APPENDIX I UNBLINDING PROCEDURES

I.1 Purpose

This appendix provides guidelines for unblinding the treatment assignments of participants enrolled in IMPAACT studies.

I.2 Scope

This appendix defines the concepts of "blinding" and "unblinding" the treatment assignment of study participants (and/or their parents/guardians), provides guidelines for when to unblind, and outlines procedures for how to unblind when it is determined that unblinding is appropriate.

I.3 Definitions

I.3.1 Blinding

The term "blinded" refers to a study in which knowledge of individual participant treatment assignments is withheld from certain individuals. These individuals may include study participants (and/or their parents/guardians), study site staff, and protocol team members.

- Single-blinded study: The site investigator is aware of which treatment the participant is receiving, but the participant is not, or vice versa
- Double-blinded study: The participant, site investigator, other site staff, and protocol team are unaware of the treatment assignment
- Partial-blinded study: Within a study arm, some of the study drugs are blinded and others are open-label (e.g., known active drugs [open] plus active drug or placebo [blinded])

The terms "unblinded" and "open-label" refer to studies in which participant and study site staff are aware of participant treatment assignments.

I.3.2 Unblinding

For purposes of this appendix, "unblinding" means revealing the treatment to which an individual participant has been assigned. This may include revealing the treatment assignment to the participant, study site staff, primary care physician and/or protocol team members.

- Full unblinding at completion of the study: Under normal circumstances, all the treatment assignments of all participants will be unblinded once the study data are complete per instructions in the protocol document. Full unblinding also occurs when sudden (or unplanned) unblinding is required due to interim results of the study or results of another study.
- Partial unblinding: When not all arms on a study are unblinded or when one or more drugs are unblinded across arms but others remain blinded. Thus, some aspect of the treatment assignment of some participants is still blinded.
- Emergency unblinding of an individual participant's treatment assignment for medical reasons: Urgent, unplanned unblinding prior to full study unblinding is performed to protect participant safety when, as determined by the site Investigator of Record (IoR) or designee, knowing the participant's treatment assignment would affect **immediate** medical management of the participant, e.g., for drug identity during an acute reaction.
- Early unblinding of an individual participant's treatment assignment for **non-urgent** medical/safety reasons: Unplanned unblinding of a participant's treatment assignment before full study unblinding is performed for reasons that are not urgent and would not affect immediate medical management but may affect other aspects of a participant's medical care/safety. Examples include:
  - A participant becomes pregnant or contracts an illness before full study unblinding, and the participant or her medical care provider requests the treatment assignment because this information might affect decisions regarding the participant's medical management.
  - A participant who is or becomes HIV-infected wants to enroll in another study in which prior receipt of an investigational product is exclusionary.
  - A participant wants to donate an organ or stem cells to a relative, and documentation of treatment assignment would facilitate evaluation as a donor.

I.4 Roles and Responsibilities

Table I-1 outlines team member roles and responsibilities for unblinding.

Table I-1. Roles and Responsibilities for Unblinding

Team Member	Responsibility
Protocol Team	• Specifies extent of blinding and incorporates unblinding guidelines in the protocol document • Determines the unblinding date in advance along with the timetable for study closure • Prepares information for site staff to communicate to study participants (and/or their parents/guardians) when their treatment assignment is discussed

Table I-1. Roles and Responsibilities for Unblinding

Team Member	Responsibility
Data and Safety Monitoring Board (DSMB) or Study Monitoring Committee (SMC)	• Reviews safety and efficacy data and may make recommendations to unblind all or part of a study prematurely
Data Management Center (DMC) User Support	• Provides emergency unblinding information to the Investigator of Record (IoR) or designee when the site pharmacist of record (PoR) is otherwise unavailable to provide this information. Available 24 hours a day/7 days a week.
NIAID/DAIDS	• Reviews DSMB recommendations to unblind all or part of a study prematurely (for studies overseen by a NIAID DSMB).
IMPAACT Management Oversight Group (MOG)	• Reviews Study Monitoring Committee (SMC) recommendations to unblind all or part of a study prematurely (for studies overseen by an SMC) • Aids the protocol team in reaching a decision to unblind, as needed
Protocol Chair	*Emergency Unblinding of Individual Participant's Treatment Assignment for Medical Reasons* • If consulted by a site IoR (not required), may provide input on the need for unblinding of an individual participant; however, protocol chair approval is not required. *Early (Non-Urgent) Unblinding of Individual Participant's Treatment Assignment for Medical/Safety Reasons* • Discusses early unblinding of an individual participant with the site IoR and relevant protocol team members, usually on a conference call or through email • Communicates the team's decision in writing (email is sufficient) to the site IoR, with a copy to relevant protocol team members • In consultation with the protocol statistician, approves release of treatment assignments *Partial Unblinding Based on Interim Study Monitoring Review Recommendation* • If a DSMB or SMC recommends partial unblinding due to interim analysis results or results of another study, decides whether to unblind the relevant arms in consultation with relevant protocol team members, network leadership and study sponsor.
Protocol Statistician	*Full or Partial Study Unblinding* • Obtains treatment assignments for a study prior to initiation of planned analyses *Early (Non-Urgent) Unblinding of Individual Participant's Treatment Assignment for Medical/Safety Reasons* • Actively takes part in discussing early unblinding with other relevant protocol team members • Along with the protocol chair, approves the release of treatment assignments

