# 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.

## 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 patient enrollment.

## 3. Definitions and Abbreviations

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| 3.1. | PRMC | Protocol Review and Monitoring Committee, which is comprised of the Executive Committee and the three working groups |
| 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 for BCM-affiliated institutions |
| 3.6. | PI | Principal Investigator |
| 3.7. | WG | Working Group of the PRMC |
| 3.8. | EC | Executive Committee of the PRMC |
| 3.9. | AC | Administrative Coordinator |
| 3.10. | NCI | National Cancer Institute |
| 3.11. | RAC | Recombinant DNA Advisory Committee |
| 3.12. | CRC | Clinical Research Center at BCM |

## 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 Protocol Review and Monitoring Committee (PRMC) before patient enrollment.
5.1.1.1. The following types of protocols do not need PRMC review:
5.1.1.1.1. Single-patient studies
5.1.2. **Subject accrual may not begin until PRMC approval is obtained.**
5.1.3. PRMC approval prior to IRB submission is strongly preferred but not required.

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## 5.2. Submission for Initial Protocol Review

5.2.1. The complete submission packet must include each of these items:

5.2.1.1. **PRMC Initial Review Coversheet**, completed within BRAIN.

5.2.1.2. **Protocol's BRAIN eSP-1 summary report**, as submitted to the IRB (or as to be submitted).

5.2.1.3. **Consent form**, as submitted to the IRB (or as to be submitted).

5.2.1.4. **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.

5.2.2. The PI must submit the protocol to the appropriate WG via the PRMC module in BRAIN:

5.2.2.1. **Cell and Gene Therapy (CAGT)**: All adult and pediatric protocols that meet one or more of these criteria must go to the CAGT WG:

- involve the infusion of whole cells or vectors designed to modify the existing genetic structure of cells in subjects
- target hemopoietic stem cell transplant patients
- are ancillary to cell or gene therapy studies
- require RAC review.

5.2.2.2. **Pediatric:** All protocols that target patients less than or equal to the age of 21 and that do not involve cell or gene therapy.

5.2.2.3. **Adult:** All protocols that target patients over the age of 21 and that do not involve cell or gene therapy.

5.2.3. It is highly recommended that the PI submit the protocol to the PRMC before IRB submission. At a minimum, the IRB protocol summary (in eSP-1 module) must be completed (in draft mode) before the protocol is submitted to the PRMC, as the PRMC module pulls the information from the eSP-1 IRB module.

5.2.4. All protocol components in the eSP-1 module will be available to the PRMC reviewer. If needed, additional attachments can be added in the PRMC module.

5.2.5. Detailed instructions for submitting via the PRMC module can be found at the PRMC website (see Section 9.2)..

## 5.3. Review Path Determination

5.3.1. The WG Chair (or designee) and AC will review the submission to determine whether it has been submitted to the correct WG. If not, the AC will reassign the protocol to the correct WG and notification will be sent to the PI.

5.3.2. The WG Chair (or designee) and AC will review the submission to determine whether the protocol requires PRMC review or is exempt.

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

5.3.3. If the protocol requires PRMC review, the WG Chair (or designee) and AC will determine whether the protocol qualifies for expedited review (Section 5.4), or requires full review (Sections 5.5 and 5.6).

5.4. **Expedited Review**

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

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

5.4.1.2. Approved and supported by a Funding Organization with Approved Peer Review and Funding Systems, as defined by the NCI. (See Reference 9.3.)

5.4.1.3. Approved by the lead site's PRMC, for multi-site institutional trials. (See Reference 9.4.) The local PI must obtain a copy of the lead site's PRMC approval, and provide that to the DLDCCC PRMC.

5.4.1.4. 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.

5.4.2. The WG Chair (or designee) will review the study for:

5.4.2.1. Prioritization within the DLDCCC

5.4.2.2. Competing studies

5.4.3. After this review, the WG Chair (or designee) will forward his/her recommendation to the PRMC Chair (or designee), who will review the recommendation with particular attention to prioritization.

5.4.4. The possible actions during expedited review are the same as for full review (see Section 5.6.4). The PI will be informed of the PRMC's decision in writing.

