1.0 PURPOSE

This document provides the requirements for study data and safety monitoring review.

2.0 SCOPE

This SOP applies to all ACTG studies and includes procedures for the oversight and monitoring for each clinical study to safeguard the well-being of study participants and to ensure study integrity.

This SOP covers DAIDS-sponsored ACTG therapeutic studies that are monitored by one of four general types of data and safety reviews: (1) a Data and Safety Monitoring Board (DSMB) review; (2) an ACTG scientific committee (SC) review conducted by an SC-convened Study Monitoring Committee (SMC); (3) a protocol team review; or (4) an independent safety monitor (ISM) review. Selected studies may be monitored by a combination of DSMB, SMC, protocol team, and/or ISM.

If the ACTG study is being conducted in collaboration with another network or research organization, the appropriate parties should develop a monitoring plan jointly or agree to adhere to the existing monitoring requirements of one of the networks.

3.0 DEFINITIONS

3.1 DSMB: An independent group formally appointed by the NIAID/DAIDS or other cosponsoring institute that reviews the safety, efficacy, and overall study conduct as specified in the study monitoring plan for each trial.

3.2 SMC: An independent group of experts formally appointed by the SC and/or NIAID/DAIDS that periodically reviews the safety, efficacy, and overall study conduct as specified in the study monitoring plan for each trial.

3.3 Study Monitoring Plan: A document outlining the system for oversight and monitoring of the conduct of the clinical investigation to ensure the safety of the participants and the validity and integrity of the data. The detailed study monitoring plan is prepared by the protocol team as a supplement to the safety and monitoring information provided in the protocol.

3.4 Independent Safety Monitor (ISM): A physician or other health professional with relevant expertise formally appointed by NIAID/DAIDS, an SMC, DSMB, or protocol team whose primary responsibility is to provide independent safety monitoring in a timely fashion.

4.0 RESPONSIBILITIES

4.1 Clinical Science Review Committee (CSRC)

- Together with the protocol team, determines the frequency and mechanism for each study’s monitoring review.
4.2 DSMB

- Oversees selected phase II trials and all phase III and IV trials, including the review of safety and efficacy data according to the study monitoring plan.

- Oversight of phase I trials may occur on a case-by-case basis.

4.3 ACTG Network Coordinating Center (NCC)

- Coordinates SMC reviews and monitors the schedule for protocol team reviews.

- Ensures interim monitoring review letters and the formal team letter, if any, developed in response to a monitoring review are distributed to participating sites and/or DAIDS, as appropriate, and are posted to the ACTG protocol-specific webpage.

4.4 Participating Clinical Research Sites

- Forward interim monitoring review letters and the formal team letter, if any, developed in response to a monitoring review to local institutional review boards (IRBs)/ethics committees (ECs).

4.5 Protocol Team

- Ensures the monitoring of safety data in pilot studies, most phase I studies, and, when necessary, observational studies and provides routine oversight regarding study feasibility (i.e., accrual, retention, dropout, lost to follow-up), the adequacy of specimen collection and processing, and data entry into the study database.

- Adheres to all ACTG policies and procedures related to the oversight and monitoring of the study.

4.6 Scientific Agenda Steering Committee (SASC)

- Oversees the conduct of all protocols implemented within its purview.

4.7 Scientific Committee (SC)

- Oversees the conduct of all protocols implemented within its purview.

- Appoints members to the SC-specific or study-specific SMC.

- Provides oversight to ensure SMC and protocol team reviews are conducted, and ensures compliance with monitoring requirements.

4.8 SMC

- Reviews the safety and efficacy data according to the study monitoring plan for all treatment studies, regardless of phase, that are not reviewed by a DSMB.
• May provide oversight for observational studies as defined in the protocol document or study monitoring plan.

4.9 Sponsoring Institute

• Provides oversight to ensure DSMB reviews are conducted and ensures compliance with monitoring requirements.
• Assigns trials to DSMBs according to the type of trial and geographic location of participating sites.

