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1.0 Protocol Review and Monitoring System Overview

The Protocol Review and Monitoring System (PRMS) at the Medical College of Wisconsin Cancer Center (MCWCC) is comprised of two stages: the Disease-Oriented Teams (DOTs) and the Scientific Review Committee (SRC). The mission of these committees is to foster the development of innovative, collaborative, and scientifically-sound studies that focus on the [illegible] 0ItTc [(9E 6f14 (v)]Tng7Tj rt)-6 (-Tw 5.11rti)-1 (8

The DOTs and SRC operate in collaboration with and are supported by the Clinical Trials Office (CTO) and maintain separate responsibilities and reporting. The PRMS review process is complementary to and independent of the Institutional Review Board (IRB) process. For cancer-related protocols, SRC approval is required before a protocol can go to the IRB for review, and both the PRMS and IRB must approve a protocol before it can be activated. The IRB focuses on the ethical and regulatory requirements for the conduct of research involving human subjects, paying particular attention to subject safety, while the SRC primarily reviews scientific quality, merit, and feasibility.

Oversight of DOT and SRC activities is provided by the MCWCC Clinical Research Executive Committee (CREC), which meets quarterly and ad hoc for urgent matters. The committee oversees and directs clinical research at the MCWCC and its affiliates. CREC establishes clinical research priorities, reviews general accrual and resource allocation issues, facilitates integration of research into the multidisciplinary clinics, and sets policy for the DOTs, SRC, and DSMC (Data and Safety [illegible]

and (if applicable) with an investigator brochure and a completed prioritization scoresheet.

Please see the MCWCC DOT Charter for more information about the DOTs.

3.0 Feasibility Review

While DOT review touches on trial feasibility, the MCWCC utilizes separate committees for more in depth feasibility review. Adult trials are reviewed by the FRC, which complements DOT and SRC review by ensuring that new studies are rigorously vetted for patient population availability, competition with trials already in the portfolio, and operational resource utilization (personnel, financial, material). The FRC is charged with identifying any issue that may impact the success of a trial, making the DOT aware of the issue, and helping to resolve the issue if possible. For pediatric trials, the Pediatric DOT performs both the DOT and feasibility review functions. These committees finalize each trial's prioritization score. A study is considered submitted to the SRC when the FRC or the Pediatric DOT has given approval.

4.0 Scientific Review Committee

The MCWCC Scientific Review Committee plays a vital role in protocol review and monitoring to ensure that clinical trials are scientifically sound and that approved trials maintain patient accrual goals and scientific progress. The specific functions of the SRC include the following:

- Maintaining a review committee of sufficient size and breadth of expertise to conduct a critical and fair scientific review of cancer-related research involving human subjects
- Conducting a thorough scientific review of all non-peer-reviewed, cancer-related clinical protocols using a standard format based on specific, pre-determined review criteria
- Assisting MCWCC investigators in the development of scientifically and clinically sound research through well-written protocols
- Considering protocol feasibility with regard to budget, resources, and competing trials
- Establishing clear criteria for determining whether ongoing clinical trials are making sufficient scientific progress, including the attainment of adequate patient accrual rates
- Monitoring all cancer-related research protocols based on the established criteria and terminating protocols that do not meet these expectations

4.1 Committee Composition and Roles

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All substantive changes to investigator-initiated and industry-sponsored protocols must be reviewed and approved by the SRC (Table 3). Amendments to cooperative group trials do not need to be reviewed. PIs should submit the following to the SRC: a summary of changes with justifications, the revised protocol with changes tracked, and the revised protocol clean.

The level of SRC review is at the Chair's discretion. Minor changes may be given an Expedited Review by the Chair, while more substantial changes will receive Full Review. When a change is related to the protection of research subjects, the IRB is obligated to review the request immediately. In this event, IRB approval will not require SRC approval.

Table 3. Amendment types reviewed by the SRC and exempted from review

Review Type	Amendment Types
SRC Review	Major changes, including but not limited to: x Inclusion or exclusion criteria x Drug dosage or delivery, treatment, schedule x Objectives or endpoints x Study design, methods, response criteria x Biostatistics, sample size (accrual goal) x Change in stopping rules x Sample collection (e.g., additional time points, sample types) x Change from institutional single-center study to multi-center study where MCW is coordinating center
Exempt from Review	Administrative changes, including but not limited to: x Personnel x Consent form x Investigator's Brochure x Recruitment material x Non-scientific changes to protocol x Clarifications to AE reporting, etc. x Amendments in response to subject safety concerns- proceed immediately to IRB review

