**Protocol Review & Monitoring System (PRMS)**

# Scientific Review Committee (SRC)

**Policies and Procedures**

Fred & Pamela Buffett Cancer Center

# CONTACT INFORMATION

## ASSOCIATE DIRECTOR FOR CLINICAL RESEARCH

Apar Kishor Ganti, M.D.

## PRMS SRC LEADERSHIP

Tanya Wildes, MD, MSCI. Chair
Adrian Black, Ph.D. Vice-Chair

## SRC MEMBERS

A list of current members is available in the PRMS Office.

## PRMS OFFICE STAFF

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## PRMS OFFICE WEBSITE

Protocol Review and Monitoring System | The Fred & Pamela Buffett Cancer Center | University of Nebraska Medical Center (unmc.edu)

## SEARCHABLE WEBSITE OF ACTIVE CLINICAL TRIALS

https://www.nebraskamed.com/clinical-trials/cancer-clinical-trials

## Previous Revisions:

Version 1.0, September 26, 2003
Version 2.0, August 12, 2004
Version 3.0, February 23, 2005
Version 3.1, August 31, 2005
Version 3.2, December 23, 2005
Version 4.0, February 15, 2006
Version 4.1 March 13, 2006
Version 4.2, August 8, 2008
Version 5.0, January 29, 2009
Version 5.1, October 6, 2009
Version 5.2, November 4, 2009
Version 6.0, December 30, 2009
Version 6.1, January 11, 2010
Version 6.2, July 9, 2010
Version 6.3, September 15, 2011
Version 7.0, December 15, 2011
Version 7.1, July 10, 2012
Version 8.0, October 8, 2012
Version 9.0, March 10, 2014
Version 9.1, June 01, 2014
Version 10.0, December 14, 2015
Version 11.0, January 23, 2017
Version 12.0, December 22, 2020

## Major Changes from Version 12 dated 12/22/2020 Version 13 dated 09/09/2024

1. Added Pragmatic Trial Definition as an NCI Primary Purpose Classification

| Abbreviations | Definitions |
|---|---|
| PRMS | Protocol Review and Monitoring System |
| SRC | Scientific Review Committee |
| DSMC | Data and Safety Monitoring Committee |
| NCI | National Cancer Institute |
| cancer center | Fred & Pamela Buffett Cancer Center |
| UNMC | University of Nebraska Medical Center |
| IRB | Institutional Review Board |
| QOL | Quality of Life |
| NCTN | National Clinical Trials Network |
| FDA | Food and Drug Administration |
| CTO | Clinical Trials Office |
| AC | Audit Committee |
| PI | Principal Investigator |
| IND | Industry |
| DFT | Disease Focus Team |
| IIT | INVESTIGATOR-INITIATED INSTITUTIONAL TRIALS |
| CTEP | Cancer Therapy Evaluation Program |
| DCP | Division of Cancer Prevention |

# SCIENTIFIC REVIEW COMMITTEE

## I. ADMINISTRATIVE POLICIES AND PROCEDURES

### A. PURPOSE

A functioning Scientific Review Committee (SRC) is a mandatory element of a National Cancer Institute (NCI) designated clinical cancer center. The SRC oversees the scientific aspects of cancer-related research involving human subjects conducted by members of the University of Nebraska Medical Center (UNMC) faculty, house officers, students, and members of the Fred & Pamela Buffett Cancer Center (cancer center). The SRC facilitates the development of innovative, collaborative, and scientifically sound studies focusing on the prevention, detection, diagnosis, and treatment of cancer and its long-term follow-up and care. The SRC helps investigators to prioritize studies to ensure the optimal allocation of cancer center resources. The SRC review process also mentors and guides inexperienced investigators in developing research proposals that will result in scientifically sound hypotheses and outcomes.

### B. SCOPE

All cancer-related studies involving human subjects or material of human origin for which the investigator directly interacts with human subjects are considered "clinical research" by the NCI and require SRC review. All new submissions to the SRC are processed according to the committee's new protocol review process (figure 1 page 8). The SRC differs from the Institutional Review Board (IRB) in that the SRC reviews the science of a project, while the IRB reviews projects to ensure the protection of human subjects. The SRC review level depends on the study design (e.g., prospective vs retrospective) and the level of subject participation for both interventional and non- interventional studies.

#### a. CANCER RELATED STUDIES THAT DO NOT REQUIRE SRC REVIEW

Trials that meet the following criteria, along with minor personnel changes that do not include a change in the PI, do not require review by the SRC.

- Database infrastructure
- Anonymous surveys
- Retrospective studies (chart reviews and existing specimen studies)
- Case studies
- *in vitro* studies utilizing human tissues that cannot be linked to a living individual
- Analysis of discarded pathological specimens without personal identifiers
- Studies involving previously consented patients where no additional consent is required
- Proposals involving previously banked materials and/or tissues
- Studies to obtain tissue or other biological samples for prospective or undetermined future research
- Studies that do not require subject consent or where subject consent is waived

#### b. CANCER RELATED STUDIES THAT QUALIFY FOR EXPEDITED REVIEW

**Studies that require the consent of human subjects**

- Cancer control, Quality of Life (QOL), or prevention, screening, or detection studies involving healthy subjects that do not have cancer as a disease end-point or outcome
- Studies that involve the promotion of a healthy lifestyle in subjects without cancer as an endpoint
- National (NCI National Clinical Trials Network (NCTN) and other NIH-supported National Trial Network) studies
- Multi-institutional study where the primary sponsor is an institution with an NCI approved SRC
- Studies that require a one-time emergency IRB approval to treat a specific cancer patient
- Expanded access programs for out-of-specification products for commercially available cellular therapies.

#### c. CANCER-RELATED STUDIES THAT REQUIRE FULL COMMITTEE REVIEW BY THE SRC

**Studies that require the consent of human subjects**

- Treatment or therapeutic intervention studies involving agents or medical devices for cancer management
- Late effects and QOL studies in cancer survivors
- Studies to develop new technology related to cancer diagnosis or disease management
- Laboratory studies of the mechanism of human cancer that maintain identifiers or involve previously banked tissues linked to subjects by identifiers
- Studies that investigate cancer etiology, prevention, or control
- Studies that investigate secondary cancer prevention, symptom management during and following treatment, and survivorship

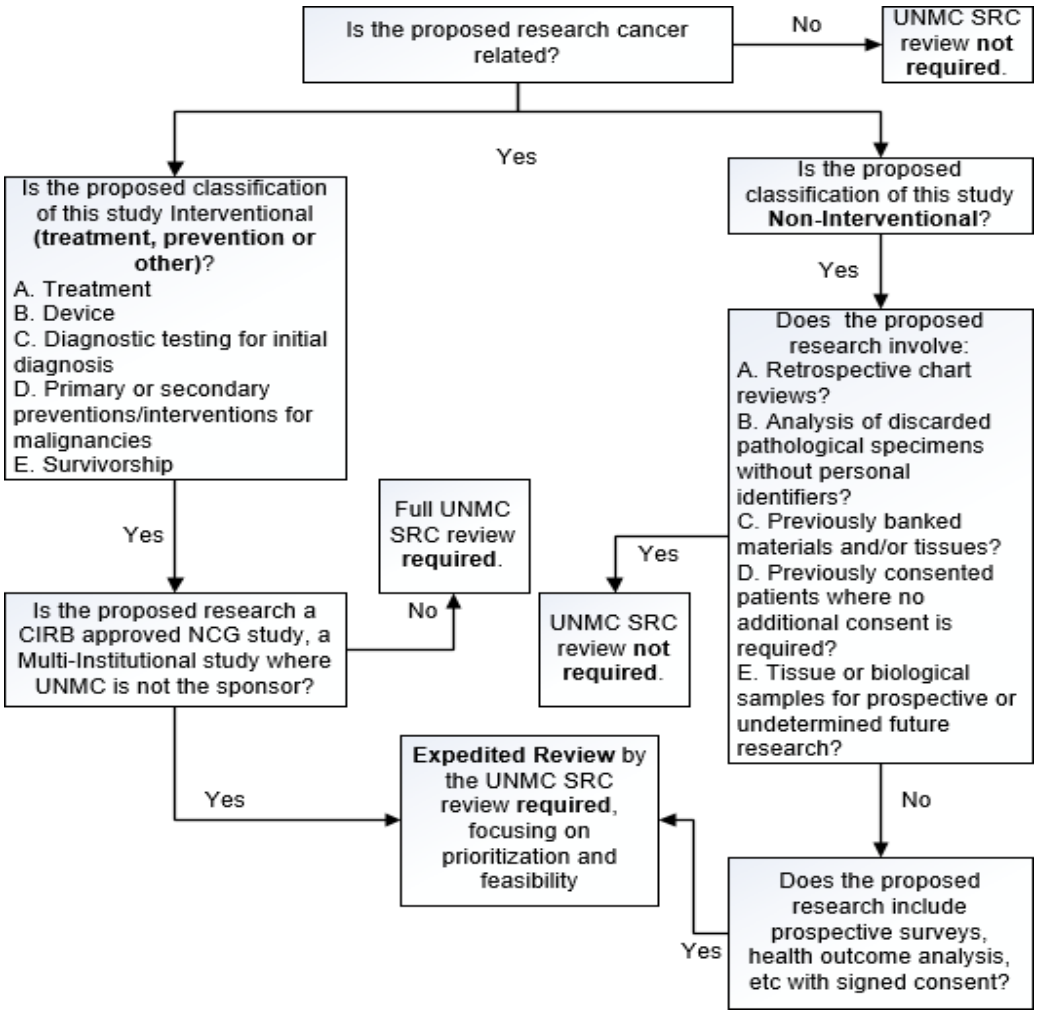
- Studies that investigate cancer risk factors (e.g., dietary studies, studies that involve surrogate endpoints such as precancerous lesions, polyps for colon cancer, genetic markers, and interventions for cancer prevention)
- Studies that address the specific effects of a cancer diagnosis or its related treatments on family members and/or control subjects without a diagnosis of cancer if they are matched or dyadic with patients with cancer.
- Prospective cohort studies

**d. FINAL DETERMINATION OF NEED FOR SRC REVIEW**

When a PI believes a study does not fall within the purview of the SRC, the PI may submit a completed IRB application only and request that the SRC Chair conduct a preliminary review. IRB review continues to be required.

Questions regarding the need for SRC review can be directed to the cancer center Protocol Review and Monitoring System (PRMS) office at prmsoffice@unmc.edu. Final determination of whether a study requires SRC review will be made by the SRC Chair.

***Figure 1: New Protocol Review Flowsheet***




**e. REPORTING RELATIONSHIPS**

The SRC reports to the cancer center Associate Director for Clinical Research. Minutes from the SRC meeting include the minutes from the cancer center Data and Safety Monitoring Committee (DSMC) and the cancer center Audit Committee (AC) and are submitted to the UNMC IRB and cancer center leadership for informational purposes.

