Medical College of Wisconsin Cancer Center

Protocol Review and Monitoring System (PRMS)

Disease-Oriented Teams

Scientific Review Committee

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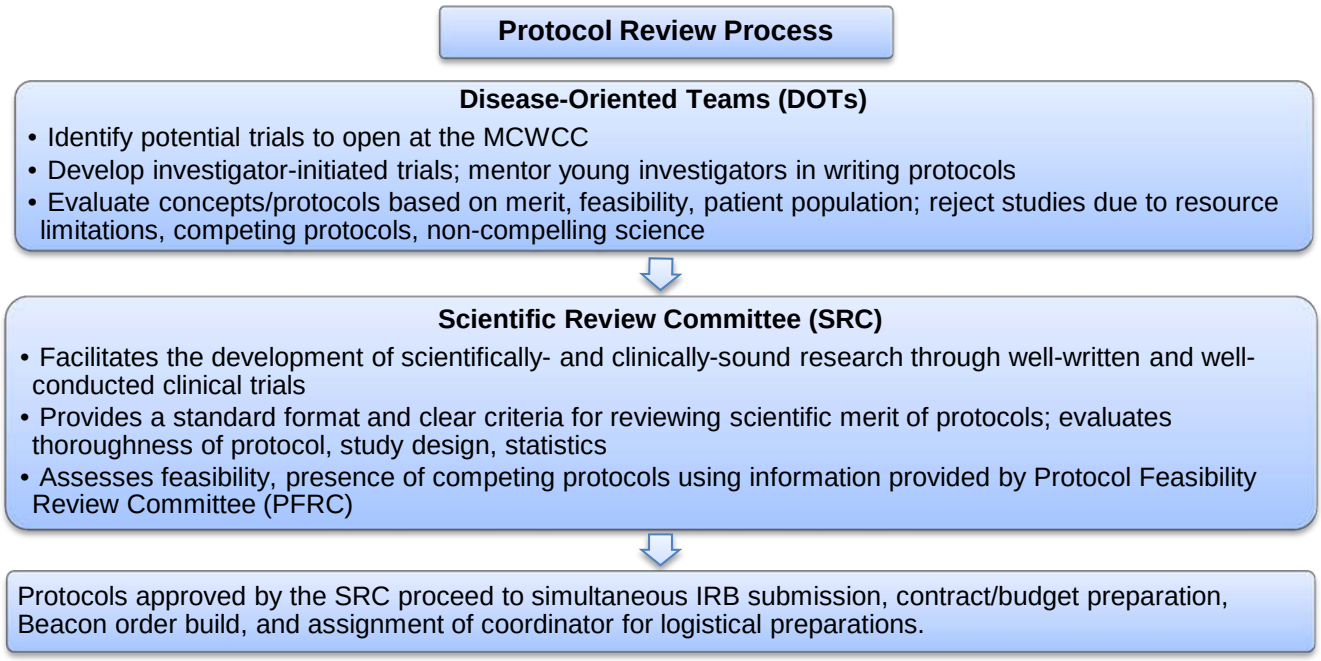
1.0 Protocol Review and Monitoring System Overview

The Protocol Review and Monitoring System (PRMS) at the Medical College of Wisconsin Cancer Center (MCWCC) is comprised of two levels: 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 prevention, detection, diagnosis, and treatment of cancer, as well as long-term follow-up and care.

MCWCC has 14 DOTs, most of which are dedicated to a specific organ/disease group. The first level of protocol review occurs within the DOTs. Each group meets monthly to exchange ideas and evaluate their research portfolio (active and pending trials). DOTs discuss the feasibility and merit of new concepts and protocols proposed by members, as well as protocol prioritization. An important function of the DOTs is to provide mentorship to members with clinical research ideas so that these concepts can be developed into high quality, fundable protocols. In addition, the IIT Steering Committee provides substantial support and guidance to PIs as they write their protocols. DOT members also review accrual to active trials and consider the closure of low accruing trials to free up resources for potentially more successful studies.

In contrast, the SRC is composed of members from a range of disease groups and modalities, as well as representatives from Basic Science, Nursing, Biostatistics, Pharmacy, and the community. The SRC meets bimonthly and reviews all proposed clinical cancer-related protocols. In addition to reviewing new protocols, the SRC monitors the scientific progress of active protocols. The SRC is empowered to close trials to further accrual if the scientific objectives of the trial are no longer relevant, or the rate of accrual to the study is too low at MCWCC to justify the cost of keeping it open.

Protocols advanced by the DOTs undergo a feasibility review by the MCWCC Protocol Feasibility Review Committee (PFRC) prior to their discussion at SRC. The PFRC determines if adequate financial and staff resources are available for the conduct of the proffered trial. In addition, this committee objectively reviews competing trials and past DOT accrual performance to help determine if the trial can be successfully executed. The PFRC reports any concerns it has to the SRC. The feasibility review is parallel to SRC submission and does not add to the protocol activation timeline.



For more details about the review process, see the MCWCC Protocol Flow Chart (Appendix A).

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 priorities for the CTO and the CTO Medical Director, 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 Monitoring Committee). CREC is chaired by the Associate Director of Clinical Research, and other members include the Associate Director of Translational Research/CTO Medical Director, Associate Director of Clinical Operations, SRC Chair, DSMC Chair, and a subset of DOT Chairs and investigators representing different disease groups and modalities.