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

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

5.5. **Full Review – Working Group**

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

5.5.2. The AC will notify the PI of the WG review date. The PI will be invited to attend that meeting to participate in the discussion of his/her protocol; however, his/her attendance is not required.

5.5.3. The protocol will be assigned a primary reviewer, a secondary reviewer, and a biostatistical reviewer.

5.5.4. The protocol will be distributed to all WG members for their review prior to the meeting.

5.5.5. At the meeting, the WG will discuss the scientific merit, rationale, study design, adequacy of biostatistics, feasibility for completion within a reasonable time frame (particularly with respect to subject accrual), prioritization, and potential duplication of studies already in progress at DLDCCC facilities.

5.5.6. During the review, the PI and/or co-investigator(s) may attend the meeting and participate in the discussion at the request of the committee. However, all investigators and conflicted reviewers must leave the room during the final discussion and vote.

5.5.7. The WG may take one of the following actions:
- 5.5.7.1. Recommend Approval: The WG has no concerns, or previous concerns have been addressed. Protocol will be forwarded to EC with a recommendation for full approval.
- 5.5.7.2. Approve with Modifications: Protocol requires minor clarifications or a response to concerns, but does not need to be re-reviewed by the full WG. The WG Chair or designee may approve the PI's response, or may request that the full WG review the response at the next meeting.
- 5.5.7.3. Table: Protocol requires significant modifications and/or the WG has significant concerns. The PI must make the required modifications, and submit the revisions and/or a response to the WG. The response will be reviewed at the next WG meeting, and the WG will again vote on the appropriate action.
- 5.5.7.4. Recommend Disapproval: The WG has serious concerns about the protocol. The protocol will be forwarded to the EC with a recommendation for disapproval.

5.5.8. The PI will be notified of the WG's decision in writing, including any required action or reply.

5.5.9. If a protocol is Approved with Modifications or Tabled, the PI must respond within three months. If no reply has been received within that time, the protocol will be disapproved.

5.5.10. Once the WG has decided on a recommendation, the protocol will be forwarded for review and final action by the EC (Section 5.6).

5.6. **Full Review – Executive Committee**

5.6.1. Once the WG has made a recommendation, the protocol will be assigned to an EC meeting for final review.

5.6.2. Quorum will consist of 50% of EC members and final outcomes will be determined by majority decision.

5.6.3. The EC will review the protocol and WG correspondence and recommendations. The PI may be invited to the meeting at the EC's discretion.

5.6.4. Possible outcomes include:
- 5.6.4.1. Approved: Protocol is fully approved. Patient accrual may begin once all other appropriate regulatory approvals are obtained (e.g., IRB, FDA, etc).
- 5.6.4.2. 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.
- 5.6.4.3. Tabled: Protocol requires significant modifications and/or the EC 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 committee meeting, and the committee will again vote on the appropriate action.
- 5.6.4.4. Disapproved: A protocol that is disapproved will not be reconsidered.

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

5.7. **Exceptions for Pre-Approval Enrollments**

5.7.1. Exception Condition A: Protocols under BCM IRB Review:

5.7.1.1. In rare instances where a protocol has been approved by the IRB and by the WG, but the EC has not yet reviewed the protocol, the PI may request an exception to enroll no more than three (3) subjects prior to final PRMC approval.

5.7.1.2. The PI must include justification for the exception.

5.7.1.3. The enrollment exception will only be granted with the concurrence of both the WG Chair (or designee) and PRMC Chair (or designee).

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

5.7.1.5. 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 NCI CIRB Review:

5.7.2.1. If a protocol is being opened under the NCI CIRB, limited local accrual may begin before PRMC approval once the protocol has met other institutional requirements for accrual (i.e., IRB review).

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

5.7.2.3. An exception is not final approval, and the protocol will continue the remainder of its course through the PRMC approval process. As these protocols will have undergone NCI CTEP review, they will be eligible for expedited PRMC review as outlined in Section 5.4.

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 EC on a periodic basis. The review will occur at least annually; the EC may also decide to conduct review more frequently, e.g., after a certain number of months, or after a certain number

of enrollments. The EC will also determine whether amendments to the protocol will be reviewed (see Section 5.11).