4.10 ISM

• Performs a review of selected safety data according to the study monitoring plan or as determined by a DSMB, SMC, or protocol team; this may include a review of individual serious adverse events (SAEs) immediately after they occur and/or periodic review of cumulative safety reports generated between scheduled interim reviews for small, early phase studies, some phase I studies, or other studies of short duration.

5.0 PROCEDURES

5.1 DSMB Review for NIAID/DAIDS Studies

5.1.1 Membership

NIAID/DAIDS has established multiple DSMBs consisting of physicians, laboratory scientists, statisticians, and ethicists, independent of the study investigators, to periodically review the emerging outcome and safety data from DAIDS-sponsored trials.

5.1.2 DSMB Review Summary Letter

Protocol Initiation Reviews
• For protocol initiation reviews (PIRs), the DSMB will produce a review summary letter to be distributed to the study chair and other key members of the network.

Interim Review Summary Letter with Routine Recommendations
• For interim reviews, the DSMB will produce a review summary to be distributed to the study chair and other key members of the network.
  o The study chair is responsible for distributing the DSMB summary report to team members, typically via the clinical trials specialist (CTS).
  o The ACTG NCC will post the review summary to the protocol specific web page (PSWP) for future reference.
• The DSMB will also produce a review summary to be distributed to site investigators for submission to local IRBs/ECs. (Presently, the DAIDS Regulatory contractor is responsible for distributing the summary to sites.)

Interim Review Summary Letter with Major Study Modifications
• When the DSMB recommends major modification of the study, the DSMB communicates its recommendations to the DSMB convening authority, who
decides to accept or reject the recommendations, in consultation with NIAID/DAIDS staff and the study leadership, as necessary.

- The DSMB will produce a review summary to be distributed to the study chair, key members of the network, and site investigators (as described above) or will, in consultation with NIAID/DAIDS, otherwise determine its distribution.

- In advance of the DSMB review, the ACTG NCC Leadership Group will schedule a conference call to take place within 24-48 hours following the DSMB review, should any recommendations significantly alter the protocol design, study conduct, or participant informed consent. The NIAID/DAIDS will notify the ACTG NCC Leadership Group manager directly following the DSMB review whether a call is necessary. Call participants will include:
  - ACTG Network PI/chair, ACTG vice chair/SASC chair, and international vice chair
  - SC chair and/or vice chair
  - ACTG Statistical and Data Analysis Center (SDAC) senior statistical coordinator for the given Board
  - ACTG protocol chairs*
  - DAIDS Therapeutics Research Program (TRP) director (and DAIDS medical officers, as deemed required by the TRP director)
  - NIAID Biostatistics Research Branch representative
  - Others as required

*Will participate on the initial part of the call to hear the DSMB recommendations and provide information to the ACTG leadership for consideration, but will generally not participate in the subsequent, closed discussion.

- The ACTG Network PI/chair and ACTG vice chair/SASC chair, in consultation with the SC leadership and NIAID/DAIDS, are responsible for reviewing the DSMB’s recommendations and making the final decision regarding the action(s) to be taken in response to the review, including the timing and mechanism for dissemination of review results. If consensus is not reached, the NIAID/DAIDS will make the final decision regarding any actions to be taken. The protocol chairs, in consultation with the team and the SC chair, then formulate an official response to the recommendations and forward the response to the ACTG Network PI/chair and ACTG vice chair/SASC chair. The CTS forwards the SC- and ACTG Network Leadership-approved, official team response to participating sites for submission to local IRBs/ECs. The team also carries out all appropriate action(s) for the study as a result of the official response to the DSMB recommendations (e.g., closing an arm or the study to accrual).

5.2 ACTG SMC Review

5.2.1 SMC Membership

- Each SC maintains a standing SMC.
  - A minimum of two ACTG investigators, one senior SDAC statistician, and one non-scientist/non-investigator (e.g., a Community Scientific Subcommittee [CSS] representative to the SC) comprise a quorum of voting SMC members. Additional investigators and non-scientists/non-investigators may be added to the standing SMC to ensure a quorum is met for each review. Depending upon the specific needs of a protocol, a
specialist investigator and/or a second statistician may be added to the SMC on an ad hoc basis.