**C. MEMBERSHIP**

1. **Appointment Terms:** Members are appointed for three-year terms, contingent on continued interest and active participation in the functions of the SRC. Memberships are renewed at the discretion of the cancer center Director or Associate Director for Clinical Research. All SRC members receive a formal orientation to the SRC and a copy of the SRC Policies and Procedures manual. Continuing education is provided at each full board SRC meeting and includes various topics on conducting research at UNMC.
2. **Voting and Non-voting Members:** SRC members are appointed by the cancer center Director on the recommendation of the Associate Director for Clinical Research. Voting members include one biostatistician, one community member, and academic unit/department representatives. Non-voting members include an IRB representative and the PRMS Administrator. Additional ad hoc members may be appointed or asked to review submissions in specific situations when the necessary specific expertise is not already present on the SRC. Academic units may include, but are not limited to the following:
   - Adult Oncology/Hematology
   - College of Nursing
   - College of Pharmacy
   - College of Public Health
   - Eppley Institute for Research in Cancer
   - Head and Neck Surgery/Otolaryngology
   - Biostatistics
   - Pathology/Microbiology
   - Pediatric Oncology/Hematology
   - Radiation Oncology
   - Surgery/Surgical Oncology

**D. MEETING SCHEDULE**

SRC meetings are held on the second Monday of each month, unless otherwise noted. A list of scheduled meetings and SRC submission deadlines is available from the cancer center PRMS office, (402) 559-8885, via prmsoffice@unmc.edu, or on the PRMS Website

**E. QUORUM**

The number of SRC members required to be present at any regularly scheduled SRC meeting in order to transact business shall be six (6) members. Those attending must include at least the following to meet quorum:

- The SRC Chair, Vice Chair, or their designee.
- (2) M.D.
- (2) Ph.D. (Laboratory based researchers)
- (1) statistician or ad hoc statistical at large member.

If attendance at the full SRC meeting falls below the quorum, the meeting will be immediately suspended, and official business will be conducted once a quorum is reestablished. If it is impossible to re-establish the quorum, the meeting will be adjourned, and the remaining reviews will be conducted at the next scheduled full SRC meeting. Should this happen, PIs may request a Subcommittee review so long as the requirements outlined in Section IV.B. apply.

**F. MEETING CONDUCT**

Full and Expedited SRC meetings are held as virtual meetings conducted electronically (via Zoom).

**G. SRC ROLES AND RESPONSIBILITIES**

**Chair**

- Appointed by the cancer center Director
- Chairs monthly SRC meetings
- Facilitates review discussions during Full Board meetings
- Corresponds with investigators
- Orients new members to SRC policies and procedures

**Reports to the Associate Director for Clinical Research, Director of the cancer center Vice-Chair**

- Voting member of the SRC appointed by the Director
- Assumes the Chair's duties as needed
- Reports to the Chair of the SRC

**PRMS Administrator**

- Non-voting member of the SRC
- Liaison between the SRC Chair, SRC Vice-Chair, the Associate Director for Clinical Research, and the Director of the cancer center
- Ensures the SRC follows applicable policies as per NCI requirements
- Responsible for maintaining and updating PRMS and SRC Policies per NCI guidelines
- Assign reviews to committee members
- Generates protocol and accrual reports
- Assists investigators and study coordinators in preparing submissions for SRC review
- Participates in new study coordinator training
- Maintains annual feedback on the SRC Policies and Procedures from SRC members, PIs, and study coordinators
- Consults on the design and revisions of the PRMS website
- Ensures that a copy of the current Policies and Procedures is available at all SRC meetings
- Maintains data on subject accrual
- Ensures adherence to protocol submission formats and supporting documentation
- Generates correspondence to investigators following the SRC's review
- Maintains data on studies reviewed by the SRC

**PRMS Office Staff**

- Non-voting members of the SRC
- Generates protocol and accrual reports
- Ensures that a copy of the current Policies and Procedures is available at all SRC meetings
- Records meeting minutes
- Maintains the data in the PRMS database

### H. REVISIONS OF POLICIES AND PROCEDURES

The SRC policies and procedures are reviewed every two (2) years by the SRC Chair, Vice-Chair, and the PRMS Office. Minor changes or adjustments (e.g., typographical errors, change in membership) can be made by the PRMS Administrator without approval by the SRC Chair or SRC Members. The Associate Director for Clinical Research and the entire SRC membership need to review major changes. The SRC must approve major changes by a simple majority vote of all SRC members. The full SRC can approve immediate policy amendments prior to a new policy version by including the proposal and the results of a vote in the SRC minutes.

## II. SRC PROTOCOL CLASSIFICATION SYSTEMS AND DEFINITIONS

All cancer-related studies must be categorized using the NCI-defined classification system. While the SRC is ultimately responsible for determining a study's classification, the PI is asked to utilize the following definitions to provide a preliminary classification of their study when submitting a new project application through ePRMS. The following definitions refer to P30 Cancer Center Support Grant (CCSG) Data Guide v3.1.4, updated April 30, 2024, CCSGDataGuide.pdf found at http://cancercenters.cancer.gov/.

1. **INSTITUTIONAL TRIALS:** In-house clinical research studies authored or co-authored by cancer center investigators and undergoing scientific peer review solely by the PRMS of the cancer center. The cancer center investigator has primary responsibility for conceptualizing, designing, and implementing the clinical research study and reporting results. It is acceptable for industry and other entities to provide support (e.g., drug, device, other funding), but the trial should clearly by the intellectual product of the center investigator. Institutional trials are further classified into the following:
   a. **INVESTIGATOR-INITIATED INSTITUTIONAL TRIALS (IIT):** Includes Multi-Institutional studies authored and implemented by investigators at the cancer center. ***Note**: National and Externally Peer-Reviewed (EPR) studies should be listed with those categories, not as Institutional studies.*
   b. **MULTI-INSTITUTIONAL TRIALS:** Institutional studies authored and implemented by investigators at another Cancer Center in which the cancer center is participating. *NOTE: NCI defines Multi-Institutional Clinical Research Studies as studies that recruit participants from two or more geographically distinct enrollment Institutions not affiliated with your cancer center (e.g., other NCI-designated Cancer Centers or other research institutions). The Institutions are usually distinct in other characteristics (e.g., demographic, socioeconomic, or clinical).*
2. **NATIONAL TRIALS:** NCI National Clinical Trials Network (NCTN) and other NIH-supported National Trial Networks: https://www.cancer.gov/research/infrastructure/clinical-trials/nctn Trials that are initiated by an NCI funded study groups and receive Cancer Therapy Evaluation Program (CTEP) or Division of Cancer Prevention (DCP) review.

3. **INDUSTRIAL TRIALS (IND):** A pharmaceutical company controls the design and implementation of these clinical research studies. The local PI has had little or no input as to the form or content of the protocol.
4. **EXTERNALLY PEER REVIEWED (EPR) TRIALS:** R01s, SPORES, U01s, U10s, P01s, CTEP, or any other clinical research study mechanism supported by the NIH or organizations on this list: Organizations with Peer Review Funding Systems.

**A. NCI CLINICAL RESEARCH CATEGORIES**

1. **INTERVENTIONAL:** 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.
2. **OBSERVATIONAL:** Studies that focus on patients with cancer 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.
3. **ANCILLARY OR CORRELATIVE**
   a. **ANCILLARY:** 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 subjects accrued to that clinical research study. Only studies that can be linked to individual subject or participant data should be reported.
   b. **CORRELATIVE:** Laboratory-based studies using specimens to assess cancer risk, clinical outcomes, response to therapies, etc. Only studies that can be linked to individual subject or participant data should be reported.

**B. NCI STUDY PHASE CLASSIFICATION**

1. **EARLY PHASE 1:** Exploratory trials, involving limited human exposure, with no therapeutic or diagnostic intent (e.g., screening studies, micro dose studies). See FDA guidance on exploratory IND studies for more information.
2. **PHASE 1:** Includes initial studies to determine the metabolism and pharmacologic actions of drugs in humans, the side effects associated with increasing doses, and to gain early evidence of effectiveness; may include healthy participants and/or subjects.
3. **PHASE 1/2:** Trials that are a combination of phases 1 and 2.
4. **PHASE 2:** Includes controlled clinical studies conducted to evaluate the effectiveness of the drug for a particular indication or indications in participants with the disease of condition under study and to determine the common short-term side effects and risks.
5. **PHASE 2/3:** Trials that are a combination of phases 2 and 3.
6. **PHASE 3:** Includes trials conducted after preliminary evidence suggested effectiveness of the drug has been obtained and are intended to gather additional information to evaluate the overall benefit-risk relationship of the drug.
7. **PHASE 4:** Studies of FDA-approved drugs to delineate additional information including the drug's risks, benefits, and optimal use.
8. **N/A:** Trials without phases (e.g., studies of devices or behavioral interventions).
9. **PILOT:** The pilot attribute can be assigned to any phase. These are studies in which the primary objective is to collect preliminary data to plan a future protocol. Included in this category are studies preparatory to the development of an application for independent peer-reviewed support, or to take maximum advantage of a unique research opportunity or idea in the basic, clinical, and or population sciences. These studies attempt to demonstrate the feasibility of conducting a randomized trial in a particular subject population. Included in this category are pilot trials that attempt to test an application or intervention in an experimental and a control group, as well as feasibility studies that test an application or intervention in an experimental group only. **These trials must be limited in duration (e.g., 1-2 years depending upon the nature of the research), and the investigator must specify future plans.**

**C. NCI PRIMARY PURPOSE CLASSIFICATIONS**

All Clinical Research Categories must have a primary purpose of Interventional or Non-Interventional (Observational or Ancillary/Correlative) Clinical Research assigned to them.

1. **Basic Science (BAS):** Protocol designed to examine the basic mechanisms of action (e.g., physiology, biomechanics) of an intervention.
2. **Device Feasibility (DEV):** Protocol designed to evaluate one or more interventions for the feasibility of the product or to test a prototype device and not health outcomes. Such studies are conducted to confirm the

design and operating specifications of a device before beginning a full clinical trial.

3. **Diagnostic (DIA):** Protocol designed to evaluate one of more interventions aimed at identifying a disease or health condition.
4. **Health Services Research (HSR):** Protocol designed to evaluate the delivery, processes, management, organization, or financing of health care.
5. **Prevention (PRE):** Protocol designed to assess one or more interventions aimed at preventing the development of a specific disease or health condition.
6. **Screening (SCR):** Protocol designed to assess or examine methods of identifying a condition (or risk factor for a condition) in people who are not yet known to have the condition (or risk factor).
7. **Supportive Care (SUP):** Protocol designed to evaluate one or more interventions where the primary intent is to maximize comfort, minimize side effects, or mitigate against a decline in the participant's health or function. In general, supportive care interventions are not intended to cure a disease.
8. **Treatment (TRE):** Protocol designed to evaluate one or more interventions for treating a disease, syndrome, or condition. *Note: This equates to therapeutic trials in previous versions of the guidelines and is the only Primary Purpose to include a trial as Interventional on the DT4.*
9. **Other (OTH):** Not in other categories.
10. **Pragmatic** Clinical Trial: A clinical trial that is designed to study a health intervention in a real-world setting that is similar or identical to the one in which the intervention will be implemented. Trials with the following characteristics can be classified as pragmatic:
    a. Unit of randomization may be other than an individual participant (e.g., the clinic, the healthcare system, or a neighborhood if a community setting)
    b. Intervention may be multi-level involving changes to:
        - Participant behavior (e.g., completing a symptom report measures online), and
        - Provider behavior (e.g., receiving the participant's symptom report and having to act on it)
    c. Data are often obtained directly from medical records and, are likely collected on a large number of participants
        - Data may be collected during a pre-intervention period and again during a post-intervention period in each clinic that is randomized
        - Participants for whom data are collected in the pre-intervention period may not be the same ones for whom data are collected in the post-intervention period.

