Medical College of Wisconsin Cancer Center

Scientific Review Committee (SRC) Charter

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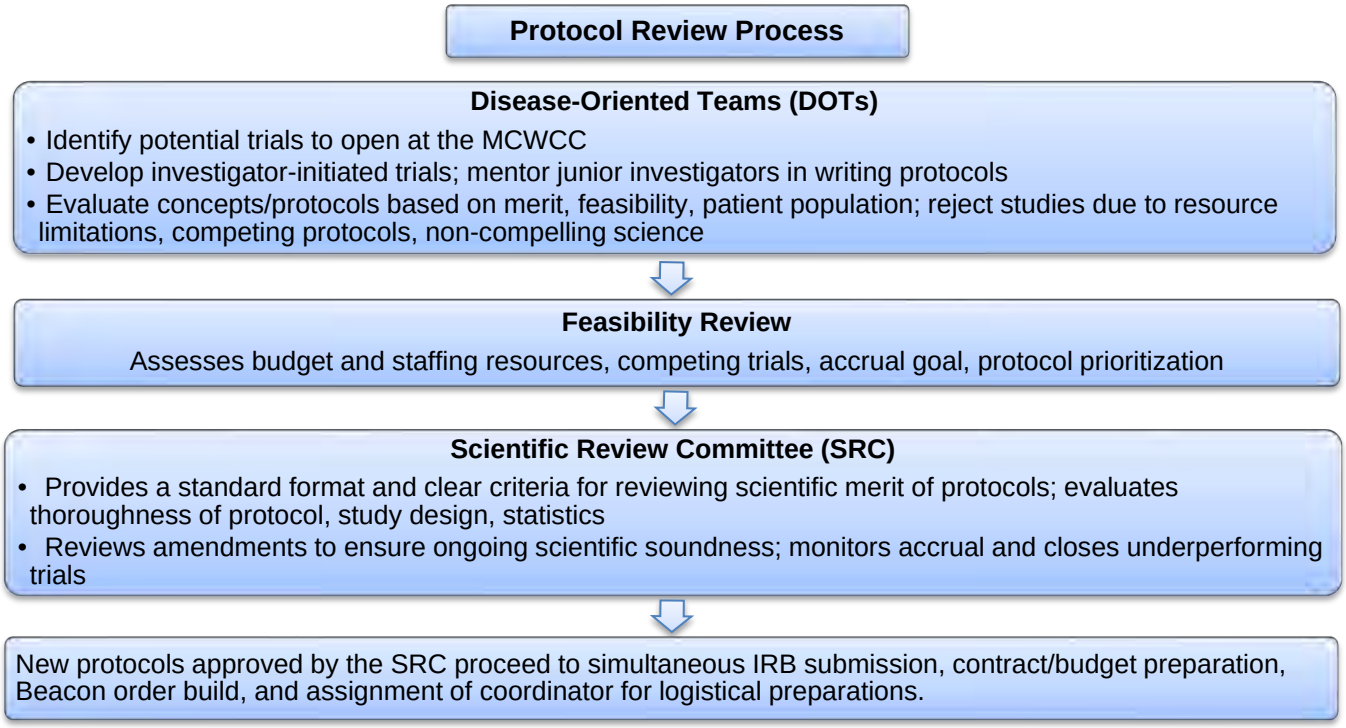
1.0 Protocol Review and Monitoring System Overview

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 prevention, detection, diagnosis, and treatment of cancer, as well as long-term follow-up and care.

MCWCC has 16 DOTs, most of which are dedicated to a specific organ/disease group. The first stage 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 oncologists from a range of disease groups and modalities, as well as representatives from Biostatistics 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 feasibility review either within the DOT (pediatrics) or by the Feasibility Review Committee (FRC; adults) prior to their submission to SRC. Feasibility review determines if adequate financial and staff resources are available for trial conduct.



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 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 Monitoring Committee). CREC is chaired by the Associate Director of Clinical Research.

2.0 Disease-Oriented Teams

The MCWCC Disease-Oriented Teams (Table 1) 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:

- Identifying opportunities for translation of scientific discovery into clinical trials
- Designing quality, investigator-initiated clinical trials that can be completed in a timely manner
- Encouraging multidisciplinary interaction, including tumor boards
- Developing and managing a clinical trial portfolio that addresses the needs of the catchment area and is in alignment with the goals of the group and MCWCC
- Reviewing and addressing trial progress, toxicities, and deviations
- Encouraging multidisciplinary grant submission and publication of research

Table 1. Disease-Oriented Teams

Bone Marrow Transplant/Cell Therapy
Breast
Central Nervous System
Gastrointestinal
Genitourinary
Gynecologic
Head and Neck
Leukemia
Lymphoma
Plasma Cell Disorders
Sarcoma
Skin
Thoracic
Adult Early Phase
Pediatrics
Population Sciences and Behavioral Health

Each DOT is composed of faculty investigators from multiple modalities specializing in the treatment of a particular organ/disease group. 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 external institutional, cooperative group, and industry-initiated trials are placed on DOT meeting agendas for group discussion. 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 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.

