National Institutes of Health (NIH)
National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS)
Safety Officer (SO) Charter

[STUDY/TRIAL NAME]
Grant No: [GRANT NO]
Contract No: [CONTRACT NO]
Cooperative Agreement No: [COOPERATIVE AGREEMENT NO]
[PI NAME AND CREDENTIALS], Principal Investigator
[INSTITUTION]

Last Approved Date: TBD

INTRODUCTION

The Safety Officer (SO) acts in an advisory capacity to the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS), National Institutes of Health (NIH) to review safety data and [study/trial] progress for the "[STUDY/TRIAL NAME]." This clinical [study/trial] is funded partially or in whole by the NIAMS and [OTHER NIH IC]. However, the NIAMS is responsible for oversight of the data and safety monitoring of this [trial/study]. The purpose of this document is to outline the NIAMS charge to the SO regarding his/her responsibilities and processes for "[STUDY/TRIAL NAME]." The NIH mandate requires safety oversight and monitoring for all clinical trials to be commensurate with risks, nature, size, and complexity of the clinical [study/trial]. The Charter is intended to be a living document to be modified at any time. Review, modification, and approval of the Charter are facilitated by Navitas Clinical Research, Inc. (NCR), the Executive Secretary, as needed.

NIAMS RESPONSIBILITIES

NIAMS staff have stewardship responsibilities for oversight of the data and safety monitoring of its clinical [studies/trials]. Responsibilities of the NIAMS include, but are not limited to:

- Ensuring that a monitoring system is in place and is appropriate for the clinical [study/trial].
- Selecting an SO that has relevant expertise for the clinical [study/trial].
- Confirming that the SO has access, in a timely manner, to study documents and milestones, and masked/unmasked data.
- Attending all SO meetings and meeting sessions. A limited, designated number of NIAMS staff attend the meetings. NIAMS staff are not members and do not have voting privileges. The NIAMS may not influence or provide input into the SO's recommendations. They may, however, raise questions to or seek clarification from the SO and the investigators during the meeting.

- Serving as the final decisional authority and accepting or rejecting recommendations from the SO. The NIAMS may also add an addendum to the formal written recommendations to provide further clarity or feedback as to their decision associated with the recommendations.

Other NIH program staff who attend the SO meetings are held to the same responsibilities.

EXECUTIVE SECRETARY

A NIAMS contractor, NCR, serves as the Executive Secretary. The Executive Secretary facilitates the introductory SO meeting and distributes routine and expedited SO reports to the NIAMS staff and the SO. When meetings are held, the Executive Secretary coordinates the meetings and web-conferences, and provides logistics support and meeting summaries. The Executive Secretary transcribes the meeting recommendations and minutes and distributes them to the NIAMS, the SO, and the study team. The Executive Secretary is the primary contact point for SO communication with the NIAMS and the Principal Investigator (PI).

SO RESPONSIBILITIES

Responsibilities of the SO are to:

- Review the research protocol, Data and Safety Monitoring Plan (DSMP), Manual of Operating Procedures (MOP), and informed consent documents, including all proposed revisions.

- Evaluate the progress of the clinical [study/trial] on an ongoing basis, as needed, including periodic assessments of data quality, participant recruitment, accrual and retention, participant risk versus benefit, performance of [study/trial] site(s), and other factors that can affect the outcome.

- Evaluate safety throughout the course of the clinical [study/trial] through the routine review of aggregated adverse event safety data, in addition to expedited review of unanticipated problems, serious adverse event reports, and protocol deviations impacting participant safety. The SO reviews the documentation provided by the study team and makes recommendations to the NIAMS regarding protection of the clinical [study/trial] participants.*

- Evaluate proposals of new clinical sites (that differ from the approved application) and make a recommendation to the NIAMS as to whether the enrollment at the site(s) is expected to enhance overall enrollment. Activities include evaluating the patient

*Questions from the investigators regarding individual study participants, such as those involving eligibility, patient care, or unblinding, are outside the purview of the SO. The PI is encouraged to consult with a designated study medical monitor and/or the IRB for guidance in these cases.

population pool, catchment area description, recruitment plan, and target enrollment for any new clinical sites.