**D. Compassionate Use, Expanded Access, or Single Subject Access Intervention Studies**

Studies used to provide an investigational therapy to a subject who is not eligible to receive that therapy in a hypothesis driven clinical trial, but who has a serious or life-threatening illness for which other treatments are not available. Compassionate use trials allow subjects to receive promising but not yet fully studied or approved cancer therapies when no other treatment option exists.

## III. PRIORITIZATION

Newly proposed Interventional research must have a priority score assigned when submitted to the SRC for review. If the newly proposed research competed with other studies with similar eligibility criteria, SRC expects the investigators to use the priority score to determine the order in which trials would be offered to potential subjects. Where trials exist with the same priority score, the SRC expects those trials to be ranked by the applicable DFT. It is the responsibility of the DFT to track the prioritization rankings of each of their studies. If two or more trials exist with the same priority score, the SRC expects that the DFT will rank those studies within that priority score as felt appropriate for those trials. The prioritization plan must be clearly defined and submitted in writing to the SRC before full SRC approval of the newly proposed study is given.

The SRC will approve a competing study if it meets one of the following criteria: 1) when it is necessary to have a portfolio of related studies appropriate to a specific subject population (high unmet medical need). 2) When existing Phase 1 studies require interruption in accrual for safety analysis after the accrual of limited cohorts. 3) when a study is targeted to the same disease and stage but has some overlap in eligibility criteria such as age, tumor biology or prior treatment history; 4) when the competing study is expected to be completed in the extremely near future; or 5) when the competing studies are active at different clinical sites.

Disease Focused Teams (DFTs) assist in the prioritization of their research study portfolio based on scientific merit and subject population. PIs are asked to discuss with the appropriate disease group to determine the priority score. Each PI is given the opportunity to offer supporting rationale to the SRC for review if they feel the prioritization score according to the ratings below is not adequate. If a trial has broad eligibility criteria across disease entities (e.g., myeloid, and lymphoid tumors), the SRC will expect one priority score for the trial, although each DFT may adjust ranking for their disease group as they see fit. During the SRC meetings, the priority score is voted on based on the following ratings and will be recorded in the Clinical Trial Management System (CTMS).

The SRC expects the PI/DFT has reviewed the current list of SRC approved therapeutic studies to determine whether there may be competing protocols. If so, a list of all competing trials with corresponding priority scores and ranks should be supplied with each submission.

| | Investigator Initiated | National | Industry | Externally Peer Reviewed |
|---|---|---|---|---|
| **Multiplier** | **20** | **15** | **10** | **5** |
| **4** | High profile clinical trial initiated by a UNMC Investigator of high and broad interest and novel therapies likely to make a substantial impact on disease or quality of life. | High profile National Phase III or randomized Phase II study with a UNMC Investigator as national PI. | High profile industry sponsored or multi-institutional Phases II or III study with a UNMC Investigator as the national PI. | High profile study for the external peer group sponsoring the study which is likely to make a substantial impact on a disease or quality of life. |
| **3** | High interest clinical trials likely to impact disease or quality of life. | | | |
| **2** | High interest clinical trials less likely to impact disease or quality of life but ask an important question. | | | |
| **1** | Studies with competing higher priority trial of interest for rare diseases or expanded access studies. | Low interest studies for rare diseases, expanded access studies or any otherwise priority 2-4 study with a higher priority competing protocol. | | |
| **0** | Inadequate Priority | | | |

Resulting Scores:

| | |
|---|---|
| 0 | Lowest Priority equal to a Rejected Study |
| 5-30 | Medium Priority for Resources |
| 45-80 | Highest Priority |

## IV. PROTOCOL SUBMISSION GUIDELINES

### A. SUBMISSION DEADLINES

The SRC submission deadline is the 1st Thursday of the month for NEW Investigator-Initiated trials or the last Friday of every month for all Industrial trials (IND) and IITs up for continuing review (CR) or requests for changes (RFC).Other trials, such as National Cooperative Groups (NCG), Multi-Institutional (Multi-Inst), and Externally Peer Reviewed (EPR) submissions, generally receive an expedited review by the SRC; therefore, the previously mentioned deadlines do not apply. However, it remains the responsibility of the PI to be aware of SRC deadlines if a submission requires review at the next scheduled meeting. A list of scheduled meetings and SRC submission deadlines is available on the PRMS Website.

Submissions must be made through the electronic Protocol Review and Monitoring System (ePRMS) module in the Clinical Trial Management Systems (CTMS). ePRMS training is required prior to receiving access to the ePRMS module in the CTMS. The Protocol Review and Monitoring System (PRMS) Office and SRC is not responsible for delays in submission reviews if ePRMS training is pending.

Submissions, which do not meet the submission deadline, will not be reviewed at the next full committee meeting unless a request is received from the PI outlining the rationale for review at the next full committee meeting. The PRMS Administrator screens all submissions for completeness and accuracy. Any submission that does not meet the minimum requirements for submission or contains errors may not be accepted for review at the next full committee meeting.

Additionally, the PI is responsible for contacting the PRMS office if a question of SRC purview exists. Submissions for evaluation of SRC review requirements should include the IRB application and submitted directly to prmsoffice@unmc.edu. The PRMS Office and SRC Chair will perform a pre-review of all Investigator-Initiated trials prior to accepting the submission for full board review to ensure minimum submission requirements have been met.

**B. REQUEST FOR SUBCOMMITTEE REVIEW**

The SRC meets once a month and has no provision for reviewing protocols that are submitted beyond the regular deadlines. If an investigator believes one of the conditions below applies to the submission, the investigator may request that a Subcommittee of the SRC review new protocols or changes to a previously approved protocol. To be eligible for a subcommittee review **one of the following conditions must apply:**

1. The study source (i.e., sponsor) or funding agency's deadline is such that consideration at a regularly scheduled SRC meeting would not be feasible given the time constraints, and the study represents an important research venture for the PI UNMC or involves an important/urgent treatment option for patients.
2. The proposed protocol change(s) involves an important treatment option for a potential patient already identified by the investigator and directly affects that patient's ability to begin treatment as outlined in the protocol.
3. Additional submission types that require rapid activation timelines are under the discretion of the SRC Chair and/or Vice Chair.

Although the subcommittee may grant approval to the investigator, the decision must be confirmed by the entire SRC at the following meeting. The IRB review is independent of the SRC review, and it remains the responsibility of the PI to adhere to applicable IRB requirements.

**C. TYPES OF SUBMISSIONS**

a. **Exempt from SRC Review:** Protocols that involve research based on the following criteria are considered exempt from SRC review and do not require submission for SRC Review:

- Anonymous Surveys
- Retrospective studies (chart reviews and existing specimen studies)
- Case studies
- Analysis of discarded pathological specimens without personal identifiers
- Studies involving previously consented patients where no additional consent is required
- Proposals involving previously banked materials and/or tissues
- Studies to obtain tissue or other biological samples for the prospective undetermined future research

The IRB may request the SRC to review research proposals for the determination of SRC purview. It is the PI's responsibility to ensure that the IRB application contains sufficient information for the SRC Chair to make an initial determination as to whether a study requires ongoing SRC review.

If the SRC Chair is unable to make an initial determination of the ongoing review status from the IRB application alone, the PI will be asked to submit additional information at the discretion of the SRC Chair. If the initial determination is that the protocol may require ongoing SRC review, the SRC may request additional documents to facilitate full SRC review, which may include a protocol and data collection forms. The full SRC submission will be processed in the same manner as all other New Project submissions.

2. **New Protocol:** Any new cancer-related clinical research study that is cancer-related involving human subjects unless it meets the criteria of exemption outlined in Section IV.B.1 above. Fig 1 summarizes the process of how the SRC makes a determination of the need for protocol review and type/level of review (i.e., full board review, expedited review, exempt from further review).

a. **Full Committee Protocol Review:** Protocols that require full committee protocol review include Interventional Investigator-Initiated Institutional Protocols, Multi-Institutional Protocols Sponsored by UNMC, and Industrial Protocols. For investigator-initiated interventional protocols with a primary purpose other than treatment, the determination of the need for full board review will depend on the nature of the intervention and the intensity/frequency of subject involvement during the research.

b. **Expedited Review:** Expedited reviews will focus on prioritization and the feasibility of conducting the proposed research at UNMC. Some examples of such research may include:

- National studies (including Alliance)
- Multi-Institutional studies from NCI designated Cancer Centers where UNMC is not the sponsor, and the sponsoring institution's SRC can be designated the SRC of record (these may be subject to varying levels of review depending on the level of scientific input from the originating institution)
  - Interventional with a primary purpose other than treatment or non-Interventional Investigator Initiated Trials with minimal subject interaction.
  - Externally Peer-Reviewed studies which have received an external scientific review.
  - Any trial where the explicit or implicit purpose of the trial is to provide access to therapy for one or more subjects without an explicitly stated data/statistically driven research-

hypothesis (i.e., single subject compassionate use or expanded access).

All Expedited Reviews must be submitted to the SRC along with all required review documents through ePRMS. If an Investigator has questions regarding the level of SRC review required, contact the PRMS Office for pre-review. The SRC Chair has the discretion to recommend a full board review based on the complexity of a study and degree of subject interaction.

3. **Continuing Review:** All protocols require annual continuing review by the SRC and are due one month before IRB expiration as applicable. Protocols may be required to undergo more frequent continuing review at the discretion of the SRC.

4. **Change(s) in Protocol:** Any change to Institutional or Industrial protocols (e.g., change in personnel, study design, drug dosing, etc.) must be reviewed and approved by the SRC. In addition, changes to Externally Peer Reviewed trials that are not reviewed by NCI or the DCP)must be reviewed and approved by the SRC. Including studies that are actively accruing subjects and those in follow-up.

   Changes to National or Externally Peer Reviewed trials that are reviewed by CTEP or DCP do not require SRC review or approval. However, changes that have been made to the protocol since the last Continuing Review must be noted when submitting the next Continuing Review.

   All changes within the protocol and/or supporting documents must be submitted for review. Smaller administrative/typographical changes may be submitted in tracked, red-lined documents as well as a clean version. Substantive (major) changes such as eligibility, sample size changes affecting statistics, or major changes to the science or design must be submitted in a fashion easily understood by the reviewer, including an identified/visible rationale for each change. Ideally, the sponsor or PI provides a complete summary document to detail this level of change.

   Minor personnel changes do not require review and approval by the SRC.

   It is the Investigator's responsibility to notify the SRC when major changes are made to a protocol or when requesting changes to the protocol information in the CTMS. Notification of a change must be done by submitting a completed SRC "Request for Change" form and submission through ePRMS. The current SRC forms, the instructions for completing the forms, and the SRC submission deadline/meeting calendar may be found on the PRMS website.

**D. SUBMISSION REQUIREMENTS**

All submissions require the assignment of a clinical research category, study phase, and primary purpose classification outlined in section II. A, B, C, and D above. These assignments are included in the protocol built in the PC Console of the CTMS, which is used for standard reporting and as part of the electronic SRC submission through ePRMS.