Protocols approved by the DOT move on to the FRC and 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,

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

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, Obstetrics and Gynecology, Radiation Oncology, Surgery, Population Science, Basic Science, Biostatistics, and an external community representative. Nursing and Pharmacy assessment takes place primarily during operational feasibility review, but representatives are ad hoc, non-voting members of SRC. 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.

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 may utilize ad hoc reviewers when additional, specialized expertise is needed to adequately review a protocol, especially an investigator-initiated trial. For example, external expert reviewers were utilized when the first cellular therapy protocols were reviewed by SRC. Population science is another area where an ad hoc reviewer may be utilized. In the event that an ad hoc reviewer is contacted, the reviewer will be responsible for providing a written evaluation of the protocol, and they should attend or call in to the full SRC meeting if possible. The disposition of the protocol is voted on by the full committee.

4.2 New Protocol Submission to the SRC

After a protocol has been reviewed and approved by a DOT and the FRC, 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.

4.3 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. 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.

4.3.1 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 2).

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 a protocol 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. Expedited Review will be done in an effort not to delay the process of subsequent IRB review and approval.

Table 2. 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 • Non-interventional investigator-initiated studies – epidemiological or observational studies involving cancer patients (*e.g.*, population science, surveillance, risk assessment, behavioral) – primary and secondary reviewer • Correlative or ancillary investigator-initiated 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 • External noninterventional studies
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

4.3.2 Amendment reviews

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: • 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

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:

- 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).

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 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. For approved protocols, the Chair sends a letter notifying the PI, DOT Chair, and research manager (if applicable) of the approval, the study's categorization for accrual monitoring (rare or not rare), its expected annual accrual goal, and its assigned risk category (for interventional IITs only). 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.

5.0 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 relevance, progress towards completion of scientific objectives, and accrual, including accrual of underserved populations such as women, minorities, children, and the elderly.

5.1 Annual Review for Scientific Relevance

On an annual basis, the SRC reviews the entire MCWCC trial portfolio for ongoing scientific relevance. For each DOT, the SRC generates a list of trials that are currently open or suspended, including the protocol's title, PI, and accrual history. The lists are sent out to the DOTs, which then add the review as an item on their next meeting agenda. For each protocol, DOTs are asked to confirm whether any change in standard of care, other progress in the field, or new safety information has arisen in the previous 12 months that impacts the scientific relevance or value of the trial. If there has been a change, the DOT is asked to describe it. Once the DOT has reviewed and responded, the DOT Chair or Vice Chair must sign off on the report, confirming its accuracy to the best of their knowledge. The SRC Chair or Co-Chair reviews the reports to determine whether any action

(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 see Appendix G for a full description.

Review Criteria

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 4) 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 4. Accrual Monitoring Guidelines

<table>
<tr><th>Trial type</th><th>Industry, external institutional (external IITs, consortium)</th><th>Cooperative group (NCTN, BMT CTN)</th><th>Investigator-initiated</th><th>Rare disease</th></tr>
<tr><td>Expected annual enrollment</td><td>At least 40% of projected, or minimum of 2 (whichever is greater)</td><td>At least 40% of projected, or minimum of 1 (whichever is greater)</td><td>At least 40% of projected</td><td rowspan="4">Initial review at 2 years, then reviewed annually for overall activity

Zero accrual at 2 years: Review screening history and ongoing scientific relevance with DOT</td></tr>
<tr><td>6 Months</td><td colspan="3">Minimum accrual met: Reviewed again at 12 months
Zero or low accrual: Warning issued, corrective action plan (CAP) requested; reviewed again at 9 months</td></tr>
<tr><td>9 Months</td><td colspan="3">Minimum accrual met: Reviewed again at 12 months
Zero or low accrual: Warning reminder issued, listed for potential closure at 12 months if no improvement</td></tr>
<tr><td>12 Months</td><td colspan="3">Minimum accrual met: Approved for 1 year
Low accrual: Reviewed by SRC for potential closure
Zero accrual: Closed to accrual</td></tr>
</table>

