Standard Operating Procedure for the National Cancer Institute (NCI), Center for Cancer Research (CCR) Office of Sponsor and Regulatory Oversight (OSRO) Safety Oversight Committees

Draft v0.48 21-Mar-23

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1.0 PURPOSE

1.1. The purpose of this document is to provide the requirements for the function of the Safety Oversight Committees (the Committee), including Data and Safety Monitoring Boards (DSMB) and Safety Monitoring Committees (SMC) for treatment or prevention studies conducted as part of the Center for Cancer Research (CCR) Intramural Research Program (IRP) and for which the Office of Sponsor and Regulatory Oversight (OSRO), National Cancer Institute (NCI), has oversight responsibilities.

The Committee is convened by the authority of OSRO and is advisory to the CCR.

Safety oversight bodies are established based on the anticipated level of potential risk to study participants and must include one or more of the following for each clinical trial:

- Data and Safety Monitoring Board (DSMB)
- Safety Monitoring Committee (SMC)

Committees will be structured to review multiple studies by disease, treatment, or body part, during each teleconference meeting. Several Committees may be required to review one study.

2.0 BACKGROUND

2.1 The National Cancer Institute Center for Cancer Research Intramural Research Program (NCI CCR IRP) is known for its synergistic approach to biomedical science. Scientists, physicians, and clinicians who make up the IRP conduct basic, clinical, and genomic and population-based research at the NIH Clinical Center and NCI offices and laboratories in Maryland. These researchers are members of two NCI components: the Division of Cancer Epidemiology and Genetics (DCEG) and the CCR that monitors the clinical trials.

2.2 Requirements for Safety Committees:

DSMB

- Regulatory mandated: Emergency settings in which the informed consent requirement is excepted.
- All randomized clinical trials of any phase.
- All clinical trials that include interim analysis as part of the trial design.

SMC

- All multi-center clinical trials.
- All clinical trials that include dose-escalation.
- All clinical trials that include a Phase I design (or safety assessment) followed by a Phase II design (or efficacy assessment) in the same Protocol.
- All clinical trials that include halting rules which require independent evaluation on whether to continue in the trial.

- All clinical trials that include products for which CCR is the legal manufacturer.

Safety Oversight assignment will occur in priority order (i.e., if one trial meets the criteria of more than one type of oversight mechanism, the most stringent mechanism will apply).

3.0 SCOPE

3.1 This document applies to the NCI CCR OSRO staff, Committee Members, and Data Coordinating Center that monitor the safety of human subjects who participate in NCI CCR sponsored clinical studies, and trials in which OSRO provides the funding for the study.

3.2 These intramural studies may be conducted at the NIH Clinical Center or at non-NIH institutions.

4.0 ROLES AND RESPONSIBILITIES

4.1 Center for Cancer Research (CCR) Clinical Director or Designee

The CCR Director or designee:

- Oversees and helps ensure the quality of medical care delivered to participants in clinical trials.
- Provides written permission to the OSRO Director or designee for OSRO Medical Monitor(s) (MMs) or other OSRO staff to attend Closed efficacy Sessions.
- Provides additional study information, if necessary.

4.2 Office of Sponsor and Regulatory Oversight (OSRO) Director or Designee

The OSRO Director or designee:

- Designates number and types of Safety Oversight Committees required for CCR studies.
- Oversees clinical studies conducted by CCR.
- Makes decisions that affect CCR studies, including reviewing and approving Conflict of Interest (COI) filings for Committee Members.
- Reviews requests for Ad hoc Meetings and honoraria.
- Requests to view safety data by arm.
- Works directly with the NCI CCR Executive Secretary (ES), the Sponsor and Regulatory Oversight Support Safety Safety Oversight Support Team (SROS SOS), to document, review, approve, and sign Committee Recommendations (Recommendations) and Meeting Minutes.
- Signs and oversees development of the Committee Charter and References.

The OSRO Director or designee oversees the activities of the SROS Team and may

designate to SROS staff all or some of their responsibilities as needed.

4.3 Medical Monitors (MMs)

Medical Monitors represent OSRO to the Committees, working to develop Meeting Agendas, reviewing, and approving documentation prior to distribution, and presenting Protocols and blinded safety data, etc. They are also responsible for requesting Committee Meetings, ensuring preparation of the necessary Reports for Committee Meetings, approving Reports before dissemination to the Committee Members, and assessing COIs reported during Committee Meetings.

4.4 Executive Secretary (ES)

The role of ES is fulfilled by the SROS SOS Team.

4.5 Principal Investigator (PI) or Designee

The PI or designee is responsible for the conduct of the study at the study site and ensures adherence to:

- Regulations and Public Health Service policies
- Protocols
- Site-specific standard operating procedures

During the Committee Meetings the PI or designee will review the generated study Reports, and present study updates as outlined in the PI presentation guideline.

4.6 SROS Pharmacovigilance (PVG)

The SROS PVG Team tracks all the reported the SAEs in the Oracle Argus Safety Database and retrieves study and subject data for Committee Meetings, as requested.

4.7 SROS Data Analytics

SROS Data Analytics retrieves the site data to generate the Committee Reports.

SROS Data Analytics:

- Using data from the study site, generates associated data for individual studies to prepare Open Reports and Closed Session Reports if requested.
- Transmits study data to the SROS SOS Team for distribution.
- Attends Committee Meetings.
- Responds to special Report requests, as directed by the Committee.
- If Closed data are requested by the Committee, unblinds data during the Closed Session.
- Provides SAE Narratives and Line Listings to SROS SOS as requested.