2.0 Disease-Oriented Teams

The MCWCC Disease-Oriented Teams are empowered to develop and maintain disease-specific research portfolios that advance the goals of the MCWCC and faculty therein. The committees meet monthly to exchange ideas and evaluate their research portfolios. The functions of the DOTs include the following:

- Recruiting clinical and translational researchers to their disease group and MCWCC membership
- Identifying opportunities for translation of scientific discovery into clinical trials
- Designing quality clinical trials that will be activated and completed in a timely manner
- Encouraging multidisciplinary interaction, including tumor boards
- Developing and managing the disease group's clinical trial portfolio, including the prioritization of trials, in alignment with the goals of the group and MCWCC
- Determining the most efficient allocation of resources including, but not limited to, personnel, patient population, tissue, blood and data
- Reviewing and addressing trial progress, toxicities, and deviations
- Encouraging multidisciplinary grant submission and publication of research

Table 1. Disease-Oriented Teams and Chairs

DOT	Chair
Head and Neck	Stuart Wong, MD
Thoracic	David Johnstone, MD
Sarcoma	John Charlson, MD
Skin	Amy Harker-Murray, MD
Breast	Christopher Chitambar, MD
Genitourinary	Peter Langenstroer, MD
Leukemia/Lymphoma	Timothy Fenske, MD
Myeloma	Parameswaran Hari, MD
Bone Marrow Transplant	Mehdi Hamadani, MD
Central Nervous System	Joseph Bovi, MD
Gastrointestinal	T. Clark Gamblin, MD
Gynecology	Denise Uyar, MD
Adult Early Phase	Ben George, MD
Pediatrics	Cindy Schwartz, MD

2.1 Committee Composition

Each DOT is composed of faculty investigators from multiple modalities specializing in the treatment of a particular organ/disease group. The DOT Chairs (Table 1) are selected by the MCWCC Associate Director for Clinical Research in conjunction with clinical department and division leaders. Chairs are selected based on their clinical research experience, dedication to clinical research, and proven track record. The chair provides leadership for all of the DOT functions listed above; in addition, the chair leads the monthly DOT meetings,

mentors junior faculty, assists CTO leadership in prioritizing CTO resources, and attends quarterly meetings with Cancer Center leadership to align research priorities and resources with Cancer Center goals. Each DOT should have a representative from all three modalities as appropriate: radiation oncology, surgery, and hematology/oncology. The DOT Chairmanship is a three-year term with possibility of renewal.

DOT meetings are also attended by CTO staff: Research Managers, clinical research nurses, clinical research coordinators, and clinical research assistants. Research Managers provide the primary support for the DOTs. The Research Manager coordinates with the Chair to set monthly meeting agendas; uses OnCore to present accrual, toxicity, and deviation data for active studies; provides updates on pending protocols; and manages the disease team's trials throughout their life cycle. CTO staff record DOT meeting minutes and attendance.

2.2 New Protocol Review

The DOT meeting is the venue for the first presentation and evaluation of ideas for potential clinical trials to open at MCWCC. Investigator-initiated concepts and protocols, as well as outside cooperative group, institutional, and industry-initiated trials are placed on the DOT agenda and presented for group discussion at meetings. DOT members evaluate protocols for scientific merit, potential for successful accrual, presence of competing protocols, and alignment with the academic goals of the disease group. Protocol prioritization, feasibility, and logistics are also considered carefully. Investigator-initiated trials (IITs) are reviewed by the DOTs in two stages: concept and draft protocol. Investigators developing a potential study first bring the concept to the appropriate DOT for review and input, and junior investigators are mentored during trial development by either the DOT Chair or an assigned senior mentor. When drafting protocols, investigators have access to protocol templates provided by the CTO, as well as the services of the MCWCC scientific writer. The second DOT review occurs after the investigator has written a draft protocol. Protocols approved by the DOT move on to the SRC for review. The DOT Chair notes the decision on the New Trial Submission Form (Appendix B), which is forwarded to the SRC with the protocol. The majority of trials that are not pursued by the DOTs are rejected because of competing trials, non-compelling science or resource limitations.

2.3 Protocol Prioritization

Protocol prioritization is emphasized at the DOT level, where members of each disease team have expertise in their respective areas, knowledge of the current research portfolio, and the best understanding of the clinical trial needs of the patients seen in their clinics. DOT members consider feasibility and logistics, resource allocation, and competing trials. When competing trials exist, PIs are asked to provide evidence to the SRC that the patient population is large enough to support multiple trials and explain how the competing trials will be prioritized during recruitment.

The PFRC review provides a level of oversight of prioritizations within DOTs, and it provides a venue for prioritization across DOTs, looking at MCWCC and CTO resources as a whole. MCWCC leadership has defined research priorities to guide the DOTs, PFRC and SRC in their decision making. Potential clinical trials are evaluated according to the following order of priority (high to low):

1. Investigator-initiated trials supported by NCI grants and contracts
2. Other externally peer-reviewed investigator-initiated trials
3. MCWCC-sponsored, peer-reviewed investigator-initiated trials
4. Investigator-initiated trials funded by other sources
5. Cooperative group or Consortium trials
6. Pharmaceutical/Industry trials

Priority is given to early phase studies providing access to cutting-edge treatments, studies with high accrual potential, and studies that may positively impact the catchment area. The PFRC assigns a prioritization score (see below) to new protocols. This score is recorded as a data element in OnCore where it is accessible to DOTs and CTO staff. High-scoring studies are given top priority for MCWCC and CTO resources.

Evaluation Factor	Categories	Points	Earned
Sponsor	NCI-funded IIT/NCTN trial with MCW PI	6	
	Institutionally funded interventional IIT	5	
	Industry funded IIT	3	
	NCTN trial	2	
	Industry trial	1	
	External Institutional/Consortium Trial	1	
Science Value	First-in-Human	4	
	Phase I	2	
Authorship Potential	First/Last Author	3	
	Middle Author	1	
Annual Accrual Potential	>10	4	
	5-10	2	
Prior DOT Accrual Performance - average accrual per open trial	>4	2	
	3-4	1	
MCWCC/DOT Strategic Priority	High	3	
	Medium	2	
	Low	1	
MCW Lab Correlates (Hypothesis-driven)	Yes	3	
Uniquely Addresses Underserved Populations in Catchment Area	Yes	3	
		Total:	

3.0 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

3.1 Committee Composition and Roles

SRC members are appointed by the MCWCC Associate Director for Clinical Research. At least 14 members serve on the SRC with representative members from each of the following: Pediatric Hematology/Oncology, Adult Hematology/Oncology, Nursing, Obstetrics and Gynecology, Radiation Oncology, Surgery, Population Science, Basic Science, Pharmacy, Biostatistics, and an external community representative (Table 2). Members are invited to participate based on disciplinary expertise, as well as proficiency in the design, conduct and analysis of specific trials. Ad hoc members may be appointed to the SRC based on the areas of research and expertise needed for specific protocol review. The CTO provides administrative support for the SRC, and the CTO Administrative Director is a standing (but non-voting) member of the SRC. The Administrative Director is responsible for discussing protocol feasibility, providing the committee with appropriate budgetary, personnel, and competing protocol information in conjunction with their role on the Protocol Feasibility Review Committee. The SRC Chair is appointed by the Associate Director for Clinical Research. The responsibilities of the Chair include the following: conducting bi-weekly SRC meetings, maintaining the integrity and quality of the SRC, assigning protocols to SRC members for review, monitoring accrual and identifying low-accruing trials, communicating committee actions to PIs, and reporting SRC activities to the MCWCC leadership. The Co-Chair performs the responsibilities of the Chair when delegated. SRC members are appointed to three-year terms that may be renewed.