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

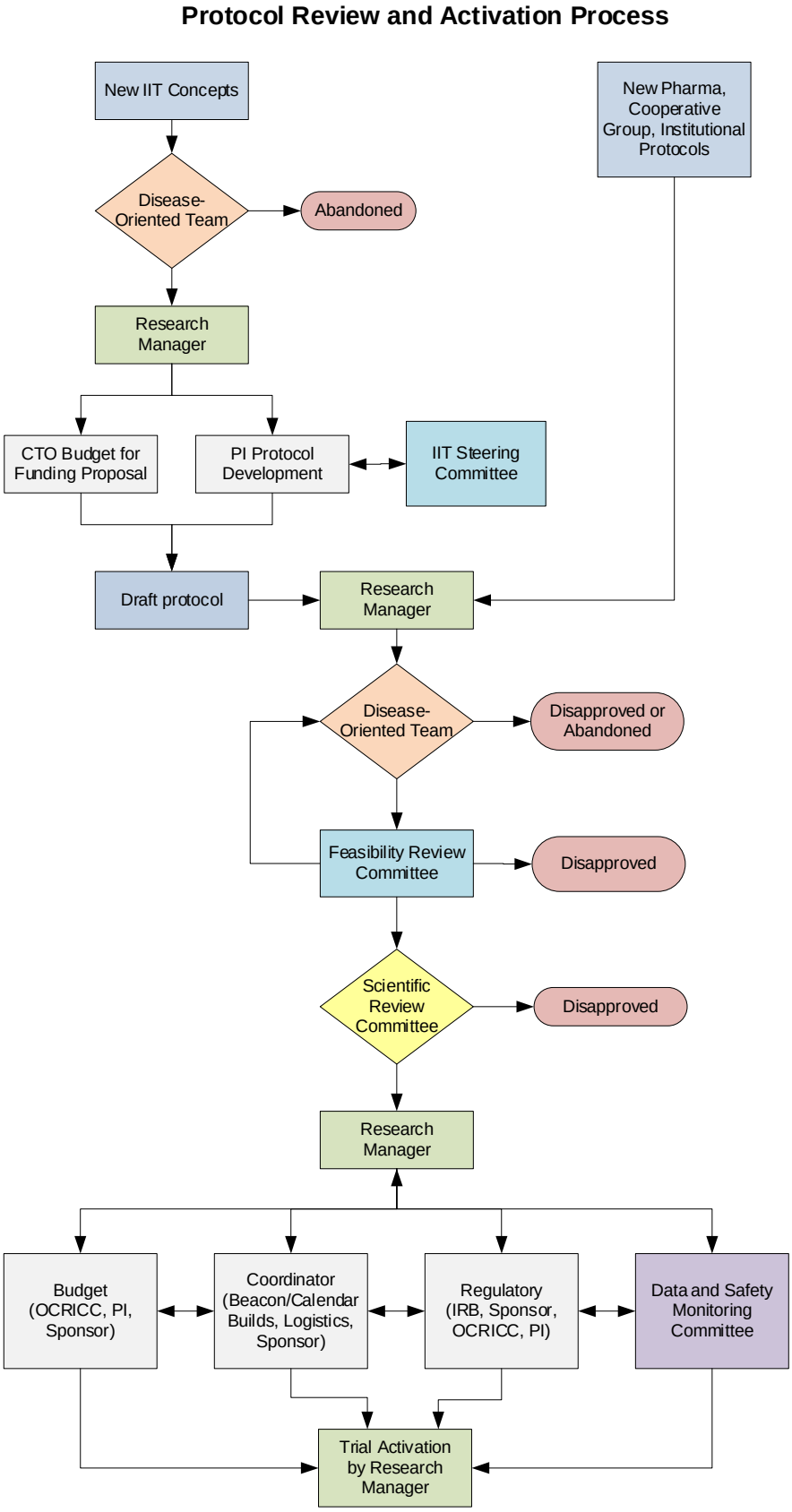
Rare disease trials: Trials involving rare diseases are expected to have slow accrual, thus they are treated more leniently. The MCWCC uses an annual incidence of ≤4/100,000 people in the United States as a guideline for defining cancers as rare. Studies on rare molecular subtypes of common cancers are also 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



