SOP#: PM-15	**Preparation of Safety Monitoring Committee (SMC) Report**
Version #: 2.1	**Next Review Date: 07/2022**
Approved Date: 12/2020	**Review Interval Period: Biennial**
NCI Clinical Director Signature:	

William L. Dahut, M.D. 12/28/2020

POLICY

The Safety Monitoring Committee (SMC) will meet quarterly to review any studies that meet the requirements for SMC review. Protocols that meet the requirements will be reviewed initially as soon as possible after the initial IRB continuing review provided the initial participant has been treated. Subsequently, each protocol will be reviewed as close to annually as the quarterly meeting schedule permits, or more frequently as required by the SMC.

PURPOSE

Identify the process for submitting reports to the Safety Monitoring Committee

RESOURCES

- NIH Policies
  - NIH Policy for Data and Safety Monitoring (Notice 06/10/1998)
  - Further Guidance on Data and Safety Monitoring for Phase I and Phase II Trials (Notice 06/05/2000)

- NIH Office of Intramural Research Policies & Guidance website
  - Policy 503 - *Data and Safety Monitoring*

PROCEDURES

STEP 1: Determination of a Protocol That Meets the Criteria for Submitting to the Safety Monitoring Committee (SMC)

A protocol will require SMC review if any of the following criteria apply:

- All NCI Center for Cancer Research (CCR) multi-institutional treatment protocols for which the NCI CCR is the coordinating site, unless the study has already a designated Data and Safety Monitoring Board (DSMB) or equivalent. These studies will be monitored across the sites for unusual, significant toxicities that are related to the investigational agents being used.

***Note*:** The SMC will not monitor a CTEP-sponsored protocol if this is the only SMC qualifying criteria for the protocol.

- All protocols using gene transfer or gene therapy methodology. Monitoring of these protocols will focus on unusual toxicities specific to gene therapy.

Note: Gene therapy studies that are reviewed by a separate entity do not require SMC review if approved by CCR Clinical Director.

- All protocols that the CCR believes require special attention due to high public interest or public perception of risk or potential conflict of interest. These include studies where the Principal Investigator (PI) or an AI holds a patent on any agent being used in the protocol. For these protocols, the review will focus on unusual, significant toxicities that are related to the investigational agents being used, as well as on the potential perception of a conflict of interest regarding issues such as the continuing study relevance versus PI benefit.
- All protocols that are deemed by the IRB to pose potentially very high risk to patients.

STEP 2: PI Notification of SMC Report Due Date

- The PI will receive email notification from the SMC Coordinator of the due date for the SMC report submission. Notifications are sent approximately **2 months** prior to the review date.

Note: If there is no protocol related treatment or no enrollment within the review period, then, the PI or proxy should inform the SMC Coordinator.

STEP 3: Collection of Data and Preparation of iRIS SMC Report Submission Form

PSO manager will collect the following information from the research team and compile the SMC Report Submission Form in iRIS.

Note: See Appendix A for a sample template that can be used for requesting data from the team.

The following information should be collected from the research team or other sources and entered into the appropriate fields in the iRIS form. Details for each question in the form are below:

- Accrual to date by year per treatment arm and site: Report accrual data per arm/cohort, using the sample table below. Reporting per dose level for phase I studies is not required.

	Arm/Cohort/ Site # 1	**Arm/Cohort/ Site # 2**	**Arm/Cohort/ Site # 3**	**Arm/Cohort/ Site # 4**
Year 1 (dates)				
Year 2 (dates)				
Year 3 (dates)				
Total				

- If there are any patents, commercial sponsorships, payments, royalties or CRADAs associated with the protocol, indicate the CRADA, patent or other number(s).
- Amendment summary: List and summarize all amendments that have been submitted since the most recent Continuing Review, including those that are pending IRB approval, and those that are planned for submission in the very near future. Amendments that contain only administrative changes should be listed as such – no summary is required. Prior amendment summaries can be found in the Study Summary/Profile section of iRIS.
- Adverse Event (AE) table (in Excel) that includes a title that specifies the protocol number and date range in which the data is being presented. The study team will provide the AE table.