5.9.2. The PI should submit the protocol for PRMC continuing review at the same time as the IRB renewal.

5.9.3. Continuing reviews are submitted directly to the EC.

5.9.3.1. If the protocol was initially submitted in BRAIN, the continuing review must be submitted in BRAIN.

5.9.3.2. If the protocol was initially submitted prior to the availability of the BRAIN module, the PI must submit the PRMC Continuing Review Coversheet and the IRB Renewal Report, as per the instruction on the coversheet.

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, the PRMC will acknowledge that the study is no longer subject to PRMC Continuing Review. Future PRMC reviews are no longer required at that point, 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 5.6.4). 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. The PRMC may also determine that continuing review is no longer necessary.

5.9.6. Continuing reviews will be discussed at the EC 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 scientific objective of the study.

5.10.1.3. Change in a BCM initiated study to become multicenter or 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. Suspension of accrual due to concerns of an IRB or DSMC/DRC/DSMB.

5.10.2. Amendments are submitted directly to the EC.

5.10.2.1. If the protocol was initially submitted in BRAIN, the amendment must be submitted in BRAIN.

5.10.2.2. If the protocol was initially submitted prior to the availability of the BRAIN module, the PI must submit the PRMC Amendment Review Coversheet and must include a copy of the amended materials (e.g., protocol, consent form, etc.), as per the instructions on the coversheet.

5.10.3. The following amendments do not require PRMC review:

5.10.3.1. Amendments to protocols that qualify for Expedited Review as defined in Section 5.4.1.

5.10.3.2. Administrative amendments.

5.10.3.3. Amendments to the consent form, except those that are the result of changes outlined in Section 5.11.1.

5.11. **Documentation**

5.11.1. The DLDCCC will maintain central PRMC files for:

5.11.1.1. Complete protocol packets, including the original packet submission, correspondence to the PI, replies/revisions from the PI, and WG and final PRMC approval letters.

5.11.1.2. Minutes from Working Group meetings.

5.11.1.3. Minutes from Executive Committee 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. The EC 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. **Concept Review**

6.1. Prior to submitting a full protocol for review, an investigator may submit a clinical trial concept to the PRMC. The purpose of this review is to provide the investigator with feedback and guidance about the study design and feasibility early in the protocol development process.

6.2. This review is available for any investigator initiated trial, but is not required.

6.3. The concept submission should include this information:

6.3.1. Hypothesis

6.3.2. Objective(s)

6.3.3. Background information

6.3.4. Subject eligibility criteria

6.3.5. Treatment regimen and schema
6.3.6. Study calendar, with research items noted
6.3.7. Statistical design, including endpoint(s), stratifications, sample size with power calculation, analysis plan, and expected accrual rate.
6.3.8. Feasibility
6.3.9. Investigational agent(s) to be used
6.3.10. Correlative studies, if applicable

6.4. Concepts are submitted to the appropriate Working Group. The WG provides its feedback to the investigator. The WG chairs will inform the EC of the WG's review and feedback. If the EC has additional feedback, it will be provided to the investigator.
6.5. The concept is not formally approved nor disapproved
6.6. Once the concept is developed into a full protocol, the protocol must go through the standard protocol review process as outlined above.

## 7. Conflicts of Interest

7.1. At all steps during the review process, any committee member (WG or EC) who is 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.

## 8. Authority

8.1. **Cancer related clinical trials may not begin subject accrual until approval by the Protocol Review and Monitoring Committee (PRMC) has been obtained.**
8.2. 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.

## 9. References

9.1. These procedures were developed in accordance with the NCI CCSG guidelines for protocol review and monitoring, as required for all NCI cancer centers.
9.2. DLDCCC PRMC Website: https://www.bcm.edu/centers/cancer-center/research/clinical-research/protocol-review-and-monitoring-committee
9.3. NCI Funding Organizations with Approved Peer Review Funding Systems: https://cancercenters.cancer.gov/documents/PeerReviewFundingOrganizations508C.pdf
9.4. CCSG Notice of Correction to PAR-13-386 (08/19/2016), Notice Number NOT-CA-16-038.