4.8 Committee Chair/Co-Chair

The Committee Chair/Co-Chair:

- Serves as the primary point of contact for the Committee and facilitates Committee Meetings and discussions.
- Communicates the Recommendations to NCI OSRO immediately following the Committee meeting.
- Works directly with the NCI CCR ES (SROS SOS) to document, review, approve, and sign Recommendations and Meeting Minutes.
- Provides consultation to CCR OSRO regarding potential safety or study-related issues, such as review of an event that may meet a halting rule.
- Suggests timeline for distribution of study-specific Reports to the Committee in preparation for a meeting or electronic Review.
- Appoints a Committee Member to serve as acting-Chair/Co-Chair in their absence, if unavailable.

4.9 Sponsor and Regulatory Oversight Support Safety Oversight Support (SROS SOS)

The SROS SOS Team facilitates communication between CCR OSRO and the Committee.

The SROS SOS, in conjunction with CCR OSRO staff as appropriate will:

- Create and maintain a master calendar showing all CCR studies and associated Committees with any study-specific review timelines.
- Assist OSRO staff with developing the Meeting Agenda and order of study review for each Committee Meeting.
- Maintain a list of current, future, and previously completed studies for which the Committee will provide or has provided Safety Oversight for access by Committee Members in the SROS SOS Committee Management System (CMS).
- Contact the Committee Members, including any consultants or Ad hoc Members, to determine availability for Safety Oversight meetings.
- Confirm attendance of the Principal Investigator (PI) or designee, prior to each Committee Meeting.
- Contact required meeting participants, for each trial on the Meeting Agenda to confirm contact information and provide the time designated for individual study review.
- Arrange and oversee telecommunications support for Committee teleconferences.
- Maintain and update the SROS SOS CMS to provide and support meeting-associated notifications, documents, COI submissions, and document review.
- Inform the Committee about planned event triggers that would call for an unanticipated meeting, stopping and holding/pause guidelines, unmasking

(unblinding), etc., on a protocol-by-protocol basis, prior to study enrollment.
- Support, track, and distribute honoraria.
- Provide general information.
- Attend Committee Meetings and write Recommendations and Meeting Minutes.

The SROS SOS:

- Requests study Report data from SROS Data Analytics and Serious Adverse Events (SAE) Narratives and Line Listings from SROS PVG Team for Committee review at least one month prior to the Committee Meeting, or as needed, for studies which have undergone previous Committee review.
- Obtains copies of the Protocol, Informed Consent Form (ICF), and any other study-related documents from the SROS Electronic Trial Masterfile (eTMF) and provides them to the Committee at least 10 working days prior to the teleconference, unless otherwise directed by the Chair/Co-Chair.
- Provides PI or designee with the PI presentation guidelines that include a list of required and potential topics and confirms receipt of the approved presentation 15 working days prior to the Committee Meeting.
- Notifies Committee Members, PI or designee, and other meeting participants of Meeting Material availability in the SROS SOS CMS within 10 working days prior to the Committee Meeting.
- Serves as the ES and monitors and limits participant entry into teleconference Committee Meetings. Assists the Committee Chair/Co-Chair and OSRO by documenting Recommendations.
- Documents confidential communications and deliberations between OSRO, study team, the Committee, and between Committee Members.
- Distributes Meeting Minutes and Recommendations to Committee Members, OSRO, and selected meeting participants through SROS SOS CMS.
- Provides the final signed Recommendations to the PI or designee for each specific study.
- Provides individual study Meeting Minutes as directed by OSRO.

4.10 General Committee Responsibilities

Committee Members are identified based on their understanding of the goals of CCR, demonstrated expertise in the relevant clinical areas, and experience conducting similar clinical trials.

The Committee will:

- Respond to availability questionnaires for teleconference meetings.
- Read and accept the Charter and provide signature for concurrence.
- Review and evaluate the study Protocol, ICF, Investigator's Brochure (IB)/ Package Insert, and in some cases, plans for data safety monitoring before the study opens to enrollment and/or prior to protocol implementation.

- Meet at regularly scheduled intervals via teleconference or participate in electronic Reviews to periodically review and evaluate Committee Reports and study materials for multiple studies as described in Section 7.0.
- Request any available data or additional analyses from the PI or designee or SROS Data Analytics pertaining to the trial that are necessary to carry out primary responsibilities.
- Confirm that the timeliness, completeness, and accuracy of the data submitted for review are sufficient to evaluate the study and ensure the welfare of study participants.
- Request an Ad hoc Meeting to discuss any significant concerns with OSRO and the study team.
- Review and recommend modifications for proposed stopping guidelines as specified in the Protocol, as well as changes to the study plan that may affect safety and/or outcome of the study, or propose a plan, if one is not submitted.
- Make recommendations concerning the continuation, modification, suspension, or termination of a trial based on the observed beneficial or adverse effects of any of the treatments under observation and monitor OSRO compliance with Recommendations.
- As directed by the Committee Chair/Co-Chair, promptly review (within the prescribed timeframe) Recommendations or other materials that will describe the decisions of the Committee, voting results, and questions to the OSRO MM, OSRO Director or designee, and study PIs or designees.
- Maintain confidentiality in internal discussions and activities, and of Reports provided.
- Verify all Meeting Materials are deleted following each review, the conclusion of the study, or at the completion of service on the Committee.

In addition to the responsibilities described above and in Section 2.0, DSMB Committees will:

- Review efficacy

Under normal operating procedures, the Committee will have no role or responsibility for final analyses and preparation of manuscripts for publication but may receive or review the Final Clinical Study Report for their information only.

