National Cancer Institute's Center for Cancer Research (CCR)
Safety Monitoring Committee (SMC)

NCI CCR SMC Charge and Criteria for Protocol Referral (Charter)

The National Cancer Institute's (NCI) Center for Cancer Research's (CCR) general Safety Monitoring Committee (SMC) is charged with advising the Office of the Clinical Director, the Institutional Review Board (IRB), and other senior leaders at the NCI CCR as appropriate on the safety and continuing scientific validity of clinical protocols being conducted by NCI CCR investigators.

The SMC's primary responsibility is to enhance patient safety by monitoring unexpected, protocol-specific safety issues that are identified during the conduct of clinical trials that fall into specific categories. Particular attention will be paid to clinical trials using novel therapies or modalities that are conducted at multiple centers with the CCR functioning as the coordinating site, as well as protocols involving gene therapy, protocols that require special attention due to high public interest or public perception of risk, and protocols that pose potentially very high risk to patients.

The SMC is responsible for monitoring:

1. NCI CCR multi-institutional enrolling treatment protocols using novel therapies and/or modalities for which the NCI CCR is the coordinating site. Particular attention will be given to studies using drugs/devices that are not FDA approved for any indication. These studies will be monitored for unusual, significant toxicities that are related to the investigational agents being used. A study will not receive initial review until at least one external participating site enrolls and initiates intervention in at least one (1) participant.

   Exceptions:
   a. Cancer Therapy Evaluation Program sponsored protocols will not be monitored by the CCR SMC if this is the only SMC qualifying criterion for the protocol.
   b. Protocols with a memorandum of understanding for split IRB review with a marrow donor program(s) (e.g., National Marrow Donor Program [NMDP] IRB) will not be monitored by the CCR SMC, if this is the only multicenter identifying criterion.

   An internal review of all CCR coordinated multicenter enrolling treatment (i.e., drug/device) protocols will occur approximately annually by the CCR OCD/designee (e.g., Office of Education and Compliance [OEC]). These reviews will be conducted independently and documented. A CCR PI/study team will be contacted only in the event of questions or concerns, or in the event that OCD reaches a decision that a study should be referred to the CCR SMC for full review.

2. All protocols using gene transfer or gene therapy methodology (with exception as below). Monitoring of these protocols will focus on unusual toxicities specific to gene therapy.

   Exceptions:
   a. Protocols using vaccine(s) as an object of the investigation, unless other review criterion are met.

3. All CCR protocols requiring independent monitoring committee. These reviews should include review of the safety of the study, but focus may be placed instead on efficacy and/or other important qualifying events or decision points within a protocol's design (e.g., independent confirmation of safety or efficacy to move from phase I to II in a single trial) at the discretion of the SMC Chair.
4. All protocols that are deemed to potentially pose very high risk to patients or require special attention due to high public interest. In the event of a difference of an opinion of a study posing very high risk, a request for determination may be made by the PI to the CCR SMC Chair, with waivers approved by the Clinical Director/designee (i.e., Deputy Clinical Director).

Protocols can be referred to the CCR SMC for consideration of review by the Clinical Director/designee, the Branch Chief of the branch in which the protocol originates, the CCR SRC (Scientific Review Committee), or the IRB.

In the event that insufficient data is available for review (e.g., study initiated enrollment and participants are too early in the treatment regimen) or no significant toxicities have been reported, the SMC Chair may waive or postpone review to a future meeting.

NOTE: Any of the above studies that are reviewed by a separate independent entity (e.g., designated Data and Safety Monitoring Board [DSMB] or equivalent), including studies reviewed by the Office of Sponsor and Regulatory Oversight (OSRO), do not require CCR SMC review. The reviewing entity should be named/described in the protocol and/or NIH Addendum.

NOTE: All NCI CCR Phase III randomized protocols are referred to the NCI CCR DSMB coordinated by the Biostatistics and Data Management Section (BDMS). These studies do not require review by the NCI CCR SMC.

Timing of protocol review by the CCR SMC:

Protocols under CCR SMC oversight will be considered for review initially as soon as possible after their annual NIH IRB continuing review date. Subsequently, each protocol will be reviewed as close to annually as the quarterly meeting schedule permits or more frequently as may be required by the CCR SMC.

For initial and subsequent reviews, protocols are not required be reviewed if there is no accrual within the review period.

For multi-institutional treatment protocols for which the NCI CCR is the coordinating site and where being multi-institutional is the only CCR SMC qualifying criterion for the protocol, initial review should occur as soon as possible after the initial annual IRB continuing review date **and** first initiation of intervention in a participant by a participating site. The same criteria for subsequent reviews will then apply.

I. Membership

The CCR Clinical Director will appoint members to the SMC, including the Chair of the SMC. Appointed members will serve for staggered terms; terms of 5 years as a committee member, with the option to renew. Membership is consistent with NCI recommendations to ensure continuity. At least one voting member will not be affiliated with NCI CCR and will need to be present for all voting actions. Voting members of the SMC will include physicians, biostatisticians, other scientists, and a lay member, such as an ethicist or patient advocate. They will be selected based on their experience, area of expertise, reputation for objectivity, absence of conflicts of interest, and knowledge of or experience with clinical trial research. The Clinical Director (or designee) will be an *ex-officio* non-voting member of the SMC. The Executive Secretary will be recommended by the Protocol Support Office (PSO) Director and confirmed by the Clinical Director, and will be an *ex-officio* non-voting member.