1. **NEW PROTOCOLS:** The most current New Protocol submission form is available on the PRMS Website https://www.unmc.edu/cancercenter/research/protocol-review-monitoring-system.html
   All new protocol submissions must include the following supplementary documents in the order listed:
   - Original Signed and Dated SRC New Protocol Submission Form
   - Priority Score, including rank where applicable, and acknowledgement of discussion with the DFTs and or co-investigators
   - Cover letter and or copy of relevant correspondence (if applicable)
   - Copy of the IRB Application for Biomedical Research form (not required for Investigator-Initiated Trials)
   - Data collection form(s) (**required** for all Investigator-Initiated Institutional and Multi-Institutional trials)
   - Investigator Brochure (if applicable)
   - Grant application (if applicable)
   - Protocol **with version and date marked on the face page**
   - Investigator Initiated Institutional Protocols, which require an IND, must be accompanied by copies of all FDA correspondence and FDA protocol approval (if approved at the time of SRC submission)

   a. **Interventional Treatment Protocols :**
      1. **Investigator-Initiated Institutional Protocols and Multi-Institution Protocols Sponsored by UNMC:** Must be submitted in the SRC Protocol format located on the PRMS website. Resources for preparing a protocol in SRC format may be obtained from the PRMS website at https://www.unmc.edu/cancercenter/research/protocol-review-monitoring-system.html or by contacting the cancer center PRMS office at prmsoffice@unmc.edu.

2. **Multi-Institutional Protocols NOT Sponsored by UNMC, National, Industrial, and Externally Peer Reviewed:** May be submitted without conversion to SRC Protocol format, provided they contain the essential elements required by the SRC scientific review, along with a completed SRC New Protocol Submission Form.
3. **Pilot Protocols:** In addition to the SRC protocol format, Interventional pilot protocols must contain sufficient information about the following items:1) justification of sample size and analysis; 2) estimated study duration; 3) future directions.

b. **Non-Interventional Protocols:**
With the exception of more complex Investigator-Initiated observational protocols) e.g., requiring statistical justification or containing repeated/complex subject interaction with the investigative team, non-interventional protocols, including non-interventional pilot studies, do not need to be in SRC protocol format. In most cases, the IRB application, and a brief discussion of the specifics of the research plan and the biostatistical considerations, where appropriate, will be sufficient. A full "New Protocol" application and complete SRC formatted protocol will be required if the IRB application does not contain sufficient information to complete the review. If the research involves laboratory-based procedures, they must be outlined in sufficient detail to allow for scientific review by the SRC.
For **instrument** development studies, the protocol must include a sufficient description of the instrument being developed and the measures of the performance characteristics to be studied (e.g., sensitivity specificity, validity, reliability, etc.). Statistical considerations must consider the degree of precision desired, and these types of protocols may require special statistical consultation.

c. **Partially Cancer-Related Protocols:**
A partially cancer-related study is defined as a study that includes subjects with cancer but also includes subjects who do not have cancer in the eligibility criteria. Depending on the study design and the primary outcome measure (i.e., cancer-related, or not) these types of protocols may not require SRC review. Protocols of this nature that qualify for full SRC review will require an estimate of the proportion of subjects with cancer for SRC tracking purposes and for tracking accrual during the SRC annual continuing review. Depending on the study design, the SRC may only request accrual information on the subjects with cancer, and this will be determined at the time of the initial SRC review. For these studies, the PI must estimate the portion of the project that is cancer-related. The portion of the study that is cancer-related can be determined by estimating the number of subjects with cancer vs. the number of subjects without cancer that are expected to be enrolled in the study.

The resulting percentage of subjects with cancer will determine the percentage of the trial that is cancer-related. Accrual goals for the study should only be reported for the cancer-related portion of the study. Only copies of the consent forms for subjects with cancer as their current disease diagnosis should be submitted to the PRMS office for accrual reporting.

2. **CONTINUING REVIEW:** The most current Continuing Review submission forms are available on the PRMS Website at Protocol Review and Monitoring System | The Fred & Pamela Buffett Cancer Center | University of Nebraska Medical Center (unmc.edu)
All continuing reviews must include the following supplementary documents:
- Original signed and dated SRC Continuing Review Submission Form
- Documented Priority Score and rank (if applicable)
- Cover letter and or copies of any relevant correspondence change (if applicable)
- Copy of the IRB Application for Continuing Review Form
- The currently approved protocol version

3. **REQUEST FOR CHANGE:** The most current Request for Change submission form is available on the PRMS website at Protocol Review and Monitoring System | The Fred & Pamela Buffett Cancer Center | University of Nebraska Medical Center (unmc.edu)
All requests for change must include the following supplementary documents:
- Original signed and dated SRC Request for Change Submission Form
- Cover letter and or copies of any correspondence related to this change (if applicable)
- Copy of the IRB Request for Change (if applicable)
- The REVISED Data collection form(s) (if applicable)
- The REVISED Investigator Brochure (if applicable)
- Copy of the schema and abstract from the grant (if the proposed change, including title change, is the result of a new request for financial support)

- The REVISED protocol with **version and date marked on the face page**, both tracked change and clean documents.
- Summary of changes

## V. ADDITIONAL REPORTING REQUIREMENTS

In addition to the requirements outlined in Sections I through IV above, PIs are responsible for real-time reporting of the following to the PRMS Office:

- Accrual of all participants through registration in the Clinical Trial Management System (CTMS) within one week of consent.
- Notification of study closure, completion, or termination; and
- Toxicity, adverse events, and adherence reports as applicable for PRMS-related reporting.

For all **Intervention and Observational** studies, PIs are responsible for ensuring that their protocol amendments are registered to NCI's Clinical Trials Reporting Program (CTRP). For specific CTRP reporting requirements, see Section X.

## VI. PROTOCOL REVIEW PROCEDURES

### A. SRC PROTOCOL REVIEW PROCEDURES

#### 1. REVIEW TYPES

**a. Full Board Review**

1. **New Project:** Investigator-Initiated trials with UNMC as lead site, Multi-Institutional trials that do not have an NCI Designated Cancer Center as lead site, and Industry trials ***NOTE:*** *Per a revision to PAR-13-386 dated 08/19/2016, the SRC of the lead site of a multi-institutional trial will conduct a full review of the protocol so long as NCI has approved the SRC. All other participating sites need only require an expedited review principally for prioritization and feasibility. If the lead site is either conditionally approved or disapproved during the study, a full review may occur at another participating NCI-designated site with an approved SRC.*
2. **Continuing Reviews:** Investigator-Initiated trials with UNMC as lead site, Multi-Institutional trials that do not have an NCI Designated Cancer Center as lead site, and Industry trials.
3. **Request for Change:** Investigator-Initiated trials with UNMC as lead site, Multi-Institutional trials that do not have an NCI Designated Cancer Center as lead site, and Industry trials, unless otherwise defined in Section VI.B and C below.

**b. Expedited Review**

1. **New Project:** National, Externally Peer Reviewed, Multi-Institutional trials with an NCI Designated Cancer Center as the lead site, Non-Interventional trials with limited subject interaction, and single-subject compassionate use protocols are reviewed principally for priority and feasibility. *Note: the SRC does not generally require prioritization of Non-Interventional trials except in unusual circumstances where patient populations overlap between studies and subjects cannot participate in both studies.*
2. **Continuing Reviews:** National, Externally Peer Reviewed, Multi-Institutional trials with an NCI Designated Cancer Center as the lead site, Final Continuing Reviews on studies that are closed to accrual studies but still active with the IRB, and single subject compassionate use protocols.
3. **Request for Change:** Externally Peer Reviewed, Multi-Institutional trials with an NCI Designated Cancer Center as the lead site, non-Interventional trials, changes involving a change in the PI only, accrual increases on non-Investigator Initiated Trials, single subject compassionate use protocols. The SRC Coordinator forwards all additional requests not outlined above for Expedited Review to the SRC Chair to determine whether Expedited review or Full Board review is required. The SRC does not require the approval of minor personnel changes. Approved expedited Reviews will be noted in the next scheduled full board meeting minutes.

**c. Subcommittee Review**

Studies, which would typically require Full Board review, may qualify for a Subcommittee Review should one of the following conditions apply:

1. The study source (e.g., sponsor) or funding agency's deadline is such that consideration at a regularly scheduled SRC meeting would not be feasible given the time constraints.
2. The study represents a vital research venture for the UNMC PI or involves an urgent treatment option for patients.
3. The proposed protocol and or accrual change(s) involves a critical treatment option for a potential subject already identified by the investigator and directly affects that subject's ability to begin treatment as outlined in the protocol.

Requests for SRC Subcommittee review must be made directly to the PRMS Office. The SRC Coordinator and or PRMS Administrator will contact the SRC Chair and or Vice-Chair, who will make

a determination of the appropriateness for Subcommittee review. The SRC Chair and or Vice Chair will designate a Subcommittee to perform the review, consisting of members as outlined in section VI.B.3.

The Subcommittee review will be concluded within five business days. Subcommittee reviews will be noted in the next scheduled full board meeting minutes.

**d. Administrative Review**

Submissions that require changes to the SRC-required fields in the protocol built in the CTMS, and are not accompanied by an amendment, and do not affect the scientific outcomes of the study, can be administratively reviewed, and released by the PRMS SRC Coordinator. Examples of these submissions include:

1. Accrual goal increases or accrual duration changes on National, Industry, Externally Peer Reviewed, or Multi-Institutional trials where UNMC is not the lead site
2. Addition, deletion, or change to an Oncology Group or Management Group

The PRMS Administrator or SRC Coordinator can request further SRC review by the SRC Chair and or Vice Chair if the intent of the submission needs to be clearly defined.

**B. ASSIGNMENT OF REVIEWERS:** The SRC Coordinator considers the conflict of interest when assigning reviews. When the expertise is absent in the SRC membership to peer-review a protocol, ad-hoc reviewers may be asked to review the protocol.

1. **Full Board Review**
   - **a. New Project:** Primary, Secondary, and Statistical Reviewer. At least one clinician will review all treatment intervention protocols.
   - **b. Continuing Review:** Primary and, at the discretion of the SRC Chair, a Statistical Reviewer.
   - **c. Request for Change:** Primary and, at the discretion of the SRC Chair, a Statistical Reviewer.
2. **Expedited Review**
   - **a. New Project:** Primary, reviewed for priority and feasibility only. *Note: the SRC is not required to prioritize Non-Interventional trials.*
   - **b. Continuing Review:** Primary and, at the discretion of the SRC Chair, a Statistical Reviewer.
   - **c. Request for Change:** Primary and, at the discretion of the SRC Chair, a Statistical Reviewer.
3. **Subcommittee Review**
   - **a. One SRC member** for a request for change or continuing review, which would typically require full board review, OR.
   - **b. Three SRC members, including at least one biostatistician,** for New Investigator-Initiated Institutional, Multi-Institutional with UNMC as the sponsor, and Industrial submissions. All treatment intervention protocols will be reviewed by at least one clinician.