Table I-1. Roles and Responsibilities for Unblinding

Team Member	Responsibility
Medical Officer (MO) or Medical Monitor (MM)	*Emergency Unblinding of Individual Participant's Treatment Assignment for Medical Reasons* • If consulted by a site IoR (not required), may provide input on the need for unblinding of an individual participant; however, MO/MM approval is not required. *Early (Non-Urgent) Unblinding of Individual Participant's Treatment Assignment for Medical/Safety Reasons* • Actively takes part in discussing early unblinding with other relevant protocol team members
Investigational New Drug (IND) Holder	*Full or Partial Study Unblinding* • Provides input in unblinding discussions, as appropriate *Early (Non-Urgent) Unblinding of Individual Participant's Treatment Assignment for Medical/Safety Reasons* • Provides input in unblinding discussions, as appropriate
Protocol Data Manager	• In all situations except emergency unblinding of an individual participant's treatment assignment, transmits unblinding request to the chief data manager or designee • Prepares unblinding memo(s) for team review and finalizes memo(s) incorporating team input
Chief Data Manager or Designee	In all situations except emergency unblinding of an individual participant's treatment assignment, is responsible for revealing the treatment assignment *Full or Partial Study Unblinding* • Prepares unblinding listings of treatment assignments for each site and distributes these to the sites along with the unblinding memo on the date the team has specified *Early (Non-Urgent) Unblinding of Individual Participant's Treatment Assignment for Medical/Safety Reasons* • Receives team-approved request for individual unblinding from the protocol data manager and provides treatment assignment to site IoR or designee
Protocol Pharmacologist	*Full or Partial Study Unblinding* • Requests approval from the protocol team to receive treatment assignments required for pharmacokinetic (PK) analyses (e.g., to identify participants on a specific drug for targeted assay). This may not require full unblinding.
Clinical Research Site (CRS) Coordinator	*Full or Partial Study Unblinding* • Follows study-specific communication guidance (typically provided in the study-specific MOP) with respect to inclusion of treatment assignment information when contacting protocol team members and/or the Data Management Center (DMC) • Along with the IoR, receives unblinding information from the DMC for full or partial study unblinding and forwards to the site personnel specified in the unblinding memo (see Section I.5.1)

Table I-1. Roles and Responsibilities for Unblinding

Team Member	Responsibility
Site Investigator of Record (IoR) or designee	*Emergency Unblinding of Individual Participant's Treatment Assignment for Medical Reasons* • Determines need for emergency unblinding (input of study sponsor or protocol team not required) • Requests treatment assignment for individual participant from the site pharmacist of record (PoR) or, if the PoR is not available, from the DMC User Support Department • Documents the unblinding and notifies relevant individuals/groups designated in the study protocol (copying the PoR) • Ensures that relevant IRB/ECs and other regulatory authorities are notified • Ensures that treatment assignments are shared only with persons who need to know and that no other unblinding is performed *Early (Non-Urgent) Unblinding of Individual Participant's Treatment Assignment for Medical/Safety Reasons* • Determines need for early unblinding in consultation with the group or individuals designated in the protocol • Requests treatment assignment using the Unblinding Request Program on the DMC website • If request is approved, receives treatment assignment memo from the Chief Data Manager at the DMC • Ensures that relevant IRB(s)/EC(s) and other regulatory authorities are notified • Ensures that treatment assignments are shared only with persons who need to know and that no other unblinding is performed
Site Pharmacist of Record (PoR)	*Emergency Unblinding of Individual Participant's Treatment Assignment for Medical Reasons* • Provides treatment assignment for individual participant to site IoR or designee upon request • Files copies of the unblinding request and the treatment assignment provided in the pharmacy records for the study • Notifies the DAIDS PAB Protocol Pharmacist of the unblinding • Ensures that the requested treatment assignment is shared only with the IoR or designee and that no other unblinding is performed