  AE data should be broken down by:
  - Study site, for multi-site studies
  - Patient subgroup, if applicable
  - Arm, if applicable
  - Donors and recipients (in transplant studies)

  The report must include:
  - System organ class
  - CTCAE term
  - Grade
  - Attribution to the IND(s), if applicable – refrain from using coded numbers. Treatment assignment code, if applicable

  Tallies by grade should include:
  - Number of events since last SMC reporting
  - Number of events since study start
  - Number of unique patients since last SMC reporting
  - Number of unique patients since study start

  Note: For all grade 5 events reported, an autopsy report should be included with the submission, if available.
- PI's AE statement: The statement should refer to AEs that have occurred since study start for protocols being reviewed for the first time and for 2 months before the last SMC review for protocols that have been previously reviewed. The relevance of the reported AEs to the overall safety of the trial should be discussed.
- New information: This should include new information that has appeared in the literature, in IND safety reports or in long term surveillance of patients who have been taken off this protocol that might impact the safety of this protocol.
- For multi-institutional trials, detail what monitoring is occurring and at what frequency monitoring takes place. Discuss the completeness of data submission by participating sites.

- PI's summary statement: Include but not to be limited to major clinical events by treatment arm or study site. In addition, include a description of any unanticipated problems or serious unresolved clinical adverse events attributable to research and/or IND agent(s). If applicable, provide the safety monitoring data for any gene therapy study. For transplant studies, include information about engraftment and the incidence and grading of acute and chronic GVHD.
- Endpoint analysis:
  - Review the protocol to determine if an interim analysis is planned. A description of planned interim analyses can be found throughout the protocol but is often discussed in the Statistical Considerations section.
  - The research team should inform the PSO manager as to whether or not an interim analysis has been performed and what the results are.
  - For studies with multiple arms/cohorts, state whether each arm is open or closed. If arms have been closed prior to completion of enrollment as outlined in statistical consideration section, include a rationale for doing so.
  - Review the protocol to determine if an early stopping rule for safety/or efficacy exists. A description of early stopping rules can be found throughout the protocol but is often discussed in the Statistical Considerations section.
  - The research team should inform the PSO manager as to whether or not the pre-specified number of patients have been enrolled that are required to evaluate for one or more early stopping rules and how the stopping rule(s) do or do not apply.
- Attachments should be included in PDF format unless otherwise described below:
  - Current approved English consent(s) taken from Protocol View - ensure the blue IRB approval stamp is present and current
  - Current clean protocol - ensure initial view settings for the document are set to show "Bookmarks Panel and Page" as the opening navigation tab. Settings to adjust this are located under File → Properties
  - Accrual report - formatted according to the sample table provided above, use attachment category "Other"
  - AE Report with data presented in Excel table as described above, use attachment category "Other"
  - Most recent SMC outcome letter – attach outcome letter and stipulations as a single PDF, use "Correspondence" as attachment category
  - Available autopsy report(s) since last SMC review - compile all reports into a single PDF with the start of each report bookmarked. Ensure initial view settings for the document are set to show "Bookmarks Panel and Page" as the opening navigation tab. Settings to adjust this are located under File → Properties, use "Other" as attachment category
  - Most recently submitted Continuing Review package – include approval letter and CR form, use "Correspondence" as attachment category

    - Unanticipated Problem reports that have occurred since the last SMC review – compile all reports with their IRB outcome letters into a single PDF with the start of each report bookmarked. Ensure initial view settings for the document are set to show "Bookmarks Panel and Page" as the opening navigation tab. Settings to adjust this are located under File → Properties, use "Other" as attachment category
- Submit for internal PSO QC.
- When routing the submission for signatures, 2 signatures are required:
    - PSO Manager should sign off as "study contact"
    - The PI

STEP 4: Receipt of Approval From SMC

Approval from the SMC will be sent to the PI and study contacts via an iRIS notification letter. Stipulations may require further response. A copy of the final approval letter and stipulation letter (if applicable) should be saved in the regulatory files and be submitted to the IRB with the next Continuing Review.

APPENDIX A - SMC SAMPLE TEMPLATE FOR DATA REQUEST

Study #: [*Study number*]

Reporting period/dates: [*Refer to SMC notification email for reporting period dates*]

Replies are requested by: [*Select a date at least 1 week prior to due date to allow ample time for QC*]

Dear [*PI and research nurse coordinator]*,

Thank you for allowing me to work on the Safety Monitoring Committee (SMC) Report for protocol # [*protocol #*]. In order to meet the SMC submission deadline, please respond with answers to the following questions no later than the date indicated above.