Table 2. Scientific Review Committee membership

Name	Expertise
Paul Ritch, MD (Chair)	Hematology/Oncology - Gastrointestinal
Kathryn Bylow, MD (Co-chair)	Hematology/Oncology - Genitourinary
Anjishnu Banerjee, PhD	Biostatistics
Carmen Bergom, MD, PhD	Radiation Oncology
William Bradley, MD	Gynecologic Oncology
Anita D'Souza, MD, MS	Hematology/Bone Marrow Transplant
Raphael Fraser, PhD	Biostatistics
Phyllis Holder, RN, MSN	Community member, Oncology Nursing
Sailaja Kamaraju, MD	Hematology/Oncology - Breast
Deepak Kilari, MD	Hematology/Oncology - Genitourinary
Jeffrey Knipstein, MD	Pediatric Neuro-oncology
Brent Logan, PhD	Biostatistics
Laura Michaelis, MD	Hematology/Oncology - Leukemia
Timothy Ridolfi, MD	Surgical Oncology
Theresa Rudnitzki, RN, MS	Clinical Nurse, Translational Research Unit
Aniko Szabo, PhD	Biostatistics
Monica Thakar, MD	Pediatric Hematology/BMT
Angela Urmanski, PharmD	Investigational Pharmacy
Li-Shu Wang, PhD	Basic Science
Sarah White, MD, MS	Interventional Radiology
Betty Oleson, BSN, RN, CCRP	CTO Administrative Director; non-voting
Jennifer Bollmer, PhD	CTO PRMS coordinator; non-voting

The SRC is supported by the PRMS Coordinator, a CTO staff member. The coordinator is responsible for maintaining the SRC records: a log of appointment and term length of SRC members, the OnCore database of protocols reviewed by the SRC, files pertaining to reviewed protocols (protocols, reviews, letters to PIs, etc.), meeting minutes documented in OnCore, and the SRC binder with paper copies of meeting agendas and attendance sheets. The coordinator also assists PIs in preparing submissions to the SRC, ensuring all documentation is complete. The coordinator is responsible for running low accrual reports in OnCore and providing a summary of low-accruing studies to the SRC Chair for review and potential closure. Lastly, the coordinator provides any other administrative support as required by the SRC Chair or committee.

SRC Ad Hoc Reviewers

The SRC has ad hoc reviewers for two types of studies: cellular therapeutics and population science. Both of these research areas require SRC members with additional specialized expertise to adequately review and potentially add value to investigator-initiated protocols. The cellular therapeutics ad hoc reviewers are all physicians from external institutions who are able to provide independent, expert assessment of in-house IITs. The population science reviewers are experts chosen from among MCW faculty. When a relevant protocol is submitted to the SRC, the Chair chooses two ad hoc reviewers to be primary and secondary reviewers on the

study. The reviewers are responsible for providing written evaluations of the protocol, and at least one of the reviewers should attend or call in to the full SRC meeting. The disposition of the protocol is voted on by the full committee.

3.2 New Protocol Submission to the SRC

After a protocol has been reviewed and approved by a DOT, it is submitted to the SRC for review. Every protocol submission is accompanied by a completed New Trial Submission Form. This multipurpose form helps the SRC categorize studies for review; provides SRC reviewers with basic information about a trial such as the target accrual, the proposed timeline, the existence of competing protocols, etc.; and alerts the CTO to the complexity of the trial for resource use estimation, funding issues, or special considerations (e.g., Investigational New Drug [IND] application). Studies involving INDs must also provide an Investigator's Brochure for the SRC's reference. For industry trials, the sponsor must select MCW as a participating site before the protocol is submitted to the SRC. The SRC prefers to review studies after funding is identified; when funding is pending, final SRC approval is held until the MCWCC Budget Office is satisfied that sufficient funding has been secured.

3.3 Feasibility Pre-Review

In preparation for the SRC meeting, new protocols on the SRC's agenda undergo a feasibility pre-review by the PFRC, which consists of the CTO Medical Director, CTO Administrative Director, MCWCC Administrative Director, and MCWCC/CTO Business Manager. The disease team Research Managers also attend when they have a protocol on the agenda. The committee discusses the protocol budget, protocol complexity, personnel availability, presence of competing trials in the disease team's portfolio, and any logistical concerns. The CTO Administrative Director communicates the relevant information to the SRC at full committee meetings. The PFRC is advisory to the SRC, and the SRC with its broader membership makes the decision whether to move forward with the trial.

3.4 SRC Protocol Review Process

The SRC Chair assigns committee members to review protocols based upon member expertise. Any SRC member serving as a PI, co-PI, or sub-investigator of a protocol coming before the committee for scientific review will not be allowed to serve as a reviewer for that protocol. The Coordinator sends the protocol, the appropriate SRC Reviewer Form, and any other supporting documentation (Investigator's Brochures, PI responses to comments, etc.) to the reviewers approximately one week before the SRC meeting. The assigned biostatistician and pharmacy representative also receive the protocol for review to ensure that statistical considerations are appropriate and valid, and that potentially adverse drug interactions are understood and acknowledged.

The SRC meets on the first and third Monday of every month from 5:00-6:00 pm in Clinical Cancer Center Conference Room N. If the volume of submissions is high, then the SRC may schedule a third meeting as needed. A meeting quorum requires the presence of 50% of voting members. Each SRC member has one vote, including the chair. On protocols where an SRC member is a PI, Co-PI, or sub-investigator, the member is not present for the vote.

3.4.1 Levels of Protocol Review

There are two levels of SRC review: Full Review and Expedited Review. The SRC Chair determines the level of review according to the type of trial (Table 3).