Voting members directly involved with a specific trial or with a conflict of interest per NIH guidelines will recuse themselves from SMC discussions of that trial. If deemed necessary, an ad hoc voting member(s) will be assigned to review a protocol where a conflict of interest exists or where special expertise is requested by the SMC Chair. A majority of the voting members must be present for all voting actions.

II. Meetings

Meetings of the SMC will be held four times a year, at intervals as close to three months as possible for the members.

The meetings will be conducted consistent with NIH Guidance for DSMB meetings. After the SMC Meeting is called to order, the SMC Chair will hold a closed session to discuss the protocols for review prior to reviewing each protocol individually and inviting members of the research teams to join the meeting, if necessary. The review of each protocol may include an open session attended by the PI, AI, Biostatistician, and/or other members of the research team. The PI may also choose to invite other study personnel if the SMC requires input after reviewing the written report. During this open session the general conduct of the trial will be discussed, and the research team will answer questions from the members of the SMC. An executive session will follow with only members of the SMC during which specific recommendations, formal requests for additional information and a vote on continuation of the protocol will be documented for inclusion in the meeting minutes.

Following the completion of the SMC meeting, an interview will be conducted with the Clinical Director/designee, as appropriate. Minutes of the deliberations and recommendations of the SMC for each meeting will be prepared. The outcome letters from the review of each protocol will be distributed to the protocol PI, the Clinical Director/designee, and/or the Branch Chief. The reports will be shared also with the IRB per current policies and procedures (e.g., at the time of next Progress Report Form submission). These documents will constitute the Official Reports from the SMC.

III. Confidentiality and Conflict of Interest

Upon acceptance of their appointment, all members of the SMC will agree to comply with the NIH Conflict of Interest Guidelines and assure confidentiality and non-

disclosure of information reviewed and that their reviews are free of conflict of interest. Each protocol will identify commercial sponsorship, if any, providing the opportunity for SMC members to disclose potential conflicts of interest.

NCI CCR SMC Internal Standard Operation Procedures

I. The SMC Charge and Criteria for protocol referral and membership and meeting procedures will be prominently posted on the CCR Intranet website. The protocol submission form and instructions for use will be on the same website. The SMC will review and renew its Charter at the first meeting of each year. All operations of the SMC will be managed by the Executive Secretary.

II. Protocols will be selected for review in one of the following ways:

   A. Protocols will be identified as requiring SMC review during the initial regulatory review process, with protocols added as required due to events or other circumstances during the course of a study. The Clinical Director/designee and/or the SMC Chair will review any studies where there is a question of SMC review requirements and work with the PSO Director/ Executive Secretary to share the outcome with the PI.

   B. The Clinical Director/designee, the PI, or the Branch Chief from the branch in which a protocol originates may request that the SMC monitor a protocol that is potentially high risk and does not specifically meet any of the other criteria required for review. The request should be forwarded to the Clinical Director/designee with a copy to the SMC Chair and the SMC Executive Secretary.

      NOTE: If the PI and/or the Branch Chief requests waiver of SMC review for a protocol meeting the criteria, a request should be made to the SMC Chair, with waivers approved by the Clinical Director/designee.

III. The Executive Secretary of the SMC will ensure that protocols identified for monitoring are submitted to the SMC for review.

IV. The Executive Secretary is responsible for preparing for and arranging the SMC meetings. Prior to the meeting, the Executive Secretary will provide the SMC members with the meeting agenda, and assign the SMC protocol submissions to each reviewing SMC member; the most recent continuing review submission, a copy of the current informed consent form, and any other information deemed relevant.

V. The Executive Secretary (with support from the Protocol Support Office) will be responsible for coordinating all communication between the NCI CCR PIs and the SMC.

VI. The Executive Secretary will work with the Chair of the SMC to prepare minutes of the meetings. Minutes will be distributed for approval through e-mail.

   A. A copy of the draft minutes will be distributed to the SMC members for review and comments.

B. Once minutes are finalized and approved by the SMC Chair, the Clinical Director/designee of the NCI CCR will be copied on the approved minutes when they are distributed to the members of the SMC.

C. Protocol specific recommendations and requests of the SMC will be forwarded to the PI, the Clinical Director/designee, and/or the Branch Chief in an outcome letter.

VII. A formal response to the SMC outcome letter by the Principal Investigator will be submitted to the SMC when required.

A. The SMC stipulations will require a response no later than prior to the next SMC meeting (i.e., usually within 10-12 weeks after the receipt of the outcome letter unless otherwise indicated). Recommendations will be made for consideration only, with no response required.

B. Responses required within 10-12 weeks must be approved by the PI prior to submission.

1. Unless otherwise negotiated with the SMC Chair, failure to provide responses or to request an extension within 10-12 weeks of the PI's receipt of the SMC stipulations could result in closure of the protocol until deficiencies are resolved.

VIII. The formal response by the PI will be reviewed by the SMC Chair, and other SMC members, as appropriate. Approval or disapproval of the response will be reported to the PI, the Clinical Director/designee, and/or the Branch Chief.

Reviewed and Approved:

James Gulley Digitally signed by James Gulley
Date: 2024.08.06 14:44:21 -04'00'

Clinical Director, National Cancer Institute