I.5 Reasons and Guidelines for Unblinding

Conventionally, full unblinding takes place after all study data have been entered into the database for all participants, data cleaning has been completed, endpoints have been reviewed (if applicable per protocol), and the protocol team has declared the study dataset to be complete. On a date pre-determined by the protocol team, treatment assignments are provided to all participating sites for each participant enrolled in the study.

It is critical to the objectives of any blinded study that the objectivity of the Protocol Team, site IoRs, other site staff, and participants (and/or their parents/guardians) be maintained. Any unblinding prior to the conventional full unblinding date can result in bias and should therefore be avoided. Unblinding of individual participant treatment assignments as participants reach study endpoints or come off study may severely compromise the integrity or objectivity of the trial. Unplanned unblinding prior to the

conventional full unblinding date should be undertaken only to protect participant safety or to fulfill safety reporting and other regulatory obligations. Unblinding plans that deviate from this appendix must be approved by the protocol statistician and the IMPAACT MOG.

Planning to unblind the treatment assignments of all participants individually as they come off study is unconventional, as the potential for bias in the reporting of results for other participants is substantial. If a protocol team plans to perform unblinding in this fashion, this must be stated in the protocol so the plan can be reviewed and approved by the IMPAACT Multidisciplinary Protocol Review Group (MPRG).

Unblinding to obtain stratification information for randomization is not permitted. The purpose of stratification is to maintain balance of prognostic factors between treatments; even if blinded participants must be stratified as "unknown," analyses can still be conducted with very little loss in efficiency, and balancing is not likely to be affected. The Subject Enrollment System can provide blinded treatment information internally to inform assignment to subsequent steps of the same study and to pre-specified rollover studies.

I.5.1 Guidelines for Emergency Unblinding of Individual Participant Treatment Assignments for Medical Reasons

The need for emergency unblinding of individual participant treatment assignments is expected to be extremely rare.

If needed **immediately** to guide management of a serious illness or medical emergency occurring in a study participant, the site IoR or designee may obtain a participant's treatment assignment from the site PoR - independent of the study sponsor or protocol team. If the site PoR is not available, the IoR or designee may obtain the treatment assignment – also independent of the study sponsor or protocol team – from the DMC's User Support Department, which is available 24 hours a day, 7 days a week (**+716 834-0900, ext. 7302; user.support@fstrf.org**).

Note: The guidelines in this section do not apply for participants who have died, because knowledge of treatment assignment will not affect immediate management in such cases.

Requests for unblinding should be made to the PoR or DMC in writing, and the PoR or DMC should provide the participant's treatment assignment directly to the requesting IoR or designee in writing. In cases of extreme emergency in which it is not possible for the unblinding request to be made in writing, the IoR or designee may make the request orally but must provide a written statement of the request within 24 hours, including the reason why the request could not initially be made in writing. In cases of extreme emergency in which it is not possible for the unblinding request to be delivered by the DMC in writing, it should be provided orally, and the DMC will provide a written confirmation of the unblinded treatment within 24 hours.

The IoR or designee must notify the relevant group or individuals specified in the study protocol (e.g., the Clinical Management Committee) of the emergency unblinding within 24 hours of the unblinding via email. The notification should include the PID, date/time of the request and reason for the unblinding but should NOT include the unblinded treatment assignment; the site PoR should be copied on the notification. Relevant site Institutional Review Board(s)/Ethics Committee(s) and regulatory authorities must also be notified. The written request for unblinding and the PoR's or DMC's written response (with the treatment assignment) must be filed in the site's pharmacy records for the study. The PoR must notify the DAIDS Pharmaceutical Affairs Branch (PAB) protocol pharmacist (via email) of the emergency unblinding within 24 hours of the unblinding.

Unblinded treatment assignments should be shared with as few individuals as possible on a need-to-know basis. Care should be taken to prevent additional unblinding to maintain study integrity. The site IoR and site PoR are responsible for preventing additional unblinding beyond those who need to know and for protecting information that may identify the participant.