Full Review: For Full Review, the protocol is made available to the entire committee. The SRC Chair identifies a primary reviewer and potentially a secondary reviewer, depending upon the type of protocol. All therapeutic protocols are reviewed by at least one physician member of the SRC. In addition, a full statistical review is performed by the representative from Biostatistics. At the meeting, the primary reviewer summarizes the protocol for the committee. Then, the primary and secondary (where applicable) reviewers present their comments and recommendations, which are discussed by the full committee. Statistical considerations are addressed by the biostatistician, pharmaceutical issues and potential adverse drug

interactions are addressed by the Pharmacy representative, and feasibility concerns are raised by the CTO Administrative Director. The assigned reviewers are required to complete and submit the appropriate SRC Reviewer Form. In the event an IIT is "Deferred" or "Disapproved" by the SRC, the PI is welcome to attend a subsequent meeting to defend his or her protocol. The PI may give a 5 minute synopsis of the trial and answer the committee's questions, but they are not present for further discussion or for the vote.

Expedited Review: Studies qualifying for Expedited Review are reviewed by the SRC Chair, who is responsible for approval or disapproval. At the Chair's discretion, a protocol may undergo Full Review instead. The outcomes of Expedited Reviews are reported to the full committee at the next scheduled meeting. These protocols may be submitted and reviewed on a rolling basis. The Expedited Review will be done in an effort not to delay the process of subsequent IRB review and approval.

Table 3. Levels of SRC review for new cancer-related protocols

Review Type	Study Type

Full Review	• Interventional studies (treatment, non-treatment)
	  ▪ Investigator-initiated – primary and secondary reviewer
	  ▪ Investigator-initiated at another site – primary and secondary reviewer
	  ▪ Industry-initiated – primary reviewer
	  ▪ Consortium – primary reviewer
	• Institutional prospective molecular or imaging diagnostic trials where information from the test affects treatment of the study subject (e.g., molecular profiling) – primary and secondary reviewer
	• Non-interventional epidemiological or observational studies involving cancer patients (*e.g.*, population science, surveillance, risk assessment, behavioral) – primary and secondary reviewer
	• Correlative or ancillary studies – primary reviewer
	  ▪ Imaging, diagnostic
	  ▪ Prospective studies of tissues, body fluids with a scientific hypothesis
	  ▪ Prospective molecular or genetic epidemiology studies that evaluate aspects of patient care but do not answer questions about impacts of particular interventions and do not use information from tests to alter treatment for study subjects

Expedited Review	• National Clinical Trials Network protocols (Cooperative groups) • Protocols that have undergone external peer review by an organization the NCI considers acceptable
Exempt from Review	• Emergency Use, Expanded Access, Treatment Use • Medical chart reviews, retrospectives • Registries, Tissue Bank studies with no scientific objective • Screening and/or questionnaire studies that gather information from subjects but do not assess the impact on subject or alter course of treatment • Population-based studies using cancer patients and healthy subjects where focus of study is not cancer-related

3.4.2 Amendment reviews

All substantive changes to investigator-initiated and industry-sponsored protocols must be reviewed and

approved by the SRC (Table 4). Amendments to cooperative group trials do not need to be reviewed. PIs must submit the following to the SRC: a summary of changes with justifications, the revised protocol with changes tracked, and the revised protocol cleaned.

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 4. Amendment types reviewed by the SRC and exempted from review

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

3.4.3 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:

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

- 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.
- 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).

3.4.4 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 Modifications:* The protocol is scientifically sound and acceptable pending clarification on the part of the PI of specific points. The PI must submit a copy of any protocol revisions to the Chair for expedited review and approval.
- *Deferred:* The study requires significant revisions to satisfy review criteria. The PI must submit a revised protocol and a written response to the SRC's concerns. The protocol will then receive an SRC re-review at a full committee meeting.
- *Disapproved:* The study is not scientifically sound, not ethical, not acceptable as written, and/or is not within the mission of the MCWCC.

The actions of the SRC are recorded in the form of minutes in OnCore where they are available to all SRC members. PIs of approved protocols are notified of SRC Approval via an OnCore-generated notification. For committee decisions requiring a response from the PI, the Chair sends a letter to the PI within seven days of the SRC meeting. PIs of protocols that were "Approved with Modifications" are expected to respond to SRC comments within 30 days. These responses are given an Expedited Review by the SRC Chair and often the reviewers as well. PIs of protocols that were "Deferred" are expected to respond to SRC comments within 60 days. PI responses to "Deferred" are re-assigned to the original reviewers whenever possible and placed on the next available meeting agenda. They go before the full committee and are evaluated with the same possible outcomes as above.

4.0 SRC Monitoring of Ongoing Protocols

Per the NCI's Cancer Center Support Grant (CCSG) guidelines, the SRC is responsible for monitoring the progress of trials open to accrual. Protocols are reviewed by the SRC for continued scientific merit, progress towards completion of scientific objectives, and accrual. 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 12 month review, and reports these to the SRC Chair. Studies meeting minimum accrual expectations are approved for another 12 months, whereas corrective action plans are requested from low-accruing studies. The DOTs also monitor study accrual and may initiate study closure or amendment.

Below is a summary of the SRC's policy. Please see Appendix G for a full description.

Review Criteria

After a study has been open to accrual 12 months, it will undergo SRC continuing review. If it meets the minimum enrollment listed in Table 5, then it is approved for another year. If its accrual does not meet the minimum target, the study team will be warned and must submit a corrective action plan. If accrual has not improved after six months, then the study will be closed.