4.3.3 Protocol Review Criteria

The SRC is responsible for reviewing the scientific merit of protocols and determining whether the research question and study design are scientifically sound and feasible. Additionally, the SRC reviews the clarity and thoroughness of the protocol document. Specifically, the SRC evaluates the following:

- x Background information – Relevant literature is summarized, citations are included, and a clear rationale for the study is presented.
- x Study objectives – The objectives are clear, appropriate, and feasible.
- x Study design – The design is appropriate for accomplishing the objectives.
- x Patient registration – Procedures for registering subjects are included, as is the contact information for the person to whom questions about eligibility and treatment should be directed.
- x Eligibility criteria – Criteria are clear, thorough, and include laboratory parameters.
- x Treatment plan – Dosage, duration, and follow-up are specified, as are subject withdrawal criteria.
- x Study calendar – A schedule of labs and procedures is provided.
- x Toxicities – The toxicity criteria are clearly stated and the grading system is identified.
- x Pharmacy considerations – Drug procurement, storage, administration, dosage, and interactions etc. are provided.
- x Endpoints – The endpoints are clear and appropriate.

- x Statistical considerations – The proposed statistical tests are appropriate for answering the study question, and the sample size will provide enough statistical power, appropriate stopping rules are included.
- x Data and safety monitoring – According to the MCWCC Data and Safety Monitoring Plan, all interventional protocols must have an appropriate data and safety monitoring plan specified. Also, protocols should have a risk-based quality assurance review plan specified.

These and other criteria are detailed in the SRC Reviewer forms (Appendix C-F).

4.3.4 Committee Actions

After reviewing a protocol, the committee votes to recommend one of the following actions:

- *Approved:* The protocol is scientifically sound and acceptable as written and may be forwarded to the IRB without modifications.
- *Approved with Clarifications:* The protocol is scientifically sound and acceptable pending clarification on the part of the PI of specifs:

(including further discussion with the DOT or potential trial closure) needs to be taken.

5.2 Accrual of Underserved Populations

The PRMS is responsible for monitoring accrual demographics to identify and address disparities and ensure that trial participants are being enrolled in proportion to their frequency in the patient population. On a quarterly basis, the SRC Coordinator generates interventional treatment accrual reports for each DOT, summarizing the DOT's accrual of female, Black/African American, Hispanic, and elderly (>65)/pediatric (<18) patients. The reports include data from the previous year and previous quarters to help DOTs understand trends. For comparison purposes, the reports also include new patient demographics from recent tumor registry data, as an approximation of the demographics of the hospital's cancer patient population.

Each quarter, the underserved accrual reports are sent to the DOTs, and DOTs are required to discuss their reports at their next available DOT meeting. Accrual reports are also reviewed by SRC and cancer center leadership.

5.3 Monitoring of Low-Accruing Trials

Low-accruing trials may fail to reach enrollment levels necessary for properly evaluating the hypotheses being tested, or the cost of maintaining them may outweigh the benefit of keeping them open at a particular center. The SRC is empowered to identify low-accruing trials and initiate their closure. The SRC Coordinator generates monthly reports in OnCore, identifies protocols due for review, and reports these to the SRC Chair. The DOTs also monitor study accrual and may initiate study closure or amendment.

Below is a summary of the SRC's policy. Please s

Years 2+	Reviewed annually after initial 12 months open *Minimum accrual met:* Approved for 1 year *Low accrual:* Warning issued, corrective action plan (CAP) requested, re-reviewed in 6 months