- The DAIDS medical officer/medical monitor (MO/MM) is a non-voting member of SMCs for ACTG studies.
- SMC members can be SC or non-SC members.
- An ACTG investigator serves as chair of the SMC.
- Standing and ad hoc voting members of the SMC may not be members of the protocol team for the study undergoing review nor directly involved in the conduct of the study at an ACTG site (i.e., Investigator of Record). If one (or more) of the standing voting SMC members is also a member of the protocol team or responsible for the conduct of the study at a site, he/she does not participate in the SMC deliberations for that protocol; and the SC chair appoints a replacement member as necessary to ensure a quorum of SMC members, as specified above.

- All SMC members will abide by SOP ACTG-107, "Network-Specific Financial Disclosure and Conflict of Interest Procedures," to disclose conflicts of interest and, when a significant financial interest has been identified, follow the appropriate management plan.
- The standing SMC membership roster for each SC is posted on the ACTG website. If the addition of ad hoc members to the SMC is deemed necessary, the protocol-specific membership will be posted on the ACTG protocol-specific web page.

5.2.2 Reviews

**General**

- The SMC may conduct its review by face-to-face meeting, conference call, or e-mail as determined by the SMC chair, the DAIDS MO/MM, and the protocol statistician(s).
- The SC coordinator organizes the SMC review. The SC coordinator leaves the call or meeting during any closed portion of the review; exceptions are allowed at the discretion of the SMC chair for the SC coordinator to remain on the call during the closed portion to address potential logistical issues, in which case the SMC chair announces the SC coordinator to the SMC prior to initiation of closed discussions.
- The protocol chair, CTS, and other collaborators can be invited to attend the open SMC review meeting, at the discretion of the SMC.
- The protocol statistician(s) attends open and closed sessions of the call or meeting, and is excused if the SMC holds an executive session.
- When conflicts arise regarding the scheduling of all members of the SMC for a review or questions arise as to which members are mandatory in order to conduct a review, the resolution is at the discretion of the SMC chairs and the DAIDS MO/MM.
- The protocol statistician is responsible for notifying the SC coordinator and protocol CTS of when the review materials are expected to be final to allow sufficient time for the coordinator to schedule the SMC to convene. The statistician is responsible for preparing, distributing, and (along with the study chair) presenting the review materials (e.g., data report, study monitoring plan).
Protocol Initiation Review (PIR)
The SMC reviews the study monitoring plan before accrual is initiated; however, it is advised that the PIR be performed prior to final protocol distribution to the sites, preferably soon after the final CSRC review of the protocol.

Protocol Interim Review
The SMC reviews interim data at least once every year. Additional reviews may occur:
- As determined by the endpoints and objectives, as prospectively written into the statistical section of the protocol and the study monitoring plan.
- When a need for an additional review is identified and requested by the SMC, SC, MO/MM for the protocol, DAIDS, or the protocol team.

5.2.3 Call Discussion Format

Open Administrative Review (Optional)
SMC reviews may include an optional open administrative review. If an open SMC review session is held, team members and other collaborators who are invited to attend are provided with reports as defined in the study monitoring plan. It is permissible for components of the open administrative report to be distributed to the team as part of routine study monitoring.

NOTE: Pooled or by-arm safety data may also be reported with limited distribution to the team leadership and may require a session with restricted attendance to discuss this data.

Closed SMC Review (Optional)
SMC reviews may include an optional closed review. If a closed SMC review session is held, attendance is limited to the members of the SMC and the study statisticians; exceptions are specified in the study monitoring plan. Distribution of the closed report outside of the list, as defined in the study monitoring plan, may be made on a case-by-case basis and must be in consultation with the SMC, ACTG chair, and SASC.