I.5.2 Guidelines for Early (Non-Urgent) Unblinding of Individual Participant Treatment Assignments for Medical/Safety Reasons

Unblinding information should be shared with as few individuals as possible.

Site IoRs or designees may request a participant's treatment assignment before a study is fully unblinded for reasons that are not urgent and do not require immediate (emergency) unblinding but may affect the participant's medical care/safety. Examples are provided in Section I.3.2 above.

The site IoR or designee will consult with the individuals or group specified in the study protocol regarding the need for unblinding (via email or teleconference) and then submit the request for unblinding using the Unblinding Request Program on the DMC website. Decisions will be made by the group or individuals designated in the study protocol on a case-by-case basis (See Section I.6.1). Early unblinding for this reason should generally not occur until all primary outcome data have been entered and cleaned, all queries related to these data have been resolved, and any clinical endpoints have been reviewed by designated reviewers. In cases in which knowledge of a participant's treatment assignment sooner may affect the participant's medical care and/or would otherwise be in the participant's best interest, this requirement can be waived.

When this type of unblinding is approved, the knowledge of the participant's treatment assignment should be limited to the fewest number of people possible on a need-to-know basis. The Protocol Data Manager will inform the Chief Data Manager of the team's decision and the Chief Data Manager will prepare a memorandum that provides the treatment assignment to the site IoR or designee and states, as determined by the protocol team, to whom the assignment may be provided by the IoR or designee. These individuals may include:

- Attending study or primary care clinician
- Study coordinator and/or study nurse
- Site PoR
- Participant

In some instances, only the site IoR (or designee) and participant's treating clinician will need to be unblinded. Protocol team members, including the protocol chair(s) and data manager, should not be unblinded.

If eligibility determination for a new study requires unblinding of a treatment assignment from a study that is still ongoing, the decision of whether to unblind must be made by the original study team. In some cases, unblinding to determine eligibility may be inappropriate until all participants have completed the study and the data are declared complete. If the participant is on study, the participant will be interacting with the community and site personnel still involved in the trial, possibly biasing the site staff for the duration of the participant's involvement in the trial.

I.5.3 Partial Unblinding for a Continuing Study

On occasion, a decision may be made to partially unblind one treatment arm or one aspect of several arms due to interim results or toxicity data. In cases such as these, the protocol team prepares a memorandum**,** which includes guidance regarding the aspects of data entry specified in Section I.5.4 below that need to be completed prior to unblinding. The chief data manager or designee sends the partial unblinding instructions and the memorandum to the sites.

I.5.4 Unblinding after a Study is Closed to Follow-Up

Unblinding a study may consist of:

- informing study participants (and/or their parents/guardians) of their blinded treatment codes
- informing the sites of the blinding codes for their study participants
- informing study chairs or other medical investigators of the study results
- informing study chairs or other medical investigators of treatment codes
- some combination of the above

When a study has been closed to follow-up, either at the scheduled closure or following a decision to close the study early, the conditions outlined below must be met before unblinding participants (and/or their parents/guardians), sites, and study investigators.

Data must be entered and cleaned for primary endpoints and toxicity. Endpoint verification must be complete. It is best if other secondary endpoint data are cleaned as well, but this requirement can be relaxed in circumstances where unblinding is deemed an immediate necessity by the protocol chair(s) and team. Laboratory samples must have been collected, but laboratory test results are not required to be finalized or keyed. The time necessary to finalize the data can be three months or more after study closure.

I.6 Procedures

I.6.1 Unblinding Individual Participant Treatment Assignments

Requests can be made to unblind individual participant treatment assignments, on a case-by-case basis, immediately for emergencies or for non-urgent situations as described in Sections I.5.1 and I.5.2.

In cases in which the site IoR or designee determines that an individual participant's treatment assignment is urgently needed for immediate medical management, the treatment assignment is to be provided (by the PoR or the DMC) independent of the sponsor and protocol team and with no additional requirements as described in Section I.5.1.

For non-urgent early unblinding of a participant for medical/safety reasons, two requirements should be met:

- Case report forms that capture self-reported and subjective data (e.g., questionnaire responses, adverse events) must be entered into the study database. This requirement may be waived if the provision of the treatment assignment sooner is determined to be in the best interest of the participant.
- After initially conferring with the group or individuals designated in the study protocol (via email or teleconference), the participant's treatment