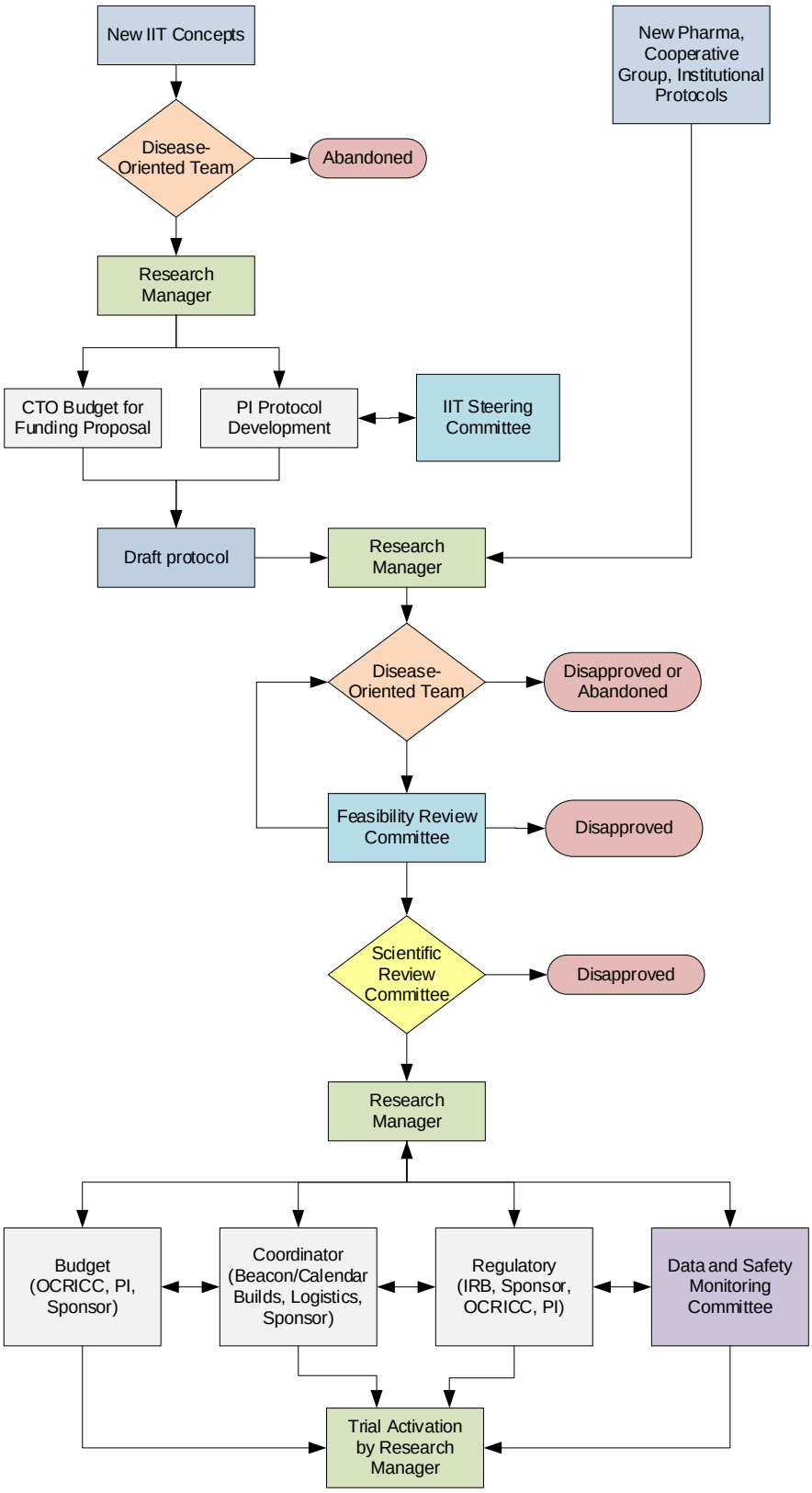
Rare disease trials: Trials involving rare diseases are expected to have slow accrual, thus they are treated more leniently. 7 K H 0 & : & & X V H V D Q D Q Q X D O 1 0 , 0 0 H R S O H L Q W K H 8 Q L W H G 6 W D W H V D V D guideline for defining cancers as rare. Studies on rare molecular subtypes of common cancers are also rare if they are distinct subgroups that receive specific, targeted therapy. Lastly, uncommon clinical situations of more common cancers are considered rare.

Trials may also be closed for lack of scientific merit, changing clinical practice patterns, loss of a key investigator, or for other reasons that would compromise the successful completion of trial objectives as determined by the SRC.

Appeals Process
When the SRC determines that a trial should be closed to accrual, the DOT Chair and PI will be notified by email. The trial's research manager, primary clinical coordinator, and regulatory coordinator will also be notified. If the DOT Chair and PI feel that there are significant extenuating circumstances, they may appeal to the SRC for reconsideration. The SRC Chair will make the final determination regarding closure.

Appendix A. Protocol Flow Chart

Protocol Review and Activation Process



Appendix B. New Trial Submission Form

Principal Investigator:	
Full Protocol Title:	
Patient-friendly Title:	
Planned study site(s):	Froedtert CW FMF FWB Drexel Moorland Community
Type of Study	MCW Investigator -Initiated NCTN/CTN External Institutional Industry/Pharmaceutical Consortium Other _____
	Drug Device Radiation Surgical Behavioral/Education Intervention Observational Other _____
	Scope of trial: Local (MCW/community) National/Multisite
	Treatment Diagnostic Epidemiologic/Observational Supportive Care Device Feasibility Ancillary Screening Health Services Research Correlative Prevention Basic Science Other _____
Phase of Study	I I/II II II/III III III/IV IV N/A Early Phase I Other _____
	Pilot Study? Yes No
Authorship	Is authorship likely? Yes No If yes: First/last author Middle author Comments:
Local accrual goal	Projected annual accrual Overall accrual duration (months) Overall local accrual goal