- Consider the impact of factors external to the clinical [study/trial] when new information, such as scientific or therapeutic developments become available and may affect safety of participants, their willingness to participate in the clinical [study/trial] or the ethics and conduct of the [study/trial].

- Assist the NIAMS by commenting on any problems with study conduct or performance.

- Ensure that the plan for maintaining the confidentiality of the clinical [study/trial] data and the results by the investigative team is appropriate.

- Review and evaluate requests for protocol modifications.

- [Review data after completion of each cohort to approve dose escalation.]

- Review in advance of the clinical [study/trial] initiation the [study/trial] specific stopping rules and plans for interim analyses as established by the PI and selected members of the study team. These plans outline the conditions under which a clinical [study/trial] may be stopped (e.g., difficulties in recruitment, retention, obtaining outcome measures, or other issues).

- Review the interim analyses and/or accumulating data at the specified interval(s) (if applicable) and as appropriate, make a recommendation to continue, terminate, or modify the clinical [study/trial] based on observed benefit or harm in accordance with the planned stopping rules.

The NIAMS may discharge the SO from his/her duties when:

a) "[STUDY/TRIAL NAME]" is complete;
b) the SO is not able to fulfill the responsibilities as outlined in the Charter;
c) the NIAMS no longer has oversight responsibilities of the clinical [study/trial]; and/or
d) the SO is found to have a real or perceived conflict of interest.

Additionally, the SO may resign at any point during the clinical [study/trial], when the SO:

a) is not able to fulfill the responsibilities of the position, as outlined in the Charter;
b) believes a real or perceived conflict of interest exists.

SO APPOINTMENT

The SO appointment typically consists of one or two individuals appointed by the NIAMS. The position consists of an individual independent of the clinical [study/trial] who has no financial, scientific, or other conflicts of interest with the PI or any Co-Investigators. The SO is typically a clinician who has the ability to assess safety matters related to the population under study and the intervention(s) involved. He/she should also have experience in clinical trials.

The SO is the contact person for expedited reportable events (i.e., serious adverse events (SAEs), protocol deviations impacting participant safety, and unanticipated problems). The expedited reportable events must be reported to the NIAMS-appointed SO, and the NIAMS through the Executive Secretary within 48 hours of the investigator becoming aware of the event. The SO provides an assessment of SAEs and unanticipated problems on relatedness and expectedness, as well as the action taken by the investigative team, and makes a recommendation to the NIAMS as to whether further action should be taken (e.g., collection of follow up information).

The SO for this clinical [study/trial] is chosen because of his/her expertise in the field of [e.g., Orthopedics, Dermatology, etc.]. Dr. [SO NAME, DEGREE] has been appointed as the Safety Officer for this clinical [study/trial].

CONFLICT OF INTEREST

The individual invited to serve as the SO must disclose any potential conflicts of interest, whether real or perceived, to the NIAMS. Conflicts of interest can include, but are not limited to, professional, proprietary, and personal interests. Any real or potential conflicts that develop during an officer's tenure as the SO must be disclosed for the NIAMS consideration at the time the potential conflict is realized. In addition, written documentation attesting to an absence of conflict of interest is required annually.

Confidentiality

The SO must sign a statement of confidentiality annually. All materials, discussions, and proceedings are completely confidential. The SO and other participants in meetings and reviewing reports are expected to maintain confidentiality.

SAFETY OFFICER REVIEW PROCESS

Prior to commencement of recruitment, the study team drafts or revises [study/trial] materials (i.e., the protocol, MOP, DSMP, consent/assent form, report templates, and any other materials required for the SO's review). The study team submits relevant materials to the Executive Secretary, who facilitates the review process with the NIAMS and the SO through email and a secure website.

- Upon completion of the initial review, the SO sends the Executive Secretary his/her comments for consideration by the NIAMS. Accepted comments and recommendations are sent to the PI for review and revision.

- At the same time, the Executive Secretary schedules an introductory web-conference among the PI/study team, the SO, and the NIAMS.
- Subsequent routine SO reviews are typically facilitated electronically through the Executive Secretary as outlined below.