Table 5. Accrual guidelines

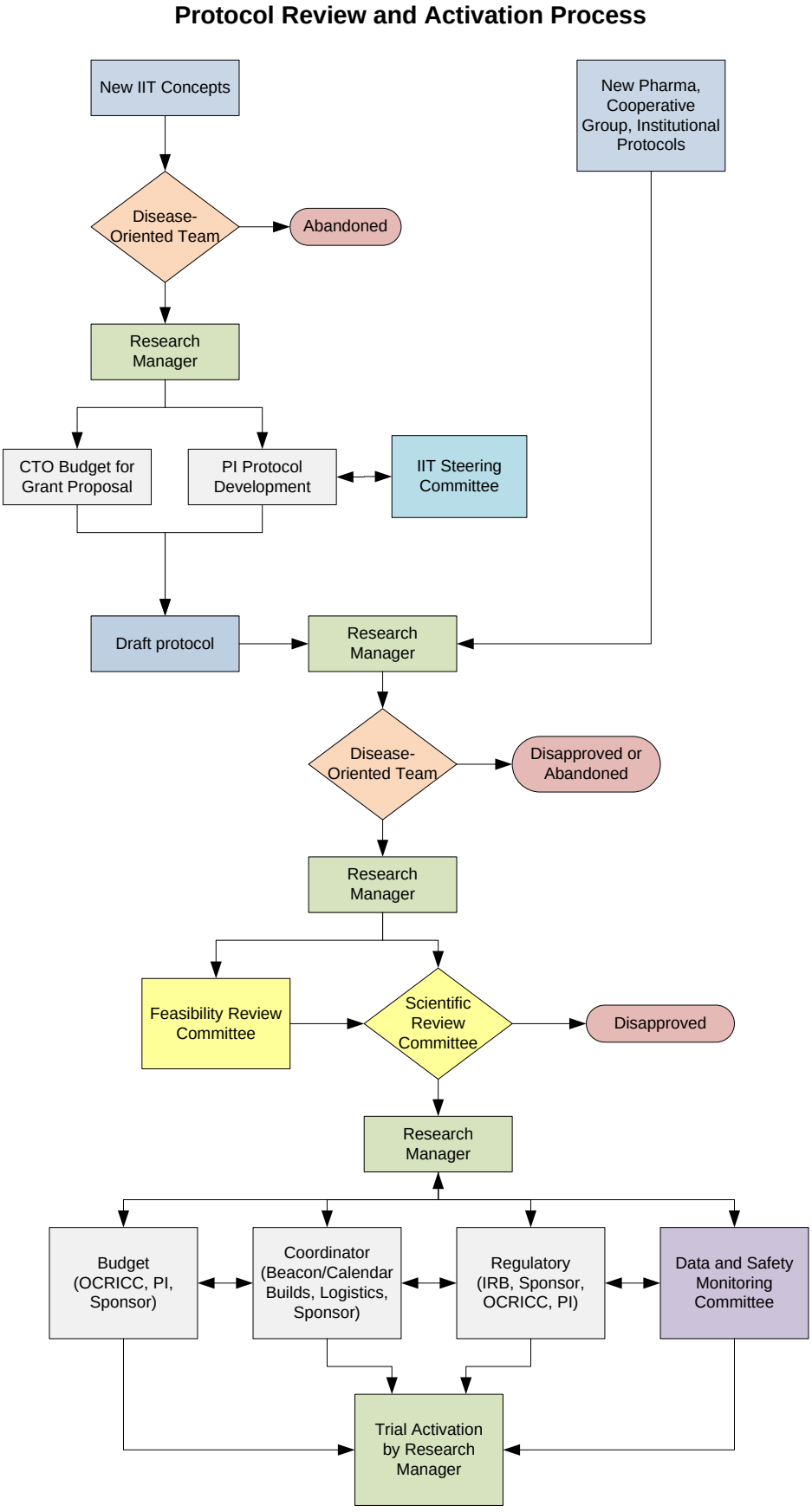
Trial Type	Expected annual enrollment
Phase I	At least 2 if multicenter, 4 if local
Industry trials	At least 2
Cooperative group trials (NCTN, BMT-CTN)	At least 1
External institutional trials (external IITs, consortium)	At least 2
Investigator-initiated trials	At least 33% of projected
Rare disease trials	Exempt

Investigator-initiated trials: The DSMC also monitors interventional IITs and will notify the SRC if it feels a trial is making insufficient progress in enrollment. Low-accruing IITs will be encouraged to take corrective action to increase enrollment, such as altering inclusion/exclusion criteria, altering study design, or activating the trial at associated community sites.

Rare disease trials: Trials involving rare diseases are expected to have slow accrual, thus they are exempt from SRC accrual monitoring. The MCWCC uses an annual incidence of ≤4/100,000 people in the United States as a guideline for defining cancers as rare. Studies on rare molecular subtypes of common cancers are also exempt if they are distinct subgroups that receive specific, targeted therapy. Lastly, uncommon clinical situations of more common cancers are considered rare and exempt.
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



Appendix B. New Trial Submission Form

This form must be filled out by the Principal Investigator.

Principal Investigator:	
Full Protocol Title:	
Patient-friendly Title:	
Planned study site(s):	☐ FMLH ☐ CHW ☐ CMH ☐ West Bend
Study Overview	
Type of Study	☐ MCW Investigator-Initiated ☐ Cooperative Group ☐ Institution (IIT from outside) ☐ Industry/Pharmaceutical ☐ Consortium ☐ Other _____
	☐ Drug ☐ Device ☐ Observational ☐ Community Research
	Scope of trial: ☐ Local ☐ National
	☐ Treatment ☐ Ancillary or Companion ☐ Epidemiologic/Observational ☐ Prevention ☐ Supportive Care ☐ Health Services Research ☐ Correlative ☐ Screening ☐ Other _____ ☐ Diagnostic ☐ Basic Science
Phase of Study	☐ Pilot ☐ I ☐ I/II ☐ II ☐ II/III ☐ III ☐ III/IV ☐ IV ☐ N/A ☐ Treatment Use* ☐ Expanded Access* ☐ Other _____ *Also fill out Appendix in Management of Expanded Access and Treatment Use Protocols SOP
Academic Credit	☐ Multi-institutional trial with no chance of authorship or credit ☐ Multi-institutional trial with no chance of authorship but with associated institutional credit (e.g., cooperative group trial) ☐ Multi-institutional trial with likelihood of authorship (named investigator or high accrual expectations) ☐ MCW investigator-initiated trial with likelihood of authorship
Value to Patients	☐ Little or no clinical importance, registry or post-licensing marketing study ☐ Phase I-III trial with potential to change clinical practices ☐ Phase II-III trial likely to change clinical practices
Accrual	
Local accrual goal	Local target accrual goal: Accrual Duration (Months): How many patients with this specific disease are seen at our institution per year (include source of data for expected enrollment, e.g. tumor registry, EPIC, CDW, etc.)?
National accrual goal	Overall target accrual goal: Current overall enrollment: Date study opened nationally: Expected closing date:
Rare disease	☐ Check box if annual incidence is ≤3 newly diagnosed persons per 100,000 persons in U.S.