**C. REVIEWER RESPONSIBILITIES**

1. **Conflict of Interest**

   If an SRC member serves as a primary or secondary investigator or a consultant (including a biostatistician) that individual will not be allowed to serve as a reviewer for that protocol. SRC members who are Principal Investigators for a trial undergoing review at a Full Board meeting will refrain from meeting participation during discussion and voting.
2. **New Project**

   Reviewers are responsible for written reviews and comments on the following items:
   - **a. Investigator-Initiated trials with UNMC as lead site, Multi-Institutional trials that do not have an NCI Designated Cancer Center as lead site, and Industry trials.**
     - **Objectives**: Are the objectives and endpoints of the protocol clearly defined?
     - **Scientific Rationale**: Does the protocol address relevant scientific questions?
     - **Study Design**: Does the proposed protocol design address the protocol's objectives and scientific rationale? Can the proposed objectives be met with the available resources of the FPBCC? Can the objectives be met within an acceptable period? Does the study design include stopping rules for safety or efficacy/futility where appropriate?
     - **Methodology**: Are the methods in the protocol adequate to answer the questions addressed in the objectives? Are there resources available within the FPBCC to conduct these methods? Is there a description of the agent's activity, dose delivery and scheduling, and dose modification criteria for treatment intervention protocols
     - **Statistics**: Is the statistical design clearly described, well-defined, and statistically sound? Are the accrual goals clearly stated? Is the sample size adequate to answer the specific objectives of the protocol? For qualitative studies, are appropriate analytical design and decision criteria included?

- **Data Collection:** Will the collected data answer the objectives of the protocol? Are the data collection and analysis methods clearly described and sound? Data forms are considered an essential part of the protocol and must be submitted to the SRC with the initial submission. The SRC may withhold review and approval of a protocol pending submission and review of data collection forms.
- **Prioritization:** For interventional treatment protocols (and for interventional protocols with a primary purpose other than treatment), is the priority relative to other competing protocols clearly stated? The PI will assign new protocols a prioritization score based on the SRC matrix (Section III) and this will be reviewed, along with protocol rank where applicable, by the SRC.
  1. **National, Externally Peer Reviewed, Multi-Institutional trials with an NCI Designated Cancer Center as the lead site and Non-Interventional trials with limited subject interaction.** This review type will focus on prioritization, accrual, and the feasibility of conducting the proposed research at UNMC. The PI will assign new protocols a prioritization score based on the SRC matrix (Section III), which the SRC will review.

3. **Continuing Review**

The purpose of a continuing review is to:
1) Monitor subject accrual.
2) Evaluate major developments that have occurred in the scientific area that affect the study's specific objectives .
3) Determine if sufficient progress is being made.

5) Monitor changes in the study's priority.
Continuing reviews will be conducted on all active protocols with ongoing accrual at least annually. Some protocols may require continuing review more frequently. A final review is conducted if a study is active, but accrual is complete.

4. **Request for Change**
   a. **Expedited Review:** Minor changes to the protocol or CTMS build include: 1) addition or deletion of the participating site; 2) a change in reporting requirements; 3) a change in study title or PI, or 4) other changes per the determination of the SRC Chair and or Vice-Chair.
      - Changes to National or Externally Peer Reviewed trials do not require SRC review or approval. Protocol changes since the last continuing review should be listed when submitting the next continuing review.
   b. **Full Board Review:** Major changes to the protocol or CTMS build include: 1) addition/reduction of a trial's total accrual goals that affect the science/statistics of the study (changes in local accrual only for feasibility reasons do not require full board review); 2) changes in methods, procedures, or study design; 3) modifications in drug dosage or delivery; 4) changes in exclusion or inclusion criteria; 5) changes to the data collection forms, or; 8) other changes per the determination of the SRC Chair and or Vice Chair.
      - While the SRC is required to have the most current copy of the Investigator Brochure (IB) on file, if changes to the IB do not cause a change to the protocol, the SRC does not require submission of a Request for Change.
   c. **Subcommittee Review of a Major Change:** An investigator may petition the SRC for a subcommittee review of a major change in protocol. The PI must contact the PRMS Office and demonstrate that delaying the implementation of the protocol change until the next scheduled meeting of the SRC would seriously impede the research project. The PRMS Administrator will contact the SRC Chair, who may decide that the submission can be sent for SRC subcommittee review and will designate up to three SRC members to perform the review. Approved expedited Reviews will be noted in the next scheduled full board meeting minutes. See Section VI.A.1.c for a more detailed explanation of the subcommittee review procedure.

**D. REVIEW OUTCOMES**

All review outcomes will be documented on the appropriate meeting agenda and minutes.

1. **New Protocol and Continuing Reviews:** After the reviewer(s) completes their review of the New Protocol and or Continuing Review submission, the reviewer(s) recommends that the SRC take one of the following actions:
   a. **Full Approval:** The study is scientifically sound and acceptable as written. Full approval is given, and the IRB and PI are notified. The SRC may elect to include additional information as a note to the PI, but full approval will not be withheld.
   b. **Conditional Approval:** The study is scientifically sound and acceptable if **minor clarifications** are provided. Full approval will be withheld until the SRC Chair makes and approves the necessary clarifications

c. **Approval with Revisions:** The study is scientifically sound and acceptable if the PI makes the SRC-required **modifications to the protocol**. Full approval is withheld until the protocol is revised to incorporate the recommended modifications. The protocol must be re-reviewed and approved by the original SRC reviewers.
d. **Tabled:** The study is not scientifically sound or acceptable as currently written and requires substantial changes and point-by-point responses to the questions raised by the SRC during its initial review. The protocol must be revised and re-submitted in its entirety to the SRC for full-board review.
e. **Disapproved:** The study is not conceptually scientifically sound.
f. **Decline to Review:** The submission does not meet the requirements outlined in section IV.D and will only be accepted for review once the appropriate changes are made.

2. **Request for Change Reviews:** After the reviewer(s) completes their review of the Request for Change, the reviewer(s) recommends that the SRC take one of the following actions:
   a. **Full Approval:** Change(s) to the study are scientifically sound and acceptable as written. The SRC may elect to include additional information as a note to the PI, but full approval will not be withheld.
   b. **Conditional Approval:** Change(s) to the study are scientifically sound and acceptable if **minor** clarifications are provided. Full approval of the change(s) will be held until the necessary modifications are made and approved by the SRC Chair.
   c. **Approval with Revisions:** Change(s) to the study is scientifically sound and acceptable if the PI **modifies to the protocol**. Full approval of the change(s) will be held until the protocol is revised to incorporate the recommended modifications and the original SRC reviewers approve the protocol.
   d. **Carried:** The submission does not contain sufficient information to determine whether the change(s) are scientifically sound and acceptable. The additional information requested by the SRC during its initial review must be submitted to the SRC for full-board review.
   e. **Disapproved:** Change(s) to the study are not conceptually scientifically sound, not acceptable as written, or **not** within the mission of the Fred & Pamela Buffett Cancer Center and cannot be implemented.
   f. **Decline to Review:** The submission does not meet the requirements outlined in section IV.D and will only be accepted for review once the appropriate changes are made.

**E. VOTING PROCEDURES:**

All SRC meetings can be held in person/virtually;

1. The Primary Reviewer or designee will recommend an action that another SRC member seconds. Voting on each motion will be recorded as the number approved, the number opposed, and the number abstained will be reflected on the meeting minutes.
2. The motion must be approved by the majority of SRC members in attendance at the full board meeting, either in person via conference call or via videoconference. Other motions may be entertained if the motion does not pass by a majority. If no additional motions are brought forth, the protocol will be tabled and sent to the SRC subcommittee for review.
3. Only those members physically in the room or attending by conference call or videoconference will be allowed to vote. Absentee voting is not permitted.
4. Under unusual circumstances, the Chair of the SRC may call for a vote by e-mail. Such circumstances may include but are not limited to the following:
   a. Where simultaneous attendance by video/phone conferencing is not feasible, and a vote is considered urgent by the committee.
   b. When changes to policies/procedures are required/desired to be implemented immediately without immediate change to the SRC Policies and Procedures (i.e., to be added/formalized with the next version of the Policies and Procedures).

## VII. REPORTING RESULTS OF SRC REVIEW

The SRC will communicate the results of all reviews and its recommendations regarding changes to the protocol or study conduct to the PI. The SRC Chair signs written communications to the PI, or where the SRC Chair has a conflict of interest related to the study, by the Vice-Chair or a member of the SRC in attendance at the SRC meeting, designated as acting chair for that protocol. If Chair, Vice-Chair or signing member cannot sign a review letter, the PRMS Administrator has signature authority with appropriate documentation of approval of the review. When able, the signing member will provide an official signed review letter for SRC records. Minutes from the SRC meetings are submitted to the UNMC Data and Safety Monitoring

Committee (DSMC), the UNMC Audit Committee and the UNMC Institutional Review Board (IRB), for informational purposes.

## VIII. DEADLINE FOR PI RESPONSES

The PI is given 30 days from the date of the SRC review letter to respond to the SRC's review. If a response is not received within 30 days, the PI and study staff (if applicable) will be contacted by the PRMS Administrator to determine the status of their response. If the SRC Chair determines the reason for the delay to be adequate, an extension will be granted. If the response deadline is still not met after an extension is granted, the SRC will recommend suspending accrual, or that the study be withdrawn, until a response has been received and approved by the SRC.

## IX. REPORTING REQUIREMENTS

### A. ACCRUAL REPORTING

A mandatory function of the SRC is to monitor accrual on all cancer-related studies. **Each PI is responsible for loading subjects consented to their trial into the Clinical Trial Management System (CTMS) with each applicable status within one week of consent.** If accrual information, including all required demographic information listed below, is not documented in the CTMS on a timely basis, the SRC may elect to suspend the trial to further accrual.

The following demographic information must be included with each subject registration in the CTMS:

1. Subject's full name (initial acceptable if full name not available).
2. Subject's UNMC medical record number.
3. Subject's date of birth.
4. Subject's gender.
5. Subject's ethnicity.
6. Subject's race.
7. Subject's zip code.
8. Subject's country if not USA.
9. Subject's registration date.
10. Subject's ICD-10- diagnosis code.

### B. ACCRUAL REPORTING FOR STUDIES NOT ENTIRELY CANCER-RELATED

For studies that are not entirely cancer-related, the PI must estimate the portion of the project that is cancer-related and must only register subjects with cancer who were accrued to the study in the CTMS. A study that is partially cancer-related is defined as a study that includes subjects with cancer but also includes subjects who do not have cancer as their current disease diagnosis. See Section IV.D.c for instructions on how to estimate the cancer-related portion of a study that is only partially cancer-related.

### C. FINAL SRC REVIEW AND STUDY COMPLETION

Once a study is closed to accrual, the SRC must be notified in writing along with the reason the study has been closed to accrual. If the SRC is notified between continuing review cycles that a study has closed to accrual, one final SRC continuing review is required. If a protocol change is required at a later date, the change must be submitted to the SRC for review.

When a study is closed or completed with the IRB, (i.e., all follow-up is completed and all data have been analyzed), the PI must promptly inform the SRC in writing along with the reason the study has been closed.

### D. STUDY WITHDRAWAL OR TERMINATION OR BY THE PI

The SRC should be promptly notified of study termination or withdrawal from SRC/IRB consideration by the PI writing along with the date and reason the study has been terminated or withdrawn.

### E. STUDY SUSPENSION OR TERMINATION BY THE SRC

If a trial is suspended or terminated by the SRC for any element under SRC purview, the PI will be notified along with the reason(s) for the actions. The investigator will have 30 days to appeal the decision in writing. The investigator's appeal will be reviewed at the following meeting of the SRC. If the investigator does not adequately address the concerns of the SRC, the appeal will be denied. The IRB will be notified in writing of the outcome of the appeal.