The purpose of a closed SMC review is to assess AEs, accrual, eligibility, and evaluability rates. Selected activity and/or efficacy parameters are presented if specified by the study monitoring plan. Information is presented by arm, when applicable. The review considers the ongoing feasibility of the study as designed and determines whether study modification is required to minimize risks to study participants.

Closed Executive Session (Optional)
SMC reviews may include an optional closed executive session to review some reports. Only SMC members attend the executive portion of the review.
5.2.4 SMC Review Summary Letter

Summary Letter with Routine Recommendations
The SMC chair prepares a review summary letter, based on the outcome of the closed review, SMC discussions, and the review materials, and submits it to the SMC for approval. Once approved by the SMC, the final summary letter will be distributed by the SC coordinator to the protocol team leadership. The summary letter should minimally include:

- Date of the review;
- The components of study conduct that were reviewed (e.g., interim safety, study monitoring plan, efficacy data);
- A formal recommendation to continue with or change the conduct of the study. Examples include but are not limited to the following -- (1) continue the study without change; (2) continue the study with specific modifications; (3) approve of the safety and data monitoring plan; or (4) suggest modifications to the study monitoring plan;
- Date of the next review.

Summary Letter with Major Modifications
- Immediately following the SMC review, any recommendations that would substantively alter the protocol design, conduct, or participant informed consent are communicated by the SMC chair to the SC chairs, SASC chair, ACTG chair, DAIDS MO/MM, and protocol chairs. The ACTG chair and SASC chair will determine whether further discussion or review by the SASC and/or the Executive Committee is necessary.
- The ACTG chair and SASC chair, in consultation with the DAIDS, are responsible for accepting or rejecting the SMC’s recommendations and will make the final decision regarding the action(s) to be taken in response to the review.
- The SC chair, in consultation with the protocol chairs, SASC chair, ACTG chair, and DAIDS, determines the timing and mechanism for dissemination of review summary results to site personnel, study participants, providers, and sites’ IRBs/ECs. The NCC assists the protocol team in preparing and disseminating results and recommendations from the review. The summary letter should minimally include:
  o Date of the review;
  o The components of study conduct that were reviewed (e.g., interim safety, study monitoring plan, efficacy data);
  o A formal recommendation(s) and instructions for implementation of said recommendation(s);
  o Date of the next review (if applicable).

Review Distribution
The CTS ensures interim SMC monitoring review letters and the formal team letter, if any, developed in response to a monitoring review are distributed to participating sites and/or DAIDS, as appropriate, and are posted to the PSWP for future reference.
5.3 Protocol Team Interim Review

5.3.1 Protocol Team Review Membership

The protocol team members who are responsible for monitoring the study will be specified in the protocol or the protocol-specific written study monitoring plan and generally include the team leadership, including the DAIDS MO/MM for the study. External experts may be included in the team review process as needed.

5.3.2 Reviews

Pilot and Phase I Studies

All pilot and phase I studies will have team reviews and SMC reviews. Team monitoring reviews of pilot and phase I studies are guided by the protocol-specific written study monitoring plan that includes which protocol team members participate, the data to be reviewed, and the frequency of reviews. A summary letter based on a team review is required every 6 months from the time the first participant is enrolled until closure to follow up. The SC coordinator notifies the protocol chairs, statistician, and CTS when this summary letter is due. If a safety issue arises prior to a 6-month review, the team will prepare the review summary letter for SC leadership review. If a safety issue that the team believes requires further evaluation to minimize participant risk arises, the team may submit a request to the SC chair for a full SMC review of the study. The SC chair then convenes an SMC review as soon as feasible following the request. In addition, protocol initiation and interim reviews by the SMC will occur per the guidelines in section 5.2.

Observational Studies

Protocols with observational designs may or may not collect safety data. In either case, a review and review summary letter are required at least every 12 months from the time the first participant is enrolled until closure to follow-up. The SC coordinator, in consultation with the SC (as needed), notifies the protocol chair, statistician, and CTS when a required review and a summary letter are due. If a safety issue arises prior to a 12-month review, the team will prepare the review summary letter for SC leadership review.