[redacted]

NCTN/CTN Pharmaceutical

Appendix C. SRC Reviewer Form for Interventional Investigator-

_____ A summary of the known and potential risks and benefits, if any, to human subjects is included.

_____ A description and justification for the route of administration, dosage, regimen, and treatment period(s).

_____ There is a description of the population that is to be studied.

_____ References to relevant literature and data that provide background for the trial are included.

_____ Sufficient background is given to understand the reason(s) for conducting this study.

_____ The objectives are stated clearly.

_____ The study design is appropriate to answer questions posed by these objectives.

_____ Subject inclusion and exclusion criteria are listed separately.

_____ The disease type/site required is described.

_____ The extent or stage of disease required is described.

_____ Information about whether the disease must be measurable or evaluable with a pertinent definition.

_____ A description of all pathology that is required is included (e.g., what type of biopsy is required? Is the initial biopsy sufficient proof of recurrent or metastatic disease or does the biopsy have to be obtained more recently?). The protocol states whether or not a verbal confirmation of the pathology report is sufficient or specifies if a separate review of pathology materials is required.

_____ If pathology materials are required, it is clear where these are to be sent.

_____ A description of the prior therapies permitted and/or not allowed is included.

_____ A description of the performance status criteria used in the study is included.

_____ A statement regarding the concomitant medications that are permitted or prohibited is included.

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_____ A statement that pregnant or lactating subjects are ineligible (if applicable) is included.

_____ A statement advising women of childbearing potential and sexually active males and females to use effective contraception while on study is included (ij /C T*[(c).2 (ed)-0.6 /o1P4 BDC -4 /C Tb(ed)-0.6 _

_____ pri (t)1.(c)-3.3(t)1.9 (2 Td [c2.9lr).1 (n)--0.6 us1.8((2 Td iff)-1.id)6 ((v)-1.5 i)-046 (n)-0 (meh)--1.9 us1.8(s)-2.4 h)0.

considered evaluable for response, the information provided matches what is specified in the statistical section.

_____ Criteria is provided for assessing response for the following categories, depending on what is permitted in the protocol:

- ____ - bidimensionally measurable disease
- ____ - unidimensional disease
- ____ - nonmeasurable evaluable disease
- ____ - leukemia/lymphoma

_____ The definitions of what constitutes a complete response, a partial response, stable disease, minimum residual disease (MRD) (if applicable) and progressive disease are defined.

All required lab tests, scans and measurements, ancillary labs, etc. should be included in chart format so that the intervals at which they are required are clear.

_____ Labs and procedures required to determine a patient's eligibil pal pMC /P DS5 (i)-0.9 -0.6(b)(qui)-6tmetaymea st adu1e le

_____ S a.6nrd(p)-0.7 (r)1iSeodSe6(e)

_____ The study-specific route of administration is included.

_____ Incompatibilities with all drug(s) are included.

_____ The source of drug (NCI, pharmaceutical company, commercially available) is included.

_____ The side effects for each drug are included.

_____ The nursing implications are included.

_____ Contact information and procedures for ordering drug are provided and clear.

What level of risk would you assign this protocol based on the following guidelines?:

: Non-treatment trials (e.g., nutritional or behavioral interventional, observational, lab sample, QoL)
: Treatment phase II or III and non-IND or non-IDE, lower risk multisite trials
: Phase I, IND, IDE, most multisite trials
: IND, IDE, cellular/gene therapy, first-in-human

x Reviewed x of subject files will be selected randomly for review (max 5 subjects at each monitoring timepoint). x			

_____ Descriptions of the statistical methods to be employed, including timing of any planned interim analysis(es) are included.

_____ A description of the measures taken to minimize/avoid bias (e.g. randomization, blinding) is included.

_____ The number of subjects planned to be enrolled is specified. In multicenter trials, the number of enrolled subjects projected for each trial site is specified.

_____ The reasons for the choice of sample size, including reflections on (or calculations of) the power of the trial and clinical justification are included.

_____ The level of significance to be used is specified.

_____ The criteria for the termination of the trial due to safety concerns (stopping rules) are specified.

_____ The procedures for accounting for missing, unused, and spurious data are specified.

_____ The procedures for reporting any deviation(s) from the original statistical plan are described and justified in the protocol and/or in the final report, as appropriate.