If the SRC's review results in the need to modify the IRB application and/or consent(s), the appropriate revisions must be submitted to both the SRC and IRB. If no response to the SRC's review is received within 60 calendar days, the study will be classified as withdrawn and must be resubmitted to the SRC for full board review if the PI wishes reconsideration. A recommendation for study termination or suspension may occur at any time for the following reasons:

1. Insufficient accrual based on the policy/process described below in section F.

2. Failure to comply with early stopping criteria or planned interim analysis.
3. Serious adverse events beyond what would be expected for the study related treatment and/or procedures.
4. Failure to comply with institutional, FDA, CTEP, NCI, or PRMS guidelines and/or reporting requirements.
5. Failure to submit required scheduled reviews to the SRC, DSMC or Audit Committee.
6. A determination by the SRC that the scientific question being asked in the trial can no longer be supported, and that continued accrual to such a trial would not be in the best scientific evidence of the patient population eligible for the trial.

## F. STUDY CLOSURE FOR INSUFFICIENT ACCRUAL

During the initial review of a protocol, a waiver of the accrual requirement may be requested/granted by the SRC Chair or Vice Chair provided one of the following criteria is met:

1. The disease being studied represents a rare cancer or a rare condition of the trial exists (i.e., molecular screen).
2. Unique studies that will provide information with a small number of accruals.

The PRMS Administrator will automatically issue waivers for Pediatric studies. Requests for waivers are submitted electronically to prmsoffice@unmc.edu and must demonstrate why a waiver is being requested. Studies are monitored for accrual progress via continuing reviews, at least annually.

All trials that do not have sufficient accrual, defined as 30% of the accrual goal for the projected cumulative accrual goal to date at the time of continuing review, and do not have a waiver, will be issued a warning letter requiring submission of a very specific corrective action plan, or description of extenuating circumstances, from the PI to the SRC within 30 days of the SRC notice. The first notice letter will ask PIs to carefully reconsider the feasibility of the study or to consider a one-time revision of accrual goals. The action plan put forth by the PI will be referred to as a "covenant" for the trial.

At the time of the subsequent continuing review, if insufficient accrual remains, the SRC will consider termination with no option to revise accrual goals a second time. Studies recommended for termination by the SRC will have an option for appeal by the PI, as defined below. Studies considered high-priority by the DFT will be given up to two continuing reviews to revise accrual goals prior to consideration of termination or study closure at the time of the next sequential continuing review. SRC recommendations to terminate a trial will be made on the basis of a majority vote at the time of the continuing review.

If accrual is insufficient at the time of continuing review, the SRC can request a response by the PI without recommendation for closure. The SRC will request the following information and generation of a covenant/action plan where applicable. The PI will have 30 days to respond to the following points:

1. Are the accrual data as submitted accurate?
2. Are there subjects on study treatment? If so, what is the plan for those subjects?
3. Is the PI planning on or considering closing accrual?
4. Is the IRB considering termination?
5. Are there outstanding circumstances that can be resolved? If so, a revised action plan must be submitted.
6. What specific actions will be taken to actively seek an increase in accrual?

If no response is received, it is the decision of the SRC Chair to approve continuation or terminate the study. The PRMS Administrator ensures that appropriate documentation of SRC waiver approvals are documented in the CTMS.

### Appeal Process

The PI of a protocol, which has been disapproved/recommended for closure by the SRC, may submit a formal appeal to overturn the intent to terminate the protocol. The formal appeal process must be sent via email to the SRC Chair, Vice-Chair, and the Associate Director for Clinical Research within 5 business days of the issuance of the SRC notification letter. The appeal must provide strong justification for overturning the SRC disapproval vote.

The SRC Chair, Vice-Chair and Associate Director for Clinical Research will work with the PI to clearly define conditions (covenant) for protocol re-approval and consequences of continued inadequate protocol progress which will be determined at the next SRC continuing review.

The SRC Chair will present the new covenant before a full board SRC meeting and will then moderate the discussion and subsequent vote to approve the re-approval covenant. The Associate Director for Clinical Research will be responsible for maintaining records and required progress of the re-approval covenant. The PRMS Office will facilitate communication between study staff, the SRC Chair and the Associate Director of Clinical Research.

If no appeal is submitted by the PI within 5 business days, the PI must submit a final progress report by the time of the next scheduled SRC review unless an alternate deadline previously agreed upon

### G. TOXICITY AND ADVERSE EVENTS REPORTING TO THE DSMC

All Investigator-Initiated institutional and multi-institutional treatment intervention protocols must include a definition of adverse events specific to the protocol. Treatment intervention (i.e., therapeutic disease related) protocols must adhere to institutional, FDA, and CTEP guidelines for toxicity and adverse event reporting (Common Terminology Criteria for Adverse Events [CTCAE] can be obtained through the Fred & Pamela Buffett Cancer Center PRMS office or at http://evs.nci.nih.gov/ftp1/CTCAE/About.html).

The UNMC Data and Safety Monitoring Committee (DSMC) monitors all internal toxicities and adverse events that occur on treatment intervention trials not monitored by an independent board specifically designed for the individual study. While the DSMC provides a monthly report to the SRC of its review, the DSMC operates under its own authority and is not a sub-committee of the SRC. See the DSMC Policies and Procedures for a more complete description of the DSMC, including routinely reported toxicities.

### H. ADHERENCE REPORTING TO THE AUDIT COMMITTEE

The Audit Committee audits and provides oversight of all Cancer Center Investigator-Initiated Institutional Multi-Institutional and Other Externally Peer Reviewed Treatment Intervention Trials not monitored by an outside body to ensure: 1) compliance with institutional regulatory guidelines; 2) that the informed consent process was acceptable; 3) that the subject met all eligibility criteria; 4) adherence to the protocol's treatment plan; 5) the appropriateness of adverse event monitoring and reporting; and 6) the adequacy of subject follow-up as stipulated in the protocol.

If significant concerns are documented that are thought to compromise the safety or scientific integrity of the study (e.g., failure to comply with the approved protocol guidelines regarding adverse event reporting, eligibility criteria, stopping rules, quality data collection, etc.) the Audit Committee can request that the SRC evaluate the audit and determine if 1) the study should be suspended until the issues are adequately addressed by the PI, 2) the study must be closed, or 3) the study can continue.

All Investigator-Initiated Institutional, Multi-Institutional and Other Externally Peer Reviewed Treatment Intervention studies will continue to be audited while subjects are receiving protocol-specific treatment. Studies will no longer be audited when subject accrual, treatment, and/or research related tests are completed.

While the Audit Committee provides a monthly report to the SRC of its review, the Audit Committee operates under its own authority and is not a sub-committee of the SRC. See the Audit Committee Policies and Procedures for a more complete description of the Audit Committee.

## X. CLINICAL TRIALS REPORTING PROGRAM (CTRP)

CTRP is a comprehensive database of regularly updated information, including accrual, on all NCI-supported clinical trials. As UNMC is an NCI Designated Cancer Center, registration is required for all **cancer-related intervention** trials open to accrual as of or after January 1, 2009 and conducted by members of the University of Nebraska Medical Center (UNMC) faculty and students, and members of the UNMC Fred & Pamela Buffett Cancer Center. In addition, all Observational trials funded by NIH and open to accrual after January 1, 2020 must be registered in CTRP.

In addition, registration of all **protocol amendments, updates**, and **status changes** to these trials and approved by the UNMC IRB as of or after March 1, 2012 is required. Quarterly accrual reporting of all subjects registered to these trials is also mandatory beginning in September 2012. Detailed information on how to register new trials, protocol amendments and updates can be found at https://wiki.nci.nih.gov/display/CTRPdoc/NCI+CTRP+Registration+User+Guide *Note: Registration with CTRP is not the same as registration with clinicaltrials.gov. CTRP is an NCI reporting requirement overseen by the SRC.* ClinicalTrials.gov *registration is an FDA reporting requirement overseen by the IRB.*

### A. PRIMARY RESPONSIBILITY FOR CTRP REGISTRATION

The primary responsibility for registration of new trials, amendments, and updates varies by the trial's NCI Classification and is described below.

a. **Institutional Trials:**
   a. **Investigator-Initiated Institutional trials with UNMC/FPBCC as the study source (i.e., sponsor) –** includes all Investigator-Initiated Institutional trials that are single-site, multi-site, supported by industry or funded by grants): As the sponsor of this trial, **it is the responsibility of the UNMC/FPBCC** PI to ensure that this trial is registered with CTRP, and to register all protocol amendments and updates with CTRP.

b. **Multi-Institutional Trials with another Institution as the study source (i.e., sponsor):** It is the responsibility of the PI at the sponsoring institution to ensure that this trial is registered with CTRP, but it remains the responsibility of the UNMC PI to ensure that UNMC is listed as a participating site for the trial. It is also the responsibility of the PI at the sponsoring institution to ensure that all protocol amendments and updates are registered with CTRP.

b. **National Trials:** These trials have already been reported to NCI through its Cancer Therapy Evaluation Program (CTEP) or the Division of Cancer Prevention (DCP). **No action is required by UNMC study staff** to register the trial with CTRP or to register protocol amendments and updates to the trial. NCI will transfer data for this trial to CTRP.

c. **Industry Trials**: It is the responsibility of the industry sponsor to register these trials with CTRP, but it **remains the responsibility of the UNMC PI** to ensure that UNMC is listed as a participating site for the trial. It is also the responsibility of the PI at the industrial sponsor to ensure that all protocol amendments and updates are registered with CTRP**.**
***NOTE:*** *CTRP does not require proprietary information to be uploaded when registering Industry sponsored trials.*

d. **Externally Peer Reviewed Trials (EPR):** If the trial has already been reported to NCI through its Cancer Therapy Evaluation Program (CTEP) or the Division of Cancer Prevention (DCP), **no action is required by UNMC study staff** to register the trial or it's amendments with CTRP. NCI will transfer data for this trial to CTRP.
Most EPR trials will fall within this definition. If an EPR trial has not been reported to CTRP through CTEP of DCP**, the SRC will advise the UNMC PI** of their CTRP reporting responsibilities in the SRC New Protocol Approval letter.

**B. QUARTERLY ACCRUAL REPORTING TO CTRP**

a. **Subject's Registered at UNMC, UNMC's Associate Locations, and participating sites on multi-site trials where UNMC is the lead site:** For all subjects registered at UNMC or at UNMC's [1]associated locations, the PRMS Office will send quarterly accrual reports to CTRP utilizing data from the CTMS.

The following identifiers and demographic information are required before a subject will be entered into the PRMS database:

- Subject's Full Name[1].
- Subject's Date of Birth (mm/dd/yyyy).
- Subject's Gender.
- Subject's UNMC Medical Record (MR) Number or other unique identifier[1].
- Subject's Ethnicity.
- Subject's Zip Code.
- Subject's Country if not USA.
- Subject's Primary Method of Payment
  PIs are required to register each subject into the CTMS **within 5 business days of registration**.

For any subject registered **who does not have** a UNMC medical record number, the above information must be provided when registering a subject in the CTMS.

b. **Subjects Registered at Participating Sites:** For Investigator-Initiated Institutional trials with UNMC as the sponsor that are being conducted at one or more participating sites, the **lead institution (UNMC) is responsible for reporting all subjects registered at UNMC, UNMC's associated locations, and at participating sites to CTRP**.

All subjects registered to these trials at UNMC and UNMC's associated locations must be reported to the PRMS Office through registration in the CTMS as described in Section IX.A above.