1. **Accrual to date by year (see sample table below) per treatment arm (reporting per dose level for phase I studies is not required) and site: (Tables will be attached in IRIS as separate documents).**

Year	**Arm/Cohort/ Site # 1**	**Arm/Cohort / Site # 2**	**Arm/Cohort/ Site # 3**	**Arm/Cohort/ Site # 4**
Year 1 (***dates***)				
Year 2 (***dates***)				
Year 3 (***dates***)				
Totals:				

2. **Are there any patents, commercial sponsorships, payments, royalties or CRADAs associated with the protocol?**

- (•) Yes
- ( ) No
- ( ) N/A

If Yes, then specify (include #):

3. **A report of all grade 3 or greater expected or unexpected adverse events that have an attribution of "possibly," "probably" or "definitely" related to the research. The report will list the highest grade of each toxicity per patient. For all grade 5 events reported, an autopsy report should be included with the submission if there is one available. Please attach an electronic version of the AE report in the form of an Excel spreadsheet to this inquiry response.**

NOTE: It is the responsibility of the research team to ensure that their AE data is current in C3D through the date provided in the notification of the impending SMC review (data entry to be completed no later than 3 weeks prior to the submission due date), to review the reports for accuracy, and to include the reports with their SMC submissions. The appropriate SMC AE reports will be available in JReview. The IT team will be notified of the review date, and they in turn will notify the team when the JReview reports are available. There will be 2 reports available for each protocol. It is important that the study team run the 'SMC – Details' report first and review the data. Once you have made any necessary edits to this report, you may then run the 'SMC - Summary' report. The summary report should be submitted with the SMC submission. Please make sure that the data is provided in a readable font.

For each protocol, the information will be broken down by:
- Donors and Recipients (In transplant studies)
- System Organ Class
- CTCAE Term
- Patient Subgroup (if applicable)
- Arm (if applicable)
- Treatment Assignment Code (if applicable)
- Attribution to the IND(s) (if applicable) - refrain from using coded numbers

Provide the following tallies by grade:
- Number of events since last SMC Reporting
- Number of events since Study Start
- Number of unique patient since last SMC Reporting
- Number of unique patients since Study Start

4. **Provide statement by the Principal Investigator regarding the relevance of the reported AEs to the overall safety of the trial:**
NOTE: The summary should refer to AEs that have occurred since the study start for protocols being reviewed for the first time and since 2 months before the last review for protocols that have been previously reviewed.

5. **Has any new information appeared in the literature, in IND safety reports or in long term surveillance of patients who have been taken off this protocol that might affect the SMC's evaluation of the safety of this protocol?**

6. **For multi-institutional trials, comment on frequency of monitoring and completeness of data submission by participating sites.**

7. **Summary Statement by the Principal Investigator: This should include but not be limited to major clinical events by treatment arm or study site. In addition, a description of any unanticipated problems or serious unresolved clinical adverse events attributable to research and/or IND agent should be included. If applicable, provide the safety monitoring data for any gene therapy study. For transplant studies, please include information about engraftment and the incidence and grading of acute and chronic GVHD.**

8. **Endpoint analysis:**

- **Is there an interim analysis planned?**

(●) Yes

( ) No

If yes, has it been performed?

(●) Yes

( ) No

If yes, describe the result(s):

- **For trials with several arms/cohorts: Provide per arm information for endpoints. State whether each arm is open or closed. If arms are closed prior to completion of enrollment as outlined in statistical section, provide rationale for doing so.**

- **Is there an early stopping rule for safety and/or efficacy?**

  For protocols that include stopping rules, it will be necessary to list each stopping and an explanation of how/why each one has or has not been met. Also, please outline the rules by cohort or arm, as relevant to the protocol, and for each stopping rule, include the number of patients who are in follow up and could still contribute an event to the stopping rule.

(●) Yes

( ) No

If yes, describe the rule(s):

If yes, have the prespecified number of subjects been enrolled that are required to evaluate for one or more early stopping rules?

- (•) Yes
- ( ) No

If yes, describe how the threshold has been crossed:

If threshold has been crossed, describe how stopping rule(s) do or do not apply:

If events that have occurred after the data cut-off date are being reported, kindly explain in the PI narrative section that they will not be included on the AE table for that reason.

Thank you,
[*PSO Manager Name*]