Funding	
Sponsor: ☐ Department ☐ Cooperative group ☐ Pharmaceutical ☐ NCI CTEP ☐ Other_____ ☐ There is no funding for this study. ☐ Additional funding is needed.	
For Investigator-Initiated Trials: Funding Source: _____ Funding Proposal #:_____ Has funding been approved? ☐Yes ☐No Amount of award/approved funding: $_____	
Study Complexity	
No. of Arms	☐ 1 ☐ 2 ☐ 3 ☐ 4 or more
Department/Team Impact	☐ One or two departments involved – Standard clinical research team ☐ Three or more departments involved – Complex coordination needed ☐ Inpatient Care Required
Radiology	Is there an imaging requirement in the protocol? ☐Yes ☐No
	If Yes- The requirements are: ☐ standard ☐ study-specific For IITs, has a radiologist been identified as a collaborator? ☐Yes ☐No
Eligibility Review	☐ Basic eligibility ☐ Complex with multi-step eligibility review
Registration/ Randomization Tasks	☐ One step ☐ Multiple steps with possible pathology/ancillary review
Frequency of Study Tasks	☐ Every 21-30 days or more ☐ Weekly ☐ Daily
Beacon Build needed?	☐Yes ☐No
Ancillary Studies	☐ Banking ☐ QoL ☐ PK samples ☐ Other
Data Collection on Treatment	☐ Basic – No AE reporting, batching of data ☐ Standard – AE reporting and data collection ☐ Complex – Real time data submission, review of source documents for endpoints, multiple data sources
Follow-up Requirements	☐ Annual or minimal follow-up ☐ At each time point of clinical activity ☐ Complex multiple clinical points
Special Requirements	☐ IND application
	☐ Clinicaltrials.gov
	☐ Coordinating center for multi-site study
	☐ Other

Faculty Research Committee approval to send to SRC:

DOT Chair Signature Date

Appendix C. SRC Reviewer Form for Interventional Investigator-Initiated Protocols

Medical College of Wisconsin Cancer Center
Scientific Review Committee (SRC)

Interventional Investigator-Initiated Reviewer Form

All reviewers are expected to attend the SRC meeting, either in person or by teleconference. SRC meetings are held on the 1st and 3rd Monday of each month at 5 PM in CLCC Conference Room N. E-mail or call Jennifer Bollmer regarding any questions or issues about your review of this protocol (jbollmer@mcw.edu, Phone: 805-1947). If you are unable to attend, please email your review to jbollmer@mcw.edu by 4 PM, the day of the meeting.

Protocol Title: _____
Principal Investigator: _____
Sponsor: _____
Funding Agency: _____
Reviewer: _____ Meeting Date: _____

OVERALL EVALUATION OF PROTOCOL - ACTION RECOMMENDED:

_____ ***Approved***: The protocol is scientifically sound and acceptable as written and may be forwarded to the IRB without modifications.

_____ ***Approved with Modifications:*** The protocol is scientifically sound and acceptable pending clarification on the part of the PI of specific points. The PI must submit a copy of any protocol revisions to the Chair for Expedited Review and approval.

_____ ***Deferred:*** The protocol requires significant revisions in order to satisfy review criteria. The PI must submit a revised protocol and written response to the SRC's concerns for re-review at a full committee meeting.

_____ ***Disapproved:*** The study is not scientifically sound, not ethical, not acceptable as written, and/or is not within the mission of the MCW Cancer Center.

Please make your assessment of each section by marking all items that are satisfactory with a "**Y**". If something is missing or needs revision, please mark with an "**N**". Mark any items that do not apply to this particular protocol with "**N/A**". Do not hesitate to add notes, comments, evaluations, etc., as you feel necessary in the "**Comments**" field following each section.

Accrual Monitoring

_____ Should this study be classified as rare disease for accrual monitoring? (incidence ≤4 per 100,000 people in US: rare cancer, rare molecular subtype of common cancer, unusual clinical situation)

Overall study accrual goal: _____
Predicted duration of accrual (in years): _____
Predicted annual accrual goal: _____

Comments:

I. Title Page and Table of Contents

_____ The protocol date and/or version number is included.

_____ The Sponsor is appropriately identified as the originating institution; information for any funding Sponsors (if applicable) is also included.

_____ The title accurately represents or includes ***all*** aspects of the protocol.

_____ The Principal Investigator (PI) is identified by name, address, phone number and email.

_____ Each affiliate that may participate is identified with local PIs and their address, phone #, and email.

_____ The Sub-Investigators or Chairs for each modality (e.g. radiation, surgery, laboratory) are identified.

_____ The Statistician is identified.

_____ A table of contents is present and each section is correctly identified and numbered.

_____ A description of the type/design of trial to be conducted is clear (e.g., double-blind, placebo-controlled, parallel design) and a schematic diagram of trial design, procedures, and stages is given.

_____ Page footers have all of the following: page numbers, protocol number or short title, version and date.

Comments:

II. Introduction (Background and Rationale)

_____ The name and description of the investigational product(s) are included (if applicable).

_____ A summary of findings from nonclinical and clinical studies relevant to the trial.

_____ 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.

Comments:

III. Objectives (Primary and secondary endpoints of the study, listed and numbered individually)

_____ The objectives are stated clearly.

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

Comments:

IV. Eligibility Criteria

_____ 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.

_____ A statement regarding a “wash-out” (if applicable) period for any medications is included.

_____ A statement regarding the concurrent diseases that are permitted or prohibited is included.

_____ Any requirements regarding the allowance of concurrent and prior malignancies are included.

_____ Required laboratory parameters, scans, and tests are included.

_____ The study is age range appropriate (e.g. ≥ 18 years). If minors are permitted, please make note of this (a minor consent and parental assent form will be required).

_____ 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 (if applicable).

_____ A statement that the patient must have signed informed consent ***prior to registration on study is included.***

Comments:

V. Patient Registration

_____ Registration procedures are clear. The data needed to register study patients is provided, including whom to call and phone number(s) if there are questions regarding eligibility, eligibility forms, or registration procedures.