5.0 MEMBERSHIP

5.1 General Membership

For all Committee types, a Committee will consist of at least 4-8 Members with experience in the disciplines and medical specialties required to interpret the data from studies under its purview and fully evaluate participant safety. DSMB Committees must also have at least one biostatistician.

Representatives of other clinical or laboratory specialties and the affected community may also serve as Members. The Committee should reflect the commitment of NCI to diversity, as possible.

5.2 Replacement of Members

If a Member decides to leave or their term expires, SROS SOS in conjunction with the OSRO Director or designee will identify a possible replacement to serve on the Committee. If the OSRO Director or designee determines a Committee Member is not participating in the Committee activities as needed, the SROS SOS will ask the Member to resign, and a replacement will be appointed. In both cases, the SROS SOS notifies the Member and provides a Certificate of Appreciation.

5.3 Meeting Quorum

A quorum must exist for a review to commence. A majority of the entire Committee membership will constitute a quorum for conducting a meeting.

If a Committee Member is unable to attend a meeting, his/her comments and recommendations may be sent electronically to the SROS SOS prior to the meeting, and he/she will be considered a participating Member.

Non-voting Ad hoc Members and/or Consultants are not considered a participating Member for the quorum.

5.4 Selection and Invitation to Participate

In conjunction with OSRO, the SROS SOS identifies potential Committee Members. The OSRO Director or designee reviews and approves the COI Disclosure form.

The OSRO Director or designee is responsible for identifying and approving the Committee Chair/Co-Chair.

Consultants may be invited to attend reviews of specific studies as non-voting Ad hoc Members to provide needed expertise for optimal review of the trial Protocol or safety data.

5.5 Terms of Membership

Committee Members may serve on the Committee for three years with an option of renewal for an additional three years, as determined by NCI OSRO. A Member will not serve more than 6 consecutive years on any individual Committee.

A study-specific non-voting Ad hoc Member is expected to serve on the Committee for the duration of the specific study and may also serve as a study-specific Member for

multiple studies.

5.6 Conflict of Interest (COI)

As an OSRO-initiated Committee, Members are required to disclose any potential COIs to NCI OSRO, as per the NCI policy on Committee operations. NCI OSRO staff utilizes the SROS SOS CMS to track, collect, and review COIs. A COI Disclosure form must be completed for each new study reviewed by the Committee (See Appendix B).

Potential conflicts which develop during a Committee Member's tenure on the Committee must be disclosed promptly to NCI OSRO. A detailed COI review is carried out at least annually. In addition, Member COI information will be updated at each Committee Meeting using a COI declaration. The SROS SOS Team will ask Committee Members whether they have either previously identified or developed any new real or perceived COI since the last Committee Meeting to NCI OSRO. When a real or perceived COI exists, OSRO staff may ask the Committee Member to respond to additional questions. At the direction of OSRO, the SROS SOS Team will inform the Committee Chair/Co-Chair as to whether a COI exists.

When a COI exists, the Member will recuse themselves from discussing and voting on the associated studies, Protocol modifications/amendments, interim analyses, and Safety Reports. If the Committee Chair/Co-Chair has a conflict, OSRO staff will appoint an acting-Chair/Co-Chair for that specific review and discussion.

Members of the Committee who are determined to be free of conflicts will participate in each Committee Meeting with automatic access to review study materials.

COIs include significant financial, personal, professional, or proprietary interests and other potential COIs self-reported by Committee Members. NCI-defined sources of potential COIs or the appearance of a COI may include (but are not limited to) the following:

- Financial ties, advisory boards, consulting services, private sources of research funding, investments, stock ownership and options, intellectual property rights, etc., to any commercial concerns likely to be affected by the outcome of the trial;
- Serve on a board of directors or an advisory committee for an entity (or its affiliated entities) having a commercial interest in the products, devices, or intellectual property related to the trial;
- Funding for basic or clinical research from a Biotechnology or Pharmaceutical company likely to be affected by the outcome of the trial under review;
- Sponsored or reimbursed travel from a Biotechnology or Pharmaceutical company likely to be affected by the outcome of the trial under review;
- Consulting activities that provide financial, investment, or other business advice to a Biotechnology or Pharmaceutical company likely to be affected by the outcome of the trial under review; and

- Professional or other affiliation that could cause others to question the objectivity of the Board deliberations, such as close personal or scientific collaboration with the PI or designee or key personnel of a study under review by the Committee.

6.0 MEETINGS

6.1 Meeting Type(s)

Committee Meetings are held electronically by video or teleconference. When agreed to by the Committee Chair/Co-Chair, ES (SROS SOS), and the OSRO MM responsible, Committee reviews may be completed electronically via email correspondence when necessary or appropriate.

In each meeting the Committee will review new Protocols and Reports from ongoing studies, as appropriate based on study timelines.

6.2 Committee Meeting Frequency

As required, the NCI CCR Committee will be convened 2-4 times a year for a one-day meeting or participate in electronic Reviews to periodically review and evaluate study materials and safety data. The minimum frequency of study reviews will be determined by OSRO commensurate to the safety and monitoring needs of each trial as documented in the Charter, but the Committee can request additional meetings as warranted. Additional reviews may be scheduled if necessary for studies requiring further review or for Ad hoc Meetings concerning ongoing trials.

6.3 Committee Charter

The Committee Charter defines the primary responsibilities of the Committee, its Membership, purpose and timing of its meetings, data to be reviewed, and procedures for ensuring confidentiality and proper communication.