5.3.3 Protocol Team Review Summary Letter

Pilot and Phase I Studies

The protocol chairs are responsible for writing a brief review summary letter. The summary letter includes:

- Date of the summary or review;
- Period covered by the review;
- A statement that interim safety data and/or other information was reviewed, along with any recommendations for changes to the study, if warranted based on the review;
- Date of the next review.

Observational Studies

The protocol chairs are responsible for writing a brief review summary letter. The summary letter includes:

- Date of the summary or review;
• Period covered by the review;
• A statement that interim safety data were or were not collected and reviewed and/or that other information was reviewed, along with recommendations for changes to the study, if warranted based on the review;
• Date of the next review.

Review Distribution
The protocol team forwards the review summary letter to the SC coordinator for SC review and approval. Upon approval, the protocol team (via the CTS) distributes the review summary letter to participating sites and/or DAIDS, as appropriate, and ensures its posting to the PSWP for future reference.

5.4 ISM Review

5.4.1 ISM Membership

An ISM may be the sole independent monitor for a study or may perform this role as part of a protocol team, SMC or DSMB. The ISM is selected based on relevant study-related expertise, cannot have any involvement in the conduct of the study, and cannot have any interests (financial, proprietary, professional, or other) that could influence monitoring responsibilities. Participation of the ISM is usually for the duration of the study.

5.4.2 Reviews

An ISM reviews individual SAE reports soon after they occur and/or reviews periodic cumulative safety monitoring reports. If the ISM is part of an SMC or DSMB, periodic reviews may occur between scheduled interim reviews. The contents and schedule of reports to be reviewed by the ISM will be specified in the safety monitoring plan.

Clinical and laboratory data, current investigator’s brochures or product inserts, safety reports, protocol revisions, and other study-related records should be made available for ISM review by the investigator or study statistician in order for the ISM to follow the conduct of the study.

5.4.3 ISM Review Summary Letter

When an ISM is the Sole Independent Monitor

Summary Letter with Routine Recommendations
• The ISM will communicate in writing a summary of the review findings, any concerns, and recommendations per the criteria outlined in the study monitoring plan.
• Unless otherwise specified, the ISM will submit the written report to NIAID/DAIDS. The NIAID/DAIDS will generally distribute the report to the study team, SMC or DSMB members, and other designated NIAID/DAIDS staff members.
• The protocol team will distribute the report to site investigators (via the CTS), who will in turn submit the report to their IRBs/ECs. The ACTG NCC will post the report to the PSWP for future reference.
• If the study is under an IND, the sponsor is responsible for submitting the summary report to the FDA and industry/pharmaceutical collaborators, as appropriate.

Summary Letter with Immediate Action Required
• If the ISM determines any findings are of a serious and immediate nature and/or recommends significant modifications or discontinuation of the study, the ISM will verbally notify NIAID/DAIDS and subsequently follow up with a written report within one day of ISM review. The NIAID/DAIDS will determine further distribution, including submission to the FDA for IND studies.

When an ISM is Part of Protocol Team Review, an SMC, or DSMB

Summary Letter
• The ISM's recommendations will be conveyed to the protocol team, SMC, or DSMB, and distribution of a summary review letter will be governed by the protocol team, SMC, or DSMB guidelines.

6.0 REFERENCES

SOP ACTG-107, "ACTG Network-Specific Financial Disclosure and Conflict of Interest Guidelines"

DAIDS SOP DWD-POL-SR-01.00, “Study Progress and Safety Monitoring”

DWD-POL-CL-018.04A4, “Charter for the Data and Safety Monitoring Boards of the Division of AIDS National Institute of Allergy and Infectious Diseases (10/18/2012)”

DWD-POL-SR-01.00A5, “DAIDS Safety Monitoring Committee (SMC) Guidelines”

DWD-POL-SR-01.00A6, “DAIDS Independent Safety Monitor (ISM) Guidelines”

7.0 INQUIRIES

Questions and comments regarding this policy may be directed to ACTGSOPs@s-3.com.