_____ If this is a multi-center trial, the protocol specifies whether patients will be registered locally or through a central office.

_____ Randomization procedures are described and are adequate.

Comments:

VI. Treatment Plan

_____ The treatment(s) to be administered is specified, including the name(s) of all the product(s), the dose(s), the dosing schedule(s) (over ___ minutes or hours; 3X per day at mealtime, etc.), and the route/mode(s) of administration (e.g. IV bolus, IV infusion, oral). The treatment periods (e.g. q 3 weeks, daily for 28 days, etc.) for subjects for each investigational treatment/group are specified.

_____ The total duration of treatment is specified, including the follow-up period(s) for subjects for each investigational treatment/ group (e.g. for a maximum of cycles, until progression, other specified time).

_____ If the study does require patients to be followed after active study treatment is over, the protocol states for how long patients will be followed (e.g. until disease recurrence, until disease progression, until death). NOTE: Any long-term follow-up should also be specified in the consent template.

_____ Medication(s)/treatment(s) permitted (including rescue medication) and not permitted before and/or during the trial are specified.

_____ Procedures for monitoring subject compliance and/or side effects (e.g. patient diaries, special patient instructions regarding self-injections, etc) are included, if appropriate.

_____ The schema completely and accurately reflects the treatment plan.

Comments:

VII. Assessment of Safety, Dose Modifications, and Dose Delays

_____ DSMC-specific data and safety monitoring plan included.

_____ Ensure AE reporting is consistent with DSMC charter. (Unexpected grade 3 and all grade 4 & 5. Grade 4 & 5 must be submitted within 5 days.)

_____ The methods and timing for assessing, recording, and analyzing safety parameters are included.

_____ The type and duration of the follow-up of subjects after adverse events is specified.

_____ Criteria for grading toxicities and criteria for dose modifications are specified (e.g. CTCAE v4.0)

_____ Instructions are included for dose modifications of *each* study drug.

_____ Instructions are included for *each* modality (chemo, radiation).

_____ Definitions for Dose Limiting Toxicity (DLT) and/or Maximum Tolerated Dose (MTD) are provided, clear, and adequate (if applicable). If no, specify what needs to be changed in the comments section.

Comments:

VIII. Subject Withdrawal Criteria

_____ Subject withdrawal criteria are included. (i.e., terminating investigational product treatment/trial treatment). There are procedures that specify:

_____ (a) When and how to withdraw subjects from investigational treatment.

_____ (b) Data collection procedures for withdrawn subjects.

_____ (c) Whether and how subjects are to be replaced.

_____ (d) The follow-up for subjects withdrawn from investigational product treatment/ trial treatment.

Comments:

IX. Endpoint Assessment

_____ Methods and timing for assessing, recording, and analyzing study endpoints are included.

_____ If this section includes information regarding the "adequate course" of therapy that a subject must receive to be

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.

Comments:

X. Study Parameters (Table format required)

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 eligibility are listed in the table. Please list any labs/procedures that do not "match up" with those described in the eligibility section.

_____ Labs and procedures to be conducted when the subject is actively being treated are listed in the table. Please list labs/procedures that should be added or that do not "match up" with those described in the study procedures and response assessment sections.

_____ Unnecessary tests are included. Consider removing the following: _____.

_____ The study parameter table clearly outlines how often all labs and procedures are to be done. The specified intervals are reasonable.

_____ The time limit for pre-study labs is defined (how many days/weeks a lab can be conducted prior to on study).

Comments:

XI. Drug Formulation and Procurement

The following is provided for ***each*** study drug:

_____ Other names, if any, for the drug(s) are specified.

_____ The classification of each drug are included (type of agent).

_____ The mode of action is included.

_____ The procedures for drug(s) storage and stability are included.

_____ The specific dosing for this study is included.

_____ The procedures for drug preparation are included (diluents to be used, etc).

_____ 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.

Comments:

XII. Quality Assurance Review

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

Low Risk: Non-treatment trials (e.g., nutritional or behavioral interventional, observational, lab sample, QoL, etc.)
Intermediate Risk: Treatment phase II or III and non-IND
High Risk: Phase I, IND, first in human, cellular/gene therapy, multi-center trial where MCW is coordinating site

_____ The protocol has an appropriate plan for quality assurance review based on level of risk. Protocol should include one of the three review schedules below:

Low Risk	Intermediate Risk	High Risk
• Low risk trials will be reviewed **every 1-2 years**. • **10%** of subject files will be selected randomly for review (max 10 subjects at each monitoring timepoint). • **Consent/eligibility** and **objective based data** will be reviewed for those files selected • **1 file** will be selected randomly for a **comprehensive review** at each monitoring timepoint. • **Regulatory documents**	• Intermediate risk trials will be reviewed **every year**. • **20%** of subject files will be selected randomly for review (max 10 subjects at each monitoring timepoint). • **Consent/eligibility** and **objective based data** will be reviewed for those files selected • **1 file** will be selected randomly for a **comprehensive review** at each monitoring timepoint. • **Regulatory documents**	• High risk trials will be reviewed **every 6 months.** • **30%** of subject files will be selected randomly for review (max 10 subjects at each monitoring timepoint). • **Consent/eligibility** and **objective based data** will be reviewed for those files selected • **1 file** will be selected randomly for **a comprehensive review** at each monitoring timepoint. • **Regulatory documents**

Comments:

XIII. Statistical Considerations

_____ 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.

Comments:

XIV. Laboratory and Correlative Requirements

_____ 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.

Comments:

Additional Comments:

Appendix D. SRC Reviewer Form for Low Risk Investigator-Initiated Protocols

Medical College of Wisconsin
Scientific Review Committee (SRC)

Low Risk Investigator-Initiated Protocol Review Form

Return by email to jbollmer@mcw.edu

Protocol Title:	
Principal Investigator:	
Sponsor:	
Reviewer:	
Meeting Date:	

Items to assess	Yes	No	Don't Know	Comments
Protocol date or version number is present				
Principal Investigator is identified by name and contact information				
Co-investigators are identified with contact information				
Statistician is identified with contact information				
Sponsor is identified				
Background (including relevant citations) supports the rationale for conducting study				
Objectives are clear and appropriate				
Inclusion/exclusion criteria are appropriate				
Accrual goal and duration of study are specified				

Patient registration procedures are clear and contact info for questions is included				
Study design is feasible and appropriate				
Is long-term follow-up required? For how long (e.g. 5 years, until disease progression, death)?				
Subject withdrawal criteria are included (subjects replaced?)				
Statistical analyses are appropriate				
Safety considerations, patient confidentiality are addressed				
If protocol is interventional, DSMC language is present				
Data management plan is included- where data will be captured (OnCore, RedCap, Excel) and who will enter (especially if study not using CTO)				
List of references is included				
Classify as rare disease for accrual monitoring? (incidence ≤4 per 100,000 people in US: rare cancer, rare molecular subtype of common cancer, unusual clinical situation)				Overall accrual goal: Predicted duration of accrual (yrs): Predicted accrual per year:
Do you recommend approval of this study?				