_____ The "adequate course" of therapy that a subject must receive to be considered evaluable for study endpoints is included. If this information is provided in any other section of the protocol, it matches what is included in the statistical section.

_____ The selection of subjects to be included in the analyses (e.g., all randomized subjects, all dosed subjects, all eligible subjects, evaluable subjects) is specified.

_____ Appropriate data points (including specific questions, responses and time points) have been identified to address the aims of the trial and facilitate case report form development.

_____ The methods for the sample collection, processing, and shipment described in the protocol are fully detailed, adequate and appropriate.

_____ The methods for sample analysis described in the protocol are fully detailed, adequate and appropriate.

_____ All involved personnel are correctly identified and correct contact information is included.

Patient registration procedures are clear and contact info for questions is included				
Study design is feasible and appropriate Is long				

cancer, rare molecular subtype of common cancer, unusual clinical situation)				

Any major problems, concerns, or comments with regard to the proposed study?

Appendix F. Monitoring of Ongoing Trials

1.0 Purpose/Background

The National Cancer Institute (NCI) requires cancer centers to monitor accrual to their open trials and close those making insufficient progress. Low-accruing trials (especially local trials) may fail to reach enrollment levels necessary for properly evaluating the hypotheses being tested, while national trials may accrue well overall but be a poor fit for a particular institution's patient population. Low-accruing trials require substantial support and resources to screen patients and maintain regulatory compliance, and they may prevent other, potentially more successful trials from opening due to concerns about limited resources and competition. In keeping with NCI Cancer Center Support Grant (CCSG) guidelines, the purpose of this document is to establish processes for monitoring accrual and closing underperforming trials. The Scientific Review Committee (SRC) will be the primary entity responsible for identifying low-accruing studies, warning Disease-Oriented Team (DOT) Chairs and principal investigators (PIs) about potential closure, and closing trials that fail to increase their rate of enrollment. However, the DOTs are strongly encouraged to closely monitor accrual and proactively address underperforming studies in their portfolios. It should be noted that trials focusing on rare cancers are expected to have low accrual; thus, they will be given special consideration.

2.0 Scope

This document applies to all prospective, hypothesis-driven, cancer-related clinical trials and studies (both interventional and noninterventional) open to accrual at the Medical College of Wisconsin Cancer Center (MCWCC).

3.0 Responsibility

MCWCC Clinical Research Executive Committee: reviews and approves changes to this SRC accrual monitoring policy

SRC Chair, Committee: monitors accrual to open trials; determines when to issue warnings and closures; reviews corrective action plans and appeals; closes underperforming trials

SRC Coordinator: identifies trials due for review; provides SRC with accrual data; maintains SRC accrual monitoring records

DOT Chairs and PIs: respond to SRC requests; provide corrective action plans

4.0 Definitions

Rare cancer trial: Trials involving rare diseases are expected to have slow accrual, and for this reason must EH WUHDWHG VHSDUDWHO\ 7KH 0&:&& GHILQHV D UDUH FDQFHU DV persons out of a population of 100,000 persons p HU \HDU ” SHU \HDU 6WXGLHV F subtypes of common cancers may also be considered if they are distinct subgroups that receive specific, targeted therapy. Lastly, uncommon clinical subsets of more common cancers will also be considered rare. All pediatric cancer will be considered rare.

5.0 POLICY

The SRC is required to monitor accrual to Cancer Center clinical trials. Trials that do not meet the expected minimum annual enrollment per this policy (Table 1) will be notified and given the opportunity to take corrective action. If enrollment does not improve, then they will be closed to further accrual.

Table 1. Accrual Monitoring Guidelines

Trial type	Industry, external institutional (external IITs, consortium)	Cooperative group (NCTN, BMT CTN)	Investigator - initiated	Rare disease
Expected annual enrollment	At least 40% of projected, or minimum of 2 (whichever is greater)	At least 40% of projected, or minimum of 1 (whichever is greater)	At least 40% of projected	Initial review at 2 years, then reviewed annually for overall activity
				Zero accrual at 2 years:

If at 6 months the trial meets the minimum enrollment listed in Table 1, then it will not require a 9-month review, and will be re-reviewed at 12 months. If at 6 months a trial's minimum accrual has not met the target, the SRC will request a corrective action plan (CAP) from the DOT Chair and trial PI. The DOT Chair and PI must respond within 30 days or the trial may be closed to further accrual. If the CAP does not sufficiently address SRC concerns, the SRC may request further action or close the study to accrual.

If the CAP is acceptable, the study will be re-reviewed at 9 months. If at 9 months a trial's minimum accrual continues to fall below