In addition, all subjects registered at participating sites must be reported to the PRMS Office by the UNMC PI through registration of all study participants in the CTMS. Subjects registered at participating sites should be registered under that study site in the CTMS.

Detailed instructions for reporting accrual to CTRP are available at
https://wiki.nci.nih.gov/display/CTRPdoc/NCI+CTRP+Accrual+User+Guide

***NOTE:*** *A UNMC/NM associated location includes but is not limited to the Bellevue Medical Center, Village Pointe Medical Center, NE Orthopedic Hospital, and UNMC/NM Clinics. This includes Children's Hospital*

*and Medical Center.*

c. **Quarterly Accrual Verification:** The PRMS Office will verify accruals to **all** studies at least quarterly. Verification requests will be sent to the Nurse and/or Clinical Research Associate (CRA). The Nurse and/or CRA will be asked to 1) review all subjects registered in the CTMS and make any necessary corrections and/or additions; and 2) update all applicable subject states dates (if applicable) for each subject registered in the CTMS. The Nurse and/or CRA must respond to the verification request within 5 business days.

3. **CTRP REGISTRATION DEADLINES FOR INSTITUTIONAL TRIALS**
   a. **New Protocols:** New protocols must be registered with CTRP **prior to the enrollment of the first subject** to the trial.
   b. **Protocol Amendments:** Amendments to the protocol must be registered with CTRP **within 20 days of UNMC IRB approval**. Amendments are to include all changes (including updates) since the last change to the protocol was submission and include changes that substantively alter:
      - the treatment administered; and/or
      - the study design; and/or
      - the sites in which patients are being enrolled on the trial.
   c. **Study Updates:** Updates are to be submitted annually **at the same time as SRC and IRB continuing review**. Updates are defined as other changes that do not substantively affect the scientific conduct of the study, the protocol design, and/or the sites in which patients are being enrolled on the trial.
   d. **Status Changes:** Status changes **must be submitted** to CTRP no later than 30 days after they have taken place. This includes changes to the overall status of the trial (i.e., active to closed to accrual).
   e. **Reporting Subjects Registered at Participating Sites:** Reporting of subject accrual at participating sites must be current and complete by the 15th of every month.
4. **CTRP REGISTRATION DEADLINES FOR INDUSTRIAL TRIALS**
   The registration deadlines for Industrial trials are the same as the registration deadlines for Institutional trials. **UNMC is not the sponsor of these trials, therefore the responsibility for meeting the registration deadlines remains with the industry sponsor.** UNMC PIs should make every effort to ensure that the industry sponsor meets the registration and accrual reporting deadlines for these trials as outlined above. Once the sponsor registers the trial, the UNMC PI must add UNMC as a participating site if the sponsor has not done so already.
5. **CTRP REGISTRATION DEALINES FOR NATIONAL AND EXTERNALLY PEER REVIEWED TRIALS**
   National Cooperative Group (NCG) trials have already been reported to NCI through its Cancer Therapy Evaluation Program (CTEP) or the Division of Cancer Prevention (DCP). **No action is required by UNMC study staff** to register the trial with CTRP or to register protocol amendments and updates to the trial. NCI will transfer data for this trial to CTRP.

   The same is true for most EPR trials as well. If an EPR trial has not been reported to CTRP through CTEP of DCP**, the SRC will advise the UNMC PI** of their CTRP reporting responsibilities in the SRC New Protocol or Request for Change Approval letters.
6. **COMPLIANCE WITH CTRP REGISTRATION AND ACCRUAL REPORTING REQUIREMENTS**
   Non-compliance with CTRP registration and reporting requirements could jeopardize UNMC's Designated Cancer Center status, and as such, the PRMS Office will monitor compliance with the registration and accrual reporting deadlines described in Section X. above. The following procedures have been implemented to monitor compliance, to resolve non-compliance issues and to report unresolved issues to the SRC for action.
   a. **Written Notification of PI's Responsibilities:** PIs will be given written notification of their responsibilities for CTRP registration and/or accrual reporting in the SRC's New Protocol, Continuing Review and Request for Change approval letters, along with the applicable deadline for meeting their CTRP responsibilities.
   b. **Compliance Monitoring by the PRMS Office:** When registration and reporting deadlines are not met, the PRMS Office will notify the PI via email, with a copy to the study's Nurse and Data Coordinators. The notification will include a link to the CTRP registration site and registration/reporting instructions. PRMS staff will provide hands-on training in the PRMS Office, should study personnel need assistance in registering and/or reporting accrual (when applicable) to CTRP.
   c. The email notification will include a deadline of **5 (five) working days** to comply with trial registration and/or accrual reporting (when applicable). It remains the PI's responsibility to notify the PRMS Office if this secondary deadline cannot be met for any reason and to propose an alternative secondary deadline.

The PRMS Administrator will approve or disapprove the proposed alternative secondary deadline, based on the reasons for delay provided by the PI and in consultation with the SRC Chair.

d. **Referral of Non-Compliance to the SRC:** If no request for an alternative secondary deadline is received from the PI and/or efforts are not being made to comply with CTRP registration and reporting deadlines, the non-compliance issue will be referred to the SRC at its next regularly scheduled meeting for corrective action.
e. **Corrective Action Plan:** When a non-compliance issue is referred to the SRC for corrective action, the SRC will vote to take one of the following corrective actions:
   - Grant the PI an additional extension of not more than 15 calendar days to complete CTRP registration and/or accrual reporting (when applicable).
   - Suspend further enrollment to the trial until CTRP registration and/or accrual reporting (when applicable) is complete.
   - Terminate the study.
f. **Right to Appeal**: The SRC will communicate the results of its corrective action plan to the PI in writing. If a trial is suspended or terminated by the SRC, the written notification to the PI will include the reason(s) for the action taken. The investigator will have 30 calendar days to appeal the SRC's action in writing. The investigator's appeal will be reviewed at the next regularly scheduled meeting of the SRC. If the investigator does not adequately address the concerns of the SRC, the appeal will be denied. The IRB will be notified in writing of the outcome of the appeal.

7. **LINK TO CTRP USER'S GUIDES**

The "CTRP Registration Site User's Guide" and the "CTRP Subject Accrual User's Guide" are available at: https://wiki.nci.nih.gov/display/CTRPdoc/NCI+CTRP+Registration+User+Guide

## Appendix A

## FRED & PAMELA BUFFETT CANCER CENTER SRC PROTOCOL FORMAT

**Protocol Format**
NCI designated Clinical Cancer Centers must conduct scientific peer review of clinical protocols. A standardized protocol format is used for the successful implementation of this process. All Fred & Pamela Buffett Cancer Center Investigator-initiated Institutional and Multi-Institutional protocols developed and sponsored by this institution involving clinical research must include the following elements or the equivalent:



(*The SRC may withhold review and approval of a new Investigator-Initiated Institutional protocol until all data collection forms are submitted and reviewed*).

This standard format is expanded in greater detail in the following pages. The protocol footer must contain: 1) the UNMC IRB number; 2) the most current protocol version number and date; and 3) the page number. All pages of the protocol must be numbered. The preferred page numbering format is "page xx of xx."

**Title Page:** At a minimum, the Title Page must include: 1) the title of the study; 2) the name and contact information for the Principal Investigator; 3) if applicable, the name and contact information for the Secondary Investigator(s) and the Statistician; 4) a cumulative list of the approved protocol revisions (version number and date); and 5) a list of appendices to the protocol (if applicable). If the study is a Multi-institutional trial, the title page must also include the name of the Lead Institution.

**Abstract**: Describe the purpose, specific aims, hypothesis, conceptual framework (if applicable), methods (design, sample size, eligibility, instruments, procedures, data analysis) and outcome implications for research and practice.

**Schema**: This should be a diagrammatic representation of the study if possible. The schema should include the main details of the study.

**Section 1.0 Objectives**: The objectives of the research study must be stated clearly. The study design must be capable of answering the questions posed by the objectives. The statistical/data analysis section must

clearly state how the data will be analyzed in relation to each of the study's objectives. Specific requirements of treatment studies are discussed below.

**Phase 1 treatment studies:** Phase 1 trials determine a safe method/dose for Phase 2 trials and define acute effects that occur with a relatively high frequency in normal tissues. In addition, these trials may examine the agent's pharmacology and may reveal evidence of anti-tumor activity. Therapeutic intent is always present in Phase 1 trials; anticancer drugs are usually not tested in patients unless preclinical activity studies have already demonstrated evidence of significant activity in lab models. The initial starting dose in humans must be justified in the protocol. The initial dose may be increased gradually by some defined procedure until a level is found which produces limiting, but tolerable toxicity and/or clear signs of therapeutic activity.

**Phase 2 treatment studies:** A Phase 2 study determines a) whether a treatment/agent has anti-**tumor** activity and b) estimates the response rate in a defined patient population. Well-designed Phase 2 trials do not permit the entry of more patients than necessary to ensure the presence or **absence** of a clinically significant level of activity. Because various tumor types have different prognostic factors, eligibility requirements, and patterns of responsiveness to a particular drug or combination of drugs or therapy, Phase 2 trials are conducted in homogenous clinical entities (e.g., metastatic breast patients with cancer with measurable disease and a normal or near normal performance status).

**Phase 3 treatment studies:** If significant activity is observed in any disease during Phase 2 testing, subsequent **clinical** trials usually compare the new drug or treatment modality with standard treatment or observation if no standard treatment exists. Relevant endpoints (e.g., time to progression, survival, quality of life) must be used to measure benefit.

**Pilot Projects:** The primary objective is to collect preliminary data to plan a future study. The trial must be limited in duration and the investigator must specify future plans. The purpose(s) may be to test the feasibility of the study in a given **population**; to **evaluate** whether the instruments are sensitive to change; or to assess the ability to recruit for the study. In these cases, no control group is necessary. Endpoints such as the proportion of eligible subjects who consent to be randomized are appropriate as a standard control group.

**Section 2.0 Introduction**: Sufficient referenced background information must be included so that the rationale for the study is clear. For example, previous work done in animals and humans should be cited. Any unpublished data relevant to the rationale must be included. Toxicology studies carried out prior to Phase 1 trials that provide the investigator with a) estimates of a starting dose for clinical trials and b) prediction of the likely effects of the drug on normal tissues must be included.

**Section 3.0 Eligibility Criteria**: This must be a specific listing of all criteria necessary to be met for a subject to be eligible for the given study. Written informed consent must be an eligibility requirement. Types of subjects (minors, fetuses, pregnant women, etc.) must be specified. Many studies also include a section of exclusion criteria. Psychological, familial, sociological, or geographical conditions which do not permit compliance with the study should be considered. Studies with objective response as an endpoint must include clear statements specifying whether tumor sites to be followed for response must be measurable, what criteria must be fulfilled to consider disease measurable, whether evaluable disease is permitted, and if so, at what sites. Specific elements for Phase 1/2 studies are described below.

**Phase 1 Trials**. Patients must have normal or near normal organ function in order that the investigator may reliably distinguish drug effects from disease effects. When there is impairment of a major organ, drug treatment may produce increased toxicity because of decreased clearance or additive injury to the organ. Since most cancer drugs will ultimately be used in some patients that have impairment of major organ function (particularly cardiac, hepatic, and renal), it is sometimes reasonable to explore their use in such patients through Phase 1 trials explicitly designed to determine safe doses and pharmacology in these settings.