Introductory SO Meeting

The introductory meeting is held by web-conference before initiation of the clinical [study/trial] to discuss whether the [study/trial] is ready to commence, establish guidelines for monitoring, and determine the format for reports. The NIAMS and the Executive Secretary prepare the agenda to 1) review the study materials, 2) discuss the plan and timing for safety monitoring, 3) make recommendations to initiate the clinical [study/trial] and/or modify the [study/trial] materials, and 4) review the Charter. During the introductory meeting, a NIAMS representative provides a training session outlining the SO process, roles and responsibilities for all meeting participants (i.e., the SO, the study team, the NIAMS staff, and the Executive Secretary).

Meeting Format and Review Process

The introductory SO meeting consists of two sessions (i.e., open and executive sessions). All invited meeting participants, including the investigators and study team, the SO, the NIAMS staff, and the Executive Secretary may attend the open session of the meeting, while the executive session is only attended by the SO, the NIAMS staff, and the Executive Secretary. The study team exits the call to allow time for the SO to present his/her recommendations to the NIAMS.

Ad-hoc meetings may be called at any time by the SO or by the NIAMS should ethical or participant safety issues arise. The suggestion to convene an ad-hoc meeting should be transmitted to the Executive Secretary, who will notify the NIAMS and the SO.

Meeting Recommendations

When meetings are held, meeting recommendations are drafted by the Executive Secretary within two working days after the meeting and are distributed for review to the SO. The Executive Secretary receives comments from the SO within two working days. The Executive Secretary will continue to follow-up with the SO until his/her review is received.

Upon receipt of the SO's review of the recommendations, the Executive Secretary will send the SO's comments to the NIAMS for review. The NIAMS carefully considers all recommendations and accepts them at its discretion. The NIAMS has the final decisional authority and may add an addendum to the recommendations prior to finalization. Once finalized, the recommendations are posted to the NIAMS Monitoring Bodies Materials website and circulated to the study team.

Once received in writing, the PI has 30 calendar days to submit a formal, written response to the recommendations, which will then be circulated to the SO and the NIAMS for their electronic review by the Executive Secretary. In some cases, the recommendations from the introductory

meeting may indicate that the clinical [study/trial] cannot begin enrollment until the PI's response to the recommendations has been submitted, reviewed, and accepted by the SO and the NIAMS. Therefore, recruitment initiation may be contingent upon the SO's and the NIAMS' review of the PI's response and the study materials, if further revisions are required.

If the SO and the NIAMS have any further questions or concerns upon review of the PI's response to the recommendations, the Executive Secretary will notify the PI for further clarification via email. It is the responsibility of the PI and at his/her discretion to distribute the SO's recommendations or other information from the meeting to all co-investigators and to assure copies are submitted to all the IRBs associated with the clinical [study/trial].

A recommendation to terminate the study may be made by the SO at any time. The NIAMS Institute Director makes the final decision about whether to accept or decline the SO's recommendation to terminate the study. The Executive Secretary will transmit the NIAMS' decision to the PI as soon as possible. Specific recommendations will be transmitted in writing at a later date.

Meeting Minutes

The Executive Secretary drafts the full meeting minutes within five working days after the meeting and distributes the full meeting minutes to the SO for review and approval. The SO has three working days to review and provide comments. The Executive Secretary will continue to follow-up with the SO until his/her review is received. Once the SO's review is received, the Executive Secretary will send the SO's comments and the full meeting minutes to the NIAMS for review. The minutes are typically finalized no later than 30 calendar days after the meeting. Once approved by the SO and accepted by the NIAMS, the Executive Secretary posts separate versions (open and executive) of the approved minutes to the NIAMS Monitoring Bodies Materials website and notifies all participants according to the session(s) they attended.

Routine Reporting

Monthly Status Updates (pre-enrollment)

A status update regarding recruitment/enrollment start-up should be provided to the NIAMS by the study team through the Executive Secretary on a monthly basis until the first participant is enrolled. These updates are also shared with the SO for his/her reference following the introductory meeting.

Monthly Enrollment Reports (during active enrollment)

All clinical trials must provide monthly enrollment reports by the 5th of each month once the first participant is enrolled into the study. These reports will contain an Actual versus Expected graph along with a CONSORT diagram and should be submitted to the NIAMS through the Executive Secretary. The reports will be shared with the SO for his/her reference.