Any other comments (major issues or problems with study?):

Appendix E. SRC Reviewer Form for Cooperative Group Protocols

Medical College of Wisconsin Cancer Center
Scientific Review Committee (SRC)

Cooperative Group Reviewer Form

Reviewer Name: _____
Date: _____
Protocol #: _____
Protocol Title: _____
Principle Investigator: _____
Cooperative Group: _____

Clinical trials management resources adequate/available? ☐ Yes ☐ No

Phase of Study:

- ☐ Pilot/Feasibility
- ☐ Phase I
- ☐ Phase I/II Disease-Specific
- ☐ Phase I/II Non-Disease-Specific
- ☐ Phase II
- ☐ Phase III
- ☐ Phase IV
- ☐ N/A

Expected FMLH/MCW Accrual Total: _____ **Expected FMLH/MCW Annual Accrual:** _____

STUDY SUMMARY

Patient Population:

Respond Yes or No

1) Will study make important clinical contribution? _____

2) Trial design is appropriate? _____

3) Is study innovative? Good science? _____

4) Was there FMLH/MCW involvement in study development? (includes career development/grant component) _____

5) Is there potential for FMLH/MCW publication? _____

6) Study is feasible, accrual goal is reasonable? _____

7) Classify study as rare disease for accrual monitoring? (incidence of ≤4 per 100,000 people in US: rare cancer, rare molecular subtype of common cancer, unusual clinical situation) _____

OVERALL EVALUATION OF PROTOCOL - ACTION RECOMMENDED:

_____ ***Approved***: The protocol is scientifically sound and acceptable as written and may be forwarded to the IRB without modifications.

_____ ***Approved with Modifications:*** The protocol is scientifically sound and acceptable pending clarification on the part of the PI of specific points. The PI must submit a copy of any protocol revisions to the Chair for Expedited Review and approval.

_____ ***Deferred:*** The study requires significant revisions in order to satisfy review criteria. The PI must submit a revised protocol and written response to the SRC's concerns for re-review at a full committee meeting.

_____ ***Disapproved:*** The study is not scientifically sound, not ethical, not acceptable as written, and/or is not within the mission of the MCW Cancer Center.

_____ _____

Reviewer's Signature Date

Appendix F. SRC Reviewer Form for Industry-Initiated Protocols

Medical College of Wisconsin Cancer Center
Scientific Review Committee (SRC)

Industry-Initiated Protocol Review Form

Protocol #: _____
Protocol Title: _____
Local PI: _____
Sponsor: _____
Funding Agency: _____
Reviewer (print): _____ Signature: _____
Date of Review: _____

Return by email to jbollmer@mcw.edu.

Please check Yes, No, or Don't Know for each category	Yes	No	Don't Know	Comments
Background supports the rationale for conducting study?				
Valid study objectives?				
Valid study design?				
Appropriate inclusion and exclusion criteria?				
Adequate response or outcome measures?				
Appropriate statistical methods?				
Is there a Data and Safety Monitoring Plan included or referenced?				
Is long-term follow-up required? For how long (e.g. 5 years, until disease progression, death)?				
Classify as rare disease for accrual monitoring? (incidence ≤4 per 100,000 people in US: rare				

cancer, rare molecular subtype of common cancer, unusual clinical situation)				
Do you recommend approval of this study?				

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

Appendix G. 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. 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 cancer-related clinical trials 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 low 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 be treated separately. The MCWCC will define a rare cancer as one with an incidence of ≤4 newly diagnosed persons out of a population of 100,000 persons per year (≤4/100,000 per year). This falls within the range of values considered reasonable by the NCI. Using this as a strict definition, nearly all pediatric cancer types would be considered rare. Studies on rare molecular 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.

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 guidelines

Trial Type	Expected annual enrollment
Phase I	At least 2 if multicenter, 4 if local
Industry trials	At least 2
Cooperative group trials (NCTN, BMT-CTN)	At least 1
External institutional trials (external IITs, consortium)	At least 2
Investigator-initiated trials	At least 33% of projected
Rare disease trials	Exempt

6.0 PROCEDURES

6.1 Pre-activation – At initial review of a new study, the SRC will determine which of the Table 1 trial types is applicable.

6.2 Monitoring of open trials

After a study has been open for 12 months (taking into account temporary suspension times), it will undergo SRC continuing review.

Monthly, the SRC Coordinator provides the SRC Chair with a report listing studies due for SRC continuing review. Included on the report is the following: study title, PI, sponsor, open/suspension dates, accrual goal, and accrual history.

If the trial meets the minimum enrollment listed in Table 1, then it is approved for another year.

Trials not meeting minimum enrollment

If a trial's annual accrual has not met the target in Table 1, 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 in six months. At six months, data from the preceding twelve months are reviewed. If the study is approved, it will be reviewed yearly according

to its originally scheduled cycle (i.e., the next review will be at the originally scheduled anniversary). Trials failing to meet minimum enrollment two reviews in a row will be closed.

Rare cancer trials

Rare cancer trials, including all pediatric trials, will be exempt from this standard process. However, the SRC reserves the right to monitor accrual to these studies and initiate trial closure if it deems they are making insufficient progress.

6.3 Trial closure

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 and final determination.

Per the current NCI CCSG guidelines (12/21/2016), "*the Protocol Review and Monitoring Committee* [SRC] *should have final authority to close trials; no appeal should be allowed to any other person or entity*."