**Phase 2 and 3 Trials**. Elements to be considered include histological confirmation of disease, stage, prior therapy, measurable vs. evaluable disease, age, sex, performance status, life expectancy, and organ function requirements. For the treatment of diseases for which highly effective systemic therapy is not available (e.g., carcinomas of the large bowel, kidney, liver, pancreas, and malignant melanoma), Phase 2 or 3 studies may be limited to patients with no prior chemotherapy. For diseases in which chemotherapy may cause frequent objective regressions with or without survival benefit, Phase 2 or 3 studies may or may not be restricted to patients with no prior therapy. For diseases which are potentially curable with systemic treatment (e.g., acute leukemia, diffuse NHL, Hodgkin's disease, testicular cancer, limited small cell lung cancer, and ovarian cancer), Phase 2 or 3 studies generally enroll patients who have had the minimum extent of prior treatment compatible with current ethical standards of care.

**Examples of specific criteria for eligibility**.

- Histologically confirmed cancer (residual, recurrent, or metastatic)
- Adequate hepatic, renal, and bone marrow function: Bilirubin <1.5 mg%, AST less than five times the upper limits of normal, creatinine <1.5 mg%, etc.
- Patient must have measurable or evaluable disease (depending on protocol).
- Patient must be inoperable with no other definitive therapy available.

**Examples of specific criteria for exclusion.**

- Prior therapy with drugs to be used in the proposed study.
- Disease process which might be adversely affected by a particular drug (e.g., congestive heart failure with Doxorubicin)
- Patients with acute intercurrent complications such as infection or post-surgical complications
- Patients below a certain age or with a poor performance status as defined by a standard performance scale.
- Patients with a history of a second malignancy.

**Section 4.0 Registration Procedure**: The date of enrollment must be clearly defined the date of consent. However, all eligibility criteria do not need to be met until the date of the first study related treatment.

Procedures for subject entry (e.g., randomized, or non-randomized) must be specified. If the study is randomized, required information includes who will be performing randomization and their contact information and the subject characteristics and stratification factors (if any) to be provided at the time of entry. For non-randomized studies, the procedure for screening and recording patient eligibility for the study must be described.

For multi-institutional studies with UNMC as the sponsor, it is important that this section clearly state who is authorized to register and screen patients and the pertinent phone numbers and location of the office, hours of operation, and what information will be required. For studies involving the processing of lab samples, this section must contain information on how the specimens are to be processed and shipped (e.g., on ice, by what carrier, etc.), what accompanying referral forms are required, to whom samples must be sent, and hours for receipt of specimens.

**Section 5.0 Treatment Plan of Research Design**: This section will vary depending on the nature of the clinical trial. The following examples are given for a drug treatment program. When applicable consider recommendations for supportive care.

**Administration Schedule**:

- Description of various treatments including dose and schedule of all drugs used.

**Dose Modifications**

- Define criteria for dose modification
- Define criteria for holding and resuming treatment.
- Define criteria for termination of treatment.

**Duration of Therapy**

- Define criteria for stopping therapy. For example, disease progression or evidence of unacceptable drug toxicity.
- Define duration of therapy for patients with stable disease.
- Define duration of therapy for responding patients.
- Define stopping rules for the entire study. If certain target(s) are reached see Section 10.

**Concomitant Medications**

- Define whether concomitant medications will be collected for the study.
- Define the classes of concomitant medications that are to be recorded.
- Define the period of time during which concomitant medications are to be recorded.

**Section 6.0 Measurement of Effect**: In this section the parameters (e.g., response, time to progression, survival) for assessing the effect of an intervention are defined. Each protocol will specifically define these endpoints. Response (e.g., complete response, partial response, stable disease, and progressive disease) must be defined. For all Investigator-Initiated Institutional protocols evaluating tumor response in solid tumors, the SRC expects that the most current Response Evaluation Criteria in Solid Tumors (RECIST) (http://ctep.cancer.gov/protocolDevelopment/default.htm) will be used to monitor treatment response unless the PI provides justification for the use of other criteria. The extent of the restaging that is required to document a complete response must be defined. The protocol must state who will provide oversight on response evaluation (e.g., the principal investigator or a designated review committee).

**Section 7.0 Study Parameters**: Study parameters are best presented in tabular form indicating tests and frequency

of measurements (see below). The following guidelines might be used for pre-study testing to determine eligibility requirements in advanced disease protocols: all baseline x-rays (CT, MRI, bone scans, SRC) should be obtained within four weeks of the planned initiation of treatment; and CBC with differential, liver function studies and chemistries must be done within one week of initiation of study related treatment.

| Test | Prior to Testing | Weekly | Before Each Drug Administration | Every 3 Months |
|---|---|---|---|---|
| History and Physical Exam | | | | |
| Measurement of Tumor | | | | |
| Performance Status | | | | |
| Hemoglobin & HCT, WBC w/diff, platelet count, BUN, serum creatinine, Glucose, bilirubin, alkaline, Phosphatase, SGOT | | | | |

**Section 8.0 Drug Formulation and Procurement**: Pharmaceutical trials must contain a section for each drug or biologic agent and dose form, its preparation, dilution, stability, method of administration precautions, and known clinical toxicities. The supplier of each drug and information about commercial availability must also be specified.

**Section 9.0 Toxicity and Adverse Event Reporting Guidelines**: All Investigator-Initiated Institutional protocols must include a definition of adverse events specific to the protocol. Treatment (i.e., therapeutic disease related) protocols must adhere to institutional, FDA, and the most current CTEP guidelines for toxicity and adverse event reporting (CTE) Common Toxicity Criteria can be obtained at http://ctep.cancer.gov/protocolDevelopment/default.htm.

The Data and Safety Monitoring Committee (DSMC) monitors all internal toxicities and adverse events that occur on Investigator-Initiated Institutional protocol and provides a monthly report to the SRC on its review. See Section C for a more complete description of the DSMC. Apart from transplant protocols that are Investigator-Initiated Institutional trials, all internal serious adverse events (expected or unexpected, regardless of attribution) must be reported to the DSMC. For transplant protocols, the DSMC recognizes that certain toxicities are routinely anticipated. The investigator can indicate that a particular toxicity is anticipated for the vast majority of research participants and that such toxicity will therefore not be reported. The DSMC will determine in its initial review of the protocol if such exclusion from standard reporting guidelines is acceptable.

**Section 10.0 Statistical Considerations**: Each protocol should be developed and discussed with a biostatistician prior to submission. Meaningful biostatistical design of clinical trials is facilitated if the biostatistician understands the background of the disease being studied such as its natural history as well as its history using current treatments. This section must address how each objective will be assessed with the criteria for statistical significance stated. The following issues must be discussed: 1) definition of analysis population; 2) determination of sample size; 3) estimated duration of study; 4) accrual goal; 5) method of analyses; and 6) criteria for stopping the trial earlier than planned.

The Principal Investigator (PI) must also provide: **1)** the endpoints of the study such as response rate, toxicity, disease-free survival, or overall survival, and **2)** patient characteristics that affect response of the disease under consideration such as performance status, extent of disease, prior therapy, metastatic sites, etc.

***NOTE:*** *Possible reasons for stopping a trial early may include but are not limited to unacceptable toxicities; the trial appears unlikely to succeed either because of poor accrual; high dropout rates, etc.; early results effectively answer the study question either positively or negatively; and it becomes unnecessary (and possibly unethical) to continue the study.*

The PI and biostatistician should consider sources of patient accrual such as other centers and 'feeder' trials (i.e., ones with higher priority) available to determine expected accrual rates. The diseases being studied, and ethical questions present in the treatment of these diseases can influence the choice of experimental design such as single stage, multiple stage, or crossover; therefore, a discussion between the PI and the biostatistician should include these considerations as well (more specific requirements can be broken down by the type of trial):

**Pilot**: While statistical justification of sample size need not be included, estimated duration of study, method of analyses, decision-making criteria, estimated accrual per year and criteria for stopping the trial earlier than

planned must be addressed. Statistical justification of sample size might include a power analysis to determine the size of the pilot sample based on what will be needed for the larger, future study's sample.

**Phase 1**: The PI must provide an estimate of the number of patients to be accrued per year. Sample size is determined by results as the trial proceeds. A sample size of 15 – 24 patients is not unusual. Phase 1 trials may require more patients per dose level depending on the biologic endpoint being measured. If a dose escalation is planned, then dose escalation plan, definition of dose limiting toxicity, and definition of maximum tolerated dose (or dose to be taken to subsequent evaluation for non-anti-neoplastic agents) must be specified. For phase 1 trials without a dose escalation, the primary safety endpoint must be specified along with acceptable and unacceptable rates for its incidence and corresponding stopping rules.

**Phase 2 and 3 Requirements**:

**A.** Estimation of the number of patients that can be accrued per year.
**B.** Estimation of the percent of accrued patients that will be fully evaluable,
1. False positive error (recommending an ineffective agent for further study). This error is usually .05.
2. False negative error (declaring an effective agent as ineffective). Typical values are .10 or .20.

**C.** One sample design (i.e., no randomization into two or more treatment groups),
1. Is there a standard treatment with known response rates?
   - If yes, what is the proportion of response of the standard treatment?
   - If no, what is the accuracy needed in estimating the proportion of response (e.g.,30 + .05)?
2. Is there a threshold value or proportion responding above which the agent being tested is deemed a suitable candidate for Phase 3 testing?
   - If yes, what is that proportion (e.g.,20 or .30)?

**D.** Two sample design (i.e., randomization into two treatment groups).
1. If two success rates are to be compared:
   - What is the success rate of the control?
   - What is the expected success rate of the treatment?
2. Is there a threshold value or proportion responding above which the agent being tested is deemed a suitable candidate for Phase 3 testing?
   - If yes, what is that proportion (e.g..20 or .30)?
   - What is the expected outcome of the control groups?
   - What is the expected outcome of the treatment group?

**Section 11.0 Records to be Kept**: A list of all records, including flow sheets, data collection forms/instruments, summary and evaluation forms must be compiled. A description of where and how these records will be maintained needs to be included to facilitate retrieval by various audit committees. This includes where and how laboratory, and diagnostic studies will be retrieved or duplicated as part of the records for all subjects. The Biostatistics Shared Resource is available to assist the investigator in the development of a research database.

**Section 12.0 Patient Consent**: The consent form must adhere to the guidelines established by the Institutional Review Board of the University of Nebraska Medical Center.

**Section 13.0 References**

**Section 14.0 Data Collection Forms**: All data collection forms must be submitted when the protocol is initially reviewed. Assistance in preparing data collection forms for reporting data may be obtained from the Biostatistics Shared Resource. The SRC may withhold review and approval if data collection forms are not submitted with the protocol.
At a minimum, the Data Collection Forms (DCF's) must include protocol specific forms to record the following data for each subject:

- * Activities Worksheet.
- Adverse Event Log.
- * Clinical Laboratory Values.
- * Concomitant Medications Log.
- Death Record.
- Drug Accountability or Dispensing Log
- Eligibility Checklist (including both inclusion and exclusion criteria to match the protocol).

- Medical History.
- * Physical Examination.
- Screening and Enrollment Log.
- Specimen Collection and Preparation Worksheet.
- Telephone Log.
- Off Study Worksheet.

***both pre-study and during the course of the study as required by the protocol**

If applicable, the following DCF's must also be submitted:

- Advertisement samples.
- Subject Randomization Form.