Routine Safety Reports

During the initial materials review, the study team will propose the format for the SO Reports utilizing the NIAMS' report templates. Once the first participant is enrolled, the SO reports are prepared by the study team at regular intervals (typically semi-annually) and submitted to the SO and the NIAMS through the Executive Secretary. Additions and modifications to the reports can be requested by the SO or the NIAMS at any time during the clinical [study/trial].

The safety reports list and summarize relevant safety data and describe the status of the clinical [study/trial] including enrollment data, demographic information, retention status, and other reports as needed. All safety reports must be submitted to the SO and the NIAMS through the Executive Secretary. The Executive Secretary will post the materials on the NIAMS Monitoring Bodies website for access by the SO, study team, and the NIAMS staff.

It is important that access to outcome data, when necessary, be limited to the study statistician and/or study-appointed safety monitor and the NIAMS-appointed SO to protect the clinical [study/trial] from bias in participant entry and/or evaluation. Any unmasked study personnel should be pre-designated and described in the MOP.

SO Checklist

The SO will review the routine safety reports prepared by the study team and recommend safe continuation or early termination of the clinical [study/trial]. The Executive Secretary will circulate the safety report to the SO along with a "Safety Officer Checklist." The checklist includes various questions and fields for comments related to the report. The SO can tailor the checklist by adding or removing items. The SO has two weeks to read, review, and complete the SO checklist from the date the report is circulated. The Executive Secretary will continue to follow-up with the SO until the SO Checklist is received. Comments, suggestions, questions, or recommendations accepted by the NIAMS are distributed to the PI by the Executive Secretary. Depending on the nature of the comments, questions, or concerns, the PI is given a time within which to respond.

Expedited Reporting

Unanticipated Problems

Unanticipated problems are 1) unexpected events that are 2) related or possibly related to participation in the research that 3) place participants or others at a greater risk of harm than was previously known or recognized. All three criteria above must be met to qualify the event as an unanticipated problem. The Office for Human Research Protections (OHRP), the Department of Health and Human Services (HHS) provides a complete definition and the following guidance for reporting unanticipated problems to the Institutional Review Board(s) (IRBs): *Unanticipated Problems Involving Risks & Adverse Events Guidance (2007)* (https://www.hhs.gov/ohrp/regulations-and-policy/guidance/reviewing-unanticipated-problems/index.html).

Unanticipated problems must be reported to the NIAMS and the SO, through the Executive Secretary, within 48 hours of the investigator becoming aware of the event. The SO reviews and provides an independent assessment of the unanticipated problems, as well as determines if further action is required.

Serious Adverse Events

All SAEs (regardless of expectedness, relatedness or if they meet the definition for unanticipated problems) must be reported to the SO and the NIAMS through the Executive Secretary within 48 hours of the investigator becoming aware of the event. The report will include a description of the event as well as the investigator's assessment of expectedness and relatedness, and other relevant information, including any actions taken. The SO will review this information and provide an independent assessment on attribution and expectedness, as well as recommendations for further action, if any.

While the NIAMS requires expedited reporting of SAEs through the Executive Secretary, the SO and the NIAMS do not provide real time assessment of SAEs. It is the responsibility of the investigator(s) to provide real time assessment and take the necessary, immediate action with regard to participant safety.

Please note that if the study is testing an intervention that is regulated by the Food and Drug Administration (FDA), there may be additional reporting requirements to the FDA and the IRB that are not part of the NIAMS reporting process and are the PI's responsibility.

Discrepancies with Assessments Concerning Unanticipated Problems

On occasion, there may be disagreements between the investigator and the SO regarding the assessment and/or management of an SAE or an event that qualifies as an unanticipated problem. The following excerpt gives guidance for cases where there is a difference of opinion between the SO (referred to as the "monitoring entity" in the excerpt below) and the investigator on unanticipated problems (https://www.hhs.gov/ohrp/regulations-and-policy/guidance/reviewing-unanticipated-problems/index.html#Q4).

