5.3.3.5. PRMC approval from the Lead Site (if applicable): The PRMC will rely on the external PRMC approval from the Lead Site to approve the study.

5.3.4. 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 PRMC 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. The PRMC will meet twice a month.

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 at the meeting will consist of a number of voting members that represents at least 50% of PRMC primary members, and final outcomes will be determined by a majority decision.
5.6.4.1. There will be an equal number (or differing by one) of primary and alternate members. An alternate member can substitute for a principal member if any of the latter are unable to attend.
5.6.4.2. Either principal or alternate members can be assigned reviews.
5.6.4.3. If a member has submitted a review, that person will be counted towards the quorum for a meeting.
5.6.5. The PRMC will review the protocol and the Program/DWG recommendations.
5.6.6. At the Committee's discretion, the PI may be invited to the meeting to present their trial; 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 a minimum within 12 months of the prior review or more frequently as required by 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. Subsequent review intervals are determined at the time of initial or continuing review. After the initial ramp-up period (quarters 5+), the accrual rate of a trial should be at least 50% of the planned rate, otherwise the PI will be queried and asked to provide a corrective action plan. If the average accrual rate beyond an additional 6 months (i.e., quarter 7+) remains below 50% of planned, then the investigator will be required to justify the trial's continued feasibility and relevance, and the trial may have to be amended to reflect a sample size and statistical plan compatible with this new accrual rate.

5.9.6. Possible outcomes are the same as for initial review (Section 5.6.7).

5.9.6.1. 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.

5.9.6.1.1. If at steady state, accrual rates are substantially below the planned rate (i.e. <25%) the trial will be closed unless there is a compelling reason for it to remain open.

5.9.6.1.2. For studies where accrual is expected to be slow and/or sporadic (examples are rare diseases such as pediatric cancer, studies of orphan therapies, or trials involving targeted therapies where the prevalence of the target determines the accrual rate) strict accrual rate criteria are not applied although monitoring for progress is still performed.

5.9.6.2. The PRMC may also determine that continuing review is no longer necessary, or that a protocol is exempt from accrual queries at continuing reviews.

5.9.7. Continuing reviews will be discussed at the PRMC meetings, and the discussion and vote will be part of the meeting minutes.

5.9.8. 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. PRMC requires that a tracked changes version of the protocol or a detailed summary of changes be submitted as part of the amendment review process. Significant scientific changes in the protocol include, but are 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. All correspondence related to the protocol's initial and ongoing reviews, including protocol submissions, correspondence to and from the PI, and PRMC approval letters.
5.11.1.2. Minutes from PRMC meetings.
5.11.1.2.1. 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.
5.11.1.2.2. 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/sites/default/files/PeerReviewFundingOrganizations.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. Appendix

Appendix A: Program/DWG Score Sheet

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Appendix A: Program/DWG Score Sheet

DWG/Program Clinical Trial Review Score Sheet		
Complete the green cells.		
Section A: Investigator to complete before the meeting.		
Disease Working Group or Program:		
Principal Investigator:		
Study ID and Title:		
Sponsor:		
Which local sites will participate? Select all that apply.	__ BCM / BSLMC (including McNair and/or Hospital) __ HHS (including Ben Taub and/or Smith Clinic) __ Houston Methodist Hospital __ MEDVAMC __ Texas Children's Hospital	
Including all sites selected above, how many subjects are expected to be accrued?		
Per year:		
Total:		
Expected duration of accrual (months):		
Are you requesting to use the CRC? (yes / no)		
What is the study type? Select one type from the "Protocol Types" tab.		

Is this study eligible for expedited PRMC review? - approved by NCI CTEP, or - supported by an NIH funding mechanism (e.g., R01, U01, U10 etc) which required full peer review as part of the funding, or - approved by the lead site's PRMC (if the lead site is a NCI designed cancer center)			
If the study has no (or inadequate) external funding, are you requesting DLDCCC support to conduct the study? Are there any competing studies (Y/N)? If Y, please describe			
Section B: DWG/Program to complete	**NOTE: for Expedited Review protocols, B1-B4 are not required**		
Date of Review			
	Score range	**Max Score**	**Assigned Score**
B1. Impact			
Does the study address a question that is important in the field	1 = least important, 5 = most important	5	
Does the study address an important catchment area issue? (disease, race/ethnicity, patient age)	1 = least important, 5 = most important	5	
Is the study strategically important for the program	1 = least important, 5 = most important	5	
Is the study important for PI career development	1 = least important, 3 = most important	3	
What is the sponsor type?	5 = BCM investigator initiated 3 = NCI NCTN 2 = other NCI cancer center 1 = Industry	5	
	Max score	23	**0**

B2. Study Design			
Are the objectives clearly stated?	1= least clear, 3 = most clear	3	
Does the background justify the reasons for conducting the study (e.g. is there sound scientic rationale)?	1 = least, 3 = most	3	
Is the study design appropriate to answer questions posed by the objectives?	1= least appropriate, 3 = moderately appropriate, 5 = most appropriate	5	
Are the outcome measures* appropriate and consistent with the study objectives? (* response criteria, toxicity criteria, etc)	1= least appropriate, 2 = moderately appropriate, 3 = most appropriate	3	
Are the eligibility (inclusion/exclusion) criteria clear?	1= least clear, 3 = most clear	3	
Is the definition of course length clear in the protocol?	1= least clear, 3 = most clear	3	
	Max score	20	**0**
B3. Feasibility			
Can the protocol interventions be delivered at this institution with current facilities/resources/expertise?	1 = unlikely, 2 = plausible, 3 = yes	3	
Can the anticipated requirements for research nurse/coordinator, Pharmacy and/or Data Management be met with current resources?	1 = unlikely, 2 = plausible, 3 =yes	3	
Is study accrual/completion likely within the stated time frame?	1 = unlikely, 2 = plausible, 3 = highly likely	3	
Are all tissue collection issues addressed?	1 = no, 2 = yes	2	
Is funding adequate?	1 = inadequately funded, 3 = borderline, 5 = adequately funded	5	
Are there competing studies	1 = no, 0 = yes	1	
	Max score	17	**0**

B4. Total Score	Max possible total score	60	**0**

Section C. DWG/Program Determination		
C1. Comments to PI	**NOTE: for Expedited Review protocols, C1 is not required.**	
Summary of comments and suggestions to the PI. If this is an IIT, include suggested protocol revisions to be made before submitting to PRMC.		

C2. DWG/Program Recommendation to PI (select one)		
Approved to submit to PRMC		
Defer for revisions		
Disapproved (study not to be submitted to PRMC)		

C3. DWG/Program Priority (select one)		
High		
Middle		
Low		