The Committee will review the Committee Charter and ratification will be by a simple majority, with a quorum as defined in Section 5.0. The Committee may not review any Protocol(s), take any actions, or make Recommendations to NCI OSRO until the Charter is ratified. To accept the Charter, each Committee Member will sign a Member Signature page (Appendix A).

Once the Charter is ratified, the Committee should review any procedures for conducting business, e.g., voting rules, increasing the minimum attendance requirements for a quorum beyond those in Section 5.0, etc., that are necessary for the Committee to discharge its responsibilities. Based on the studies reviewed, the Committee may request revisions and subsequent ratification of the Charter from the OSRO Director or designee, who will have the final say on any proposed modifications to the Charter.

6.4 Meeting Participants

Committee Members are expected to attend all scheduled meetings. The PI or designee, study team members and other NCI staff should also attend as required and appropriate.

Committee Meetings are closed to the public.

6.5 Meeting Materials

Meeting Materials including the Meeting Agenda, Contact List, Reports, and required study documents and presentations are provided by the SROS SOS and SROS Data Analytics.

6.6 Meeting Conduct

Based on the Agenda, SROS SOS will notify meeting attendees of the designated time their study will be reviewed by the Committee and facilitate their attendance. SROS SOS will monitor and limit participant entry into teleconference Committee Meetings to ensure only participants for the specific study being reviewed are allowed access. SROS SOS will lock the meeting and continue monitoring callers to prevent unauthorized entry.

7.0 STUDY-RELATED INFORMATION AND REPORTS FOR COMMITTEE REVIEW

7.1 New Protocol Review

In each Committee Meeting new studies under the Committee purview will be reviewed. The Committee will review the Protocol, ICF, presentation from the PI/designee, study-related documents, halting rules, statistical methods, set triggers for data review or analyses, establish guidelines for monitoring, and finalize Report formats. The guidelines for monitoring should also address stopping the study for safety concerns and, in the case of a DSMB Committee, for efficacy.

The goal of CCR OSRO is to obtain consensus from all Committee Members, however if consensus is not reached, each recommendation will be considered by the OSRO MM and OSRO Director or designee as described in Section 8.0.
As described above in Section 4.0, in preparation for the review of a new study, the relevant SROS SOS staff will obtain copies of the Protocol, ICF, and any other protocol-related documents from the SROS eTMF. Unless the Chair/Co-Chair indicates otherwise, these documents will be made available to the Committee at least 10 working days prior to the teleconference.

7.2 Periodic Committee Safety Review Meetings

For studies which have undergone previous Committee review, the following information will be made available at least 10 working days prior to the meeting:

- All Protocol amendments since the previous Committee review.

- A report on any changes to the IB that have occurred since the last review, if they are relevant to the study.
- Subject accrual.
- Adverse Events (AEs) and SAE Narratives and Line Listings.
- Investigational New Drug (IND) Safety Reports.
- Any dose modification occurring between reviews.
- Outcome data, if appropriate.
- Study documents related to the context of the Committee review, such as Protocol violation reports, communication records between PI or designee and pharmaceutical Sponsor, IND Sponsor, Institutional Review Board (IRB), or Food and Drug Administration (FDA); and other relevant new information including results from studies of the same or similar agents or important preclinical testing results.

Periodic Safety Reports will be prepared by SROS Data Analytics and a consulting statistician, as needed, and will be distributed to the Committee, as requested. Data files used for Interim Reports will be edited following established procedures. Interim analysis of efficacy data is performed only if approved in advance and will be reviewed in a Closed Session.

Subsequent Committee Meetings are held to review and discuss study data according to the study timelines as documented on the SROS SOS master calendar. The purpose of the review is to evaluate safety and study conduct on an ongoing basis. The study may be stopped at any time if significant safety concerns are identified by the Committee.

7.3 Electronic Review

Committee Members may be asked to review data electronically and provide their assessment by email or through the SROS SOS CMS. Electronic Reviews and associated communications are conducted similarly to Closed Sessions and limited to Committee Members only. The SROS SOS is copied on these communications for documentation purposes.

7.4 Ad hoc Meeting

Committee Members may be asked to convene an unplanned Meeting for a specific purpose, such as when a study halting rule is met. The Chair/Co-Chair, and OSRO MM, as applicable, determine the need for an Ad hoc Meeting. The Meeting will be scheduled by the SROS SOS with confirmation from the OSRO Director or designee.

As these meetings are usually in response to serious emergent issues, all parties involved will provide any required documents to the SROS SOS for posting to the SROS SOS CMS as soon as available.

For an Ad hoc Meeting, the Committee may request special Reports. The SROS SOS notifies OSRO of this request and once approved, OSRO requests these Reports from

SROS Data Analytics.

7.5 Final Meeting

Once all studies reviewed under the Committee purview conclude, additional meetings are not required unless consultation is needed by the Committee or if a potential safety concern or study-related issue arises.

7.6 Meeting Format

Open Session:

- The Open Session is focused on the general conduct and progress of the study. Information to be reviewed includes accumulated study data, scientific validity, integrity, quality, study progress, futility, and accrual, AEs, SAEs, toxicity issues, Protocol compliance and study conduct, demographic characteristics, and disease status of study participants, site performance, participant safety, quality control, timeliness and completeness of follow-up, endpoint data, and when appropriate efficacy. During these Sessions, the blinding of data, if present, will be maintained.
- Open Session discussions include Committee Members (study specific, Ad hoc, and Consultants), and OSRO staff. Open Session discussions might also include representatives of the Sponsor and/or FDA, steering Committee Members, or others with trial responsibilities. The PI or designee, other members of the study team, and members of SROS Data Analytics should attend as needed to present results and respond to questions. The SROS SOS will prepare Meeting Minutes for the Open Session, which will be reviewed and approved by the Committee Chair/Co-Chair and if the Chair/Co-Chair requests, the entire Committee, and OSRO Director or designee.