> *If the investigator determines that an adverse event is not an unanticipated problem, but the monitoring entity subsequently determines that the adverse event does in fact represent an unanticipated problem (for example, due to an unexpectedly higher frequency of the event), the monitoring entity should report this determination to the investigator, and such reports must be promptly submitted by the investigator to the IRB (45 CFR 46.103(b)(5)).*

Please note: The SO and the investigator may have iterative discussions regarding the assessment and may later come to agreement regarding the assessment and/or management of an SAE or unanticipated problem. In cases where the SO and investigator come to an agreement after discussions and the event is determined not to be an unanticipated problem, the investigator is

not required to report the event as an unanticipated problem to the IRB. Such discussions should take place promptly so not to delay appropriate reporting to the IRB.

As it relates to SAEs, if resolution cannot be achieved after the investigator has had the opportunity to provide a rationale for their assessment of the event and does not agree to amend the report to match the NIAMS' and SO's assessment, the NIAMS will further discuss the appropriate action that should be taken to resolve the difference in assessment between the parties. If a resolution cannot be accomplished over email, an ad-hoc meeting will be coordinated between the parties, including but not limited to the investigator, the SO, and the NIAMS.

Dependent upon the outcome of the ad-hoc meeting, one of the following may occur:

- The investigator will update the report to reflect the NIAMS' and SO's adjudication and resubmit it to the SO and the NIAMS for review. If the updated adjudication changes the reporting requirements for the event (e.g., an SAE now meets the criteria for an unanticipated problem), these new reporting requirements should be met.
- The investigator will leave the report as is with their original adjudication and notify their IRB of the difference in the adjudication of the event, as well as provide a copy of the IRB communication to the NIAMS.

As the SO is advisory to the NIAMS, the NIAMS makes the final decision regarding the recommended adjudication of the event being shared with the investigator. Once the NIAMS makes a final decision about the adjudication of the event, further discussion with the monitoring body will not be needed. During this process of determining the adjudication of the event, the investigator should adhere to all applicable (IRB, FDA, etc.) reporting requirements and timelines for the event based on their original assessment.

Protocol Deviations

Protocol deviations that impact participant safety should be reported to the NIAMS and the SO (through the Executive Secretary) within 48 hours of the investigator becoming aware of the event. Protocol deviations that occur but do not affect participant safety are submitted in aggregate with the routine SO report. The investigator must also adhere to the Institution's policy on reporting protocol deviations to the IRB.

Please note: Additional reporting may be required if the deviation meets the definition of an unanticipated problem as described in the OHRP guidance above.

Protocol Amendments

All protocol amendments should be reviewed and approved by the NIAMS, SO, and the IRB prior to implementation. Requests for protocol amendment approvals may be submitted by the PI for review by the NIAMS and the SO between regularly scheduled reports. Approvals may be conducted via email correspondence or a web-conference may be scheduled if immediate discussion is warranted. The PI and study team (and any other internal study committees such as a Steering Committee) should ensure that they have come to an internal consensus with any

proposed changes prior to submitting the amendment to the NIAMS and the SO for review. The PI is notified by the Executive Secretary of the approved changes. IRB review of protocol amendments are separate from this process and are the PI's responsibility.

Communication with the SO

To maintain the independence of the SO, the PI and study team shall only communicate SO-related requests, questions, or concerns through the NIAMS or the Executive Secretary. The SO should only communicate with the PI through the Executive Secretary and the NIAMS.

Release of Clinical [Study/Trial] Data

Publications and abstracts containing primary clinical [study/trial] results are the responsibility of the investigator(s), and prior review or approval by NIAMS or the SO is not required. However, the perspective of the SO and NIAMS staff can add value to such publications/abstracts, and their comments may be useful to the investigator(s). Therefore, the PI is strongly encouraged to provide the NIAMS with a copy of all abstracts or manuscripts reporting primary clinical [study/trial] results well in advance of submission to a journal or scientific meeting. The NIAMS will distribute the manuscript/abstract to the SO and collect and provide their comments to the PI. The PI may then consider changes to the abstract or manuscript based on comments received from the NIAMS and the SO.

NIAMS SO Ombudsman

Any concerns related to the NIAMS staff attendance or participation in SO meetings may be directed to the NIAMS Deputy Director.