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
Study Overview	
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:
Accrual	
Local accrual goal	Projected annual accrual _____ Overall accrual duration (months) _____ Overall local accrual goal _____ 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: Date accrual opened nationally: Current overall enrollment: Expected closing date:
Rare disease	☐ Check box if annual incidence is ≤4 newly diagnosed persons per 100,000 persons in U.S. (rare cancer, rare molecular subtype of common cancer, or unusual clinical situation)
Competing Trials	
Will this study compete with any currently accruing or pending trials? ☐ Yes ☐ No If yes, indicate which trial(s) and describe prioritization plan for enrollment:	

Funding Source

☐ NCTN/CTN ☐ Pharmaceutical ☐ MCW Cancer Center ☐ There is no funding for this study.
☐ Consortium ☐ Department ☐ Other_____ ☐ Additional funding is needed.
☐ NCI CTEP ☐ External Institutional
Is the budget negotiable? ☐Yes ☐No Comments:

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	**Eligibility Review** ☐ Basic ☐ Complex/multi-step	**Registration/Randomization** ☐ One step ☐ Multiple steps	**Frequency of Study Tasks** ☐ Daily ☐ Weekly ☐ Every 21-30 days 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
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, etc.
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
Beacon Build needed?	☐Yes ☐No

Additional Comments

Disease-Oriented Team 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 Clarifications:*** 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)
Intermediate Risk: Treatment phase II or III and non-IND or non-IDE, lower risk multisite trials
High Risk: Phase I, IND, IDE, most multisite trials
Special Status: IND, IDE, cellular/gene therapy, first-in-human

QA Review Schedule and Content

Low Risk	Intermediate Risk	High Risk	Special Status
• Reviewed **every 2 years** • **10%** of subject files will be selected randomly for review (max 5 subjects at each monitoring timepoint). • **Consent/eligibility** and **objective-based data** will be reviewed for those files selected • **Regulatory** documents	• Reviewed **every year** • **20%** of subject files will be selected randomly for review (max 5 subjects at each monitoring timepoint). • **Consent/eligibility** and **objective-based data** will be reviewed for those files selected • **Regulatory** documents	• Reviewed **every 6 months** • **30%** of subject files will be selected randomly for review (max 5 subjects at each monitoring timepoint). • **Consent/eligibility** and **objective-based data** will be reviewed for those files selected • **Regulatory** documents	• Reviewed **every 3 months (may be more often with PI discretion)**. The first subject will be reviewed shortly after dosing. • **30%** of subject files will be selected randomly for review (max 5 subjects at each monitoring timepoint). • **Consent/eligibility** and **objective-based data** will be reviewed for those files selected • **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 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 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 be treated separately. The MCWCC defines 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). 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. 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
6 Months	*Minimum accrual met:* Reviewed again at 12 months *Zero or low accrual:* Warning issued, corrective action plan (CAP) requested; reviewed again at 9 months			*Zero accrual at 2 years:* Review screening history and ongoing scientific relevance with DOT
9 Months	*Minimum accrual met:* Reviewed again at 12 months *Zero or low accrual:* Warning reminder issued, listed for potential closure at 12 months if no improvement			
12 Months	*Minimum accrual met:* Approved for 1 year *Low accrual:* Reviewed by SRC for potential closure *Zero accrual:* Closed to accrual			
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			

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

Monthly, the SRC Coordinator provides the SRC Chair with a report listing studies due for SRC continuing review: studies that have been open 6, 9, or 12 months or are due for annual review. Temporary study suspensions are taken into account in the timing of reviews. Included on the report is the following: study title, PI, sponsor type, open/suspension dates, accrual goal, and accrual history.

Timeline and actions

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 the target in Table 1, a warning will be issued noting that the trial will be listed for potential closure at 12 months.

If at 12 months the trial meets the minimum enrollment listed in Table 1, then it is approved for another year. At 12 months, trials with zero accrual will be closed, and low-accruing trials may be closed.

At 24 months and each subsequent year, trials meeting minimum enrollment listed in Table 1 will be approved for another year. Trials falling below the target in Table 1 will receive a CAP request from the SRC and will be reviewed for potential closure after 6 months.

Rare disease trials

Studies classified as rare disease will not be held to the 40% accrual threshold. SRC will initially review these trials two years from activation and then annually thereafter for overall activity. As a part of this review, the SRC will consider the study's screening and consent history, continued scientific relevance, and dialogue with the PI and DOT. Zero-accruing studies will warrant discussion with the DOT to determine the feasibility of identifying eligible patients at our cancer center. Following this review process the study may be subject to request for a CAP or may receive a closure letter.

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 NCI's current CCSG guidelines, the SRC "*should have final authority to close trials; no appeal should be allowed to any other person or entity*."