Closed Session:

- The Closed Session is focused on the unblinded statistician(s) presenting the grouped safety data and, if appropriate, efficacy data. Grouped data should be presented by coded treatment arm but will not be unblinded unless requested by the Committee Members, or prespecified in the study Protocol.
- Closed Session discussion and attendance include Committee Members, the SROS SOS Team, and study unblinded statistician(s). For safety reviews the OSRO MM may attend with written approval from the OSRO Director or designee. Permission to attend Closed efficacy Sessions requires written permission from CCR Director or designee; in response to a request from the OSRO MM or other OSRO staff.

Closed Executive Session:

- This Session is a deliberative period for the Committee Members and the ES to determine conclusions and reach a consensus on the data presented. In the case of a trial for registration or other significant purpose, other appropriate

parties may attend a Closed safety and efficacy review only when deemed appropriate by the Committee and when given written permission from the OSRO Director or designee.

- The Committee may call on study physicians, statisticians, and/or OSRO MMs as needed to request additional information. The Committee Chair/Co-Chair can call to move to a Closed Executive Session at any time during the Open or Closed Session and return to the previous Session type as needed.
- No communication, written or oral, of the deliberations or Recommendations will be made outside the Committee Meeting except those required to aid in forming a consensus regarding the Recommendations and carrying out the normal functions of the Committee. Trial outcome results are strictly confidential and must not be divulged to any non-Member of the Committee until a recommendation to release the results has been accepted and implemented.

7.7 Committee Reports

Reports should be formatted for ease of use by the Committee Members. Acceptable formats include:

- Single, unique MS Word, MS Excel, or Adobe PDF files.

When multiple files are required, they should be combined to minimize the number of files for downloading and review.

- Indexed zip (compressed) files are not acceptable.

When transmitting the Report or data review packet to SROS SOS by link or email, SROS Data Analytics must:

- Label the Reports clearly for the Open or Closed Session.
- Provide a list of files, identifying each Report and type.
- Confirm Open Session Reports were reviewed and approved by the OSRO MM and can be posted to the SROS SOS CMS.
- Confirm Closed Session Report is for Committee Members only, and the SROS SOS will confirm receipt.
- Notifies the OSRO MM when a Closed Report was prepared prior to sending the Report electronically to the SROS SOS.
- Ensure the Closed Report access is password-protected and removable for posting by the SROS SOS to the SROS SOS CMS.

Meeting Materials provided for all Sessions are confidential and will be deleted by each Committee Member following procedure as defined in Section 4.0.

Open Session Committee Reports:

- Open Session presentations or Reports will be prepared by the appropriate PI or designee, and/or SROS Data Analytics with input from NCI OSRO staff, if engaged in study support. Whenever possible, these Reports will be

distributed via the SROS SOS CMS.

- Open Report information includes data on study conduct, Protocol compliance, site performance, quality control, follow-up, and baseline characteristics.

Closed Session Committee Reports:

- All studies conducted under CCR are Open-label studies, however if the Committee requires Closed Reports these will be distributed to Committee Members and other meeting participants, including the ES, on a restricted basis. In the event Closed Session Reports are generated, Reports may be made available to the designated OSRO MM only in certain special circumstances and in compliance with the NCI Committee Policy.

- Closed Session Reports are prepared by SROS Data Analytics and distributed by SROS SOS to Committee Members only and posted to the SROS SOS CMS.

7.8 General Communication

To avoid COI, the study team may not communicate directly with any Committee Members.

7.9 SAE Reporting and Halting Rules

The OSRO MM is responsible for evaluating SAEs and events that may meet halting rules. Upon receipt of adequate information, the OSRO MM assesses the information and notifies SROS SOS Team to inform the Committee, if required by the Protocol.

If OSRO determines that a halting rule has been met, the study is halted, and the appropriate parties are notified by the SROS SOS. As described above in Section 4.0, the SROS SOS Team will retrieve the SAE Narratives and Line Listings from the SROS PVG or SROS Data Analytics Teams to be distributed to the Committee Members, and meeting participants in preparation for a Committee Ad hoc Meeting or electronic Review. Based off the information provided, the Committee will provide Recommendations for study continuation, modification, or termination, according to the study Protocol. The study halt remains in place until formal communication is received from the OSRO MM indicating the study halt can be lifted.

8.0 VOTING

It is expected that in most situations the Committee will work to obtain a consensus regarding the suitability of information provided to it, and any Recommendations made to NCI OSRO. Each Member is formally polled to provide their consensus. However, if consensus is not reached, each Member recommendation will be considered by the OSRO MM and OSRO Director or designee.

9.0 RECOMMENDATIONS

9.1 Committee Recommendations

Recommendations will be developed for each study reviewed by the Committee (See Appendix C). Unless otherwise specified, the Recommendations from an Open Session will be agreed upon by the entire Committee and submitted to the Committee Chair/Co-Chair by the SROS SOS for approval. The Recommendations are sent to the OSRO Director or designee for concurrence and documentation of any action from OSRO. Upon review and concurrence, the Committee Chair/Co-Chair and OSRO Director or designee will sign the Recommendations. The final signed Recommendations for an individual study will be distributed to the PI or designee and all individuals on the approved Contact List via the SROS SOS CMS 5 working days following the Committee Meeting.

If OSRO chooses to reject or partially accept a Committee Recommendation, this decision, accompanied by a rationale will be communicated in writing to the Committee as part of the Recommendations.

The OSRO Director or designee:

- Ensures timely safety reporting to the FDA and other regulatory authorities, as required.
- Submits the Committee Summary of Recommendations to the FDA and other regulatory authorities, as required.

In fulfillment of the NIH Guidance on Reporting Adverse Events to Institutional Review Boards for NIH-Supported Multicenter Clinical Trials (June 11, 1999) the PI or designee is responsible for disseminating the Recommendations to the site investigators, as well to the overseeing Single IRB or the site IRB/ECS, whichever is applicable, in accordance with local ethics review policy. The IND Sponsor will distribute the Recommendations to Health Authorities, and industry collaborators, when applicable. These Recommendations do not include Closed Session information.

9.2 Immediate Action Report

The ES will notify the OSRO Director or designee of any findings of a serious or immediate nature or Committee Recommendation to discontinue all or part of a trial. In situations where the OSRO MM is excluded from Session participation, the ES will communicate these solely to the OSRO Director or designee and the details of the

Recommendations and Closed Session data will not be shared with the study investigators at this time.

OSRO will review the Committee Recommendation and the rationale (including background information/Closed Session discussions). The OSRO Director or designee will make the decision whether to accept the Committee Recommendation. The details of the Recommendations and Closed Session will not be shared with the study investigators at this time. If NCI OSRO accepts the Committee Recommendation to discontinue all or part of a trial, this will be communicated by the OSRO staff.

10.0 MEETING MINUTES

10.1 Open Session

The Open Session Meeting Minutes will reflect the Committee discussion, Recommendations, and Action Items for all studies reviewed. The SROS SOS will prepare the draft Meeting Minutes of the Open Session and distribute them to the OSRO MM for review within 10 working days following Committee Chair/Co-Chair approval of the Recommendations. Once approved by the OSRO MM, the Open Session draft Meeting Minutes will be distributed to the Committee Chair/Co-Chair for review and approval. The final signed Open Session Meeting Minutes should be made available within 30 calendar days of the Meeting on the SROS SOS CMS and distributed via email to the Committee only. If the Meeting Minutes are requested by the PI or designee, study team, or Sponsor, separate Meeting Minutes will be developed from this document for the individual study and will be distributed, as directed by OSRO.

10.2 Closed Session

In the event a Closed Session is held, the Closed Session Meeting Minutes will describe the proceedings of the Closed Session, including the listing of Recommendations, and are labeled as 'Closed.' The Closed Session Meeting Minutes are provided to the Committee Members only. The Closed Session Reports and Meeting Minutes are kept secure by the SROS SOS and stored within the SROS SOS CMS.

Note: If requested by the FDA, the SROS SOS will provide the requested Closed Session Meeting Materials (according to established confidential OSRO procedure) to the designated representative for submission to the FDA.

10.3 Explanation of Committee Recommendations

If the Committee recommends the trial should be stopped, recruitment halted, or the Protocol amended due to safety concerns (e.g., higher overall death rate in the investigational arm than the control arm), OSRO requires substantial justification and documentation in the Meeting Minutes of the reviewed results. This justification is confidentially provided to designated OSRO senior officials without data unblinding.

10.4 Meeting Recordings

Meetings are recorded by the ES to ensure accuracy of the Meeting Minutes. All recordings will be destroyed by the SROS SOS at the conclusion of the study or with direction from OSRO.

11.0 TERMS AND ABBREVIATIONS

AE	**Adverse Event**
CCR	**Center for Cancer Research**
CMS	**Committee Management System**
COI	**Conflict of Interest**
CRO	**Contract Research Organization**
CV	**Curriculum Vitae**
DAG	**Data Analytics Group**
DCC	**Data/Clinical Coordinating Center**
DSMB	**Data and Safety Monitoring Board**
ES	**Executive Secretary**
eTMF	**Electronic Trial Masterfile**
FDA	**Food and Drug Administration**
IB	**Investigator's Brochure**
IND	**Investigational New Drug**
IRB	**Institutional Review Board**
MM	**Medical Monitor**
NCI	**National Cancer Institute**
OSRO	**Office of Sponsor and Regulatory Oversight**
PI	**Principal Investigator**
PVG	**Pharmacovigilance**
SAE	**Serious Adverse Event**
SDCC	**Statistical and Data/Clinical Coordinating Center**
SMC	**Safety Monitoring Committee**
SOS	**Safety Oversight Support**
SROS	**Sponsor and Regulatory Oversight Support**

12.0 REFERENCES/LINKS

The below online information is current as of the effective date of this policy

- NIH Policy for Data and Safety Monitoring, June 10, 1998. http://www.grants.nih.gov/grants/guide/notice-files/not98-084.html

- Further Guidance on A Data and Safety Monitoring Board for Phase I and Phase II Trials, June 5, 2000. http://www.grants.nih.gov/grants/guide/notice-files/NOT-OD-00038.html

- Guidance on Reporting Adverse Events to Institutional Review Boards for NIH-Supported Multicenter Clinical Trials (June 11, 1999). https://grants.nih.gov/grants/guide/notice-files/not99-107.html

- Office of the Secretary; Office for Human Research Protections. The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research, The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (18 April 1979). From: https://www.hhs.gov/ohrp/regulations-and-policy/belmont-report/

- Ellenberg, Susan S., Fleming, Thomas R. & DeMets, David L. (2002). Data Monitoring Committees in Clinical Trials, A Practical Perspective. John Wiley and Sons, LTD: West Sussex, England.

- Commissioned by the National Heart Institute (1988). Organization, review, and administration of cooperative studies (Greenberg Report): A Report from the Heart Special Project Committee to the National Advisory Heart Council, 1967. Controlled Clinical Trials 9(2): 137-148.

- World Health Organization on behalf of the Special Programme for Research and Training in Tropical Diseases (TDR) (2005). Operational Guidelines for the Establishment and Functioning of Data and Safety Monitoring Boards. Geneva, Switzerland, TDR/GEN/ Guidelines/05.1. From: http://apps.who.int/iris/bitstream/10665/69171/1/TDR_GEN_Guidelines_05.1_eng.pdf

- U.S. Department of Health and Human Services; Food and Drug Administration; Center for Biologics Evaluation and Research (CBER); Center for Drug Evaluation and Research (CDER) and Center for Devices and Radiological Health (CDRH) (March 2006). Guidance for Clinical Trial Sponsors: Establishment and Operation of Clinical Trial Data Monitoring Committees (OMB Control No. 0910-0581, Expiration Date: 11/30/2024). Rockville, MD. From: http://www.fda.gov/RegulatoryInformation/Guidances/ucm127069.htm

- ICH E2A: Clinical Safety Data Management: Definitions and Standards for Expedited Reporting (CPMP/ICH/377/1995), June 1995.

- ICH E2B (R3): Clinical Safety Data Management: Data Elements for Transmission of

Individual Case Safety Reports (EMA/CHMP/ICH/287/1995), July 2013.

- ICH E6 (R2): Good Clinical Practice: Integrated Addendum to ICH E6(R1) (EMA/CHMP/ICH/135/1995), March 2018.

- 21 CFR 11: Electronic Records; electronic Signatures

- 21 CFR 50.24(a)(7)(iv): Exception from informed consent requirements for emergency research.

- 21 CFR 312.32: IND Safety Reporting

- 21 CFR 812: Investigational Device Exemptions

- 204 Investigators' Responsibility Policy, January 2022. From: https://ccrod.cancer.gov/confluence/display/CCRCRO/Policies

- 306 (R3) Independent Data and Oversight Policy, December 2022. From: https://ccrod.cancer.gov/confluence/display/CCRCRO/Policies

- 401 Conflict of Interest Policy, January 2022. From: https://ccrod.cancer.gov/confluence/display/CCRCRO/Policies

- 410 Final Clinical Study Reports for Studies under CCR-held INDs or IDEs Policy, January 2022. From: https://ccrod.cancer.gov/confluence/display/CCRCRO/Policies

13.0 CHARTER VERSION HISTORY

Version #	Date of Revision (dd-Mmm-yy)	Replaces	NCI Division Authorization (and Date)	Rationale for Change	Committee Acceptance Recorded by (and Date)
v0.46	22-Dec-22	v0.45	Joni Love, RN, BSN 20-Dec-22	NCI Policy 306 R3 Independent Data and Safety Oversight Policy dated 20-Dec-22	N/A
v0.47	17-Mar-23	v0.46	Joni Love, RN, BSN 13-Mar-23	Directed by OSRO Director, and NCI Policy 306 R3 Independent Data and Safety Oversight Policy dated 20-Dec-22	N/A

14.0 CHARTER AVAILABILITY

This NCI OSRO Committee Charter document is located electronically on the SROS SOS CMS: INSERT LINK

Guidelines for NCI Appointed Data and Safety Monitoring Boards: INSERT LINK

Further Guidance on a Data and Safety Monitoring for Phase I And Phase II Trials
https://grants.nih.gov/grants/guide/notice-files/NOT-OD-00-038.html

NIH Policy for Data and Safety Monitoring
https://grants.nih.gov/grants/guide/notice-files/not98-084.html

Appendices

Appendix A. Member's Signature Page

Member Signature Page

Due to the geographically dispersed Committee, a separate signature page was created for each Member.

Role: DSMB/SMC Chair/Co-Chair/Member

Member Information: First Name Last Name, Credentials

Re: DSMB/SMC Charter Version: to complete Dated: to complete

I have reviewed the attached DSMB/SMC Charter and approve it as written. I understand my role as a Member of this DSMB/SMC Committee.

Signature: _____ Date: _____

Printed name: _____

Appendix B. DSMB/SMC Conflict of Interest (COI) Disclosure Form

NATIONAL INSTITUTES OF HEALTH NATIONAL CANCER INSTITUTE CENTER FOR CANCER RESEARCH

OFFICE OF SPONSOR AND REGULATORY OVERSIGHT

NOTE: In this document the term "you" will be used to indicate applicability to you AND your spouse, dependent children, or any household members or relatives with which you currently have close personal relationships.

Instructions:

- Check the appropriate response for each question. If the answer is "yes" to any question, please provide the additional information as requested.
- You must provide a copy of your current detailed curriculum vitae when submitting this disclosure form.

A. PROFESSIONAL

1. Are you
   a. directly involved in the conduct of the study to be reviewed?
   b. in a direct supervisory relationship with one or more members of the research team; or serving in a data and safety monitoring role while being supervised by an individual who is part of the research team?
   c. involved as a plaintiff, defendant, or expert witness in litigation related to the interventions or products being tested, or in competing products or interventions?

☐ Yes ☐ No

2. Are you serving as a part-time, full-time, paid, or unpaid employee of any organizations
   a. that are involved in the study(ies) under review (e.g., involved in protocol development or supervise a member of the study team)?
   b. whose products or services will be used or tested in the study(ies) under review?
   c. whose products or services would be directly and predictably affected in a major way by the outcome of the study(ies)?

☐ Yes ☐ No

If yes, please identify the organization; describe employment status of you or your family member(s) and indicate what products or services would be affected.

_____

_____

3. ___Are you currently serving as
   a. an officer, member, owner, trustee, director, expert advisor, or consultant of an organization with a direct role or stake in the study(ies) under review?
   b. a director, officer, or other decision-maker for a commercial collaborator of the human subjects research?

☐ Yes ☐ No

If yes, please provide the name of the organization and the role of you and/or your family member(s).

c. Within the past 5 years have you served or anticipate serving as a co-author on a scientific paper with the principal investigator (PI) for the protocol under review, even if the subject matter is not addressed in the current study being reviewed.

☐ Yes ☐ No

B. PROPRIETARY

4. Do you
   a. obtain royalties that derive from intellectual property or tangible materials relevant to the development and commercialization of any product being reviewed; or are you personally named as an inventor on patents or patent applications relevant to the product(s) being reviewed in the human subjects research or products in direct competition with the product(s) being reviewed?
   b. own or control intellectual property rights or other proprietary rights in any of the products being reviewed or in products in direct competition with such products under review?

☐ Yes ☐ No

C. FINANCIAL

5. Do you currently receive any funding, payment, compensation, or honoraria, in any form from the commercial sponsor of the human subjects research?

☐ Yes ☐ No

If yes, please provide the name of the commercial sponsor and the type of compensation.

_____

6. Do you
   a. hold stock in excess of $5,000 in any single entity whose study is under review?
   b. have financial interest or assets in organizations with which the individual with data safety monitoring responsibilities is connected?
   c. receive payments based on the research recruitment or outcomes; receive payments as consultant/advisor to a commercial sponsor; or accept payment from the human subjects research sponsor?

☐ Yes ☐ No

If yes, please provide the name of the organization/commercial sponsor and the type of compensation.

_____

Member certification:

- I/my spouse, dependent children, or any household members or relatives with whom I have currently personal relationships do not have any financial or other interest with any of the collaborating or competing

pharmaceutical firms or other organizations involved in the study that constitute a potential conflict of interest.

- I will notify OSRO promptly if a change occurs in any interests or activities during the tenure of my responsibilities that may create a potential conflict of interest.
- I will disclose interests that may create a potential conflict to the DSMB/SMC prior to any discussion so that they can be reflected in the minutes along with the determination of the DSMB on how to handle such potential conflict(s).
- I am aware of my responsibilities for maintaining the confidentiality of any non-public information that I receive or become aware of through this activity, and for avoiding using such information for my personal benefit, the benefit of my associates, or the benefit of organizations with which I am connected or with which I have a financial involvement.

_____	_____	_____
Member Name Printed	Signature	Date

<u>This box is for OSRO Use ONLY:</u>

OSRO review of eligibility:

☐ I have reviewed the conflict of interest disclosure information provided, in addition to the current curriculum vitae; and find the member **is eligible** to serve as a DSMB/SMC member at this time.

☐ I have reviewed the conflict of interest disclosure information provided, in addition to the current curriculum vitae; and find the member **is eligible** to serve as a DSMB/SMC member at this time with the disclosure of:

_____

☐ I have reviewed the information provided and find that the proposed member **not eligible** to serve as a DSMB/SMC member at this time due to an unmanageable potential conflict of interest, which is:

_____

_____	_____	_____
Director, OSRO or designee	Signature	Date

Appendix C. Recommendations Form Completed for Each Study Reviewed

Committee Name: XXXX
Protocol xx-xxxx, Title

The **Data and Safety Monitoring Board (DSMB)** OR **Safety Monitoring Committee (SMC)** met on: dd-Mmm-yy for an/a Initial/ New Protocol Review/ Periodic Committee Safety Review/ Ad hoc Meeting that included/reviewed: Insert Purpose from Meeting Agenda OR Insert documents/reports reviewed.

Materials provided for review:

List all materials provided for the review in alphabetical order by document type. Insert document type (e.g., Safety Report, Memo from DMID, etc.) and file names. If there are two of the same type of document, list them in chronological order by date or version.
For example:
Contact List: xx-xxxx DSMB Initial Meeting Contact List Final v1.0 ddMmmyy.doc

Recommendations from the DSMB OR SMC:

Example for Initial Meeting or New Protocol Review Meeting: this should be standard per the agenda—if confirmed:

- The Charter is acceptable.
- The Safety Report Shells are acceptable.
- The planned safety considerations are acceptable.
- The planned stopping rules are acceptable.
- The interim analysis plan is acceptable as presented OR with modifications insert specific modifications.
- The study should proceed as planned OR; while these changes are being implemented OR with modifications insert specific modifications.

Example for Periodic Committee Safety Review Meetings:

- The study should continue as is currently being conducted. No Ad hoc meeting or additional information is necessary.
- No safety signals or issues were identified.
- The changes made to dose changes AND/OR enrollment of Cohort x was appropriate.
- The study should proceed as planned OR; while these changes are being implemented OR with modifications insert specific modifications.

Example for Ad hoc Meetings:

- The study should proceed as planned OR; while these changes are being implemented OR with modifications insert specific modifications.
- No safety signals or issues were identified.
- The changes made to dose changes AND/OR enrollment of Cohort x was appropriate.

Name, Credentials	Date
DSMB OR SMC Chair/Co-Chair	

Office of Sponsor and Regulatory Oversight (OSRO) has reviewed and agrees with the recommendations.

OR

Office of Sponsor and Regulatory Oversight (OSRO) has reviewed the recommendations and has implemented the following:

-

Name, Credentials	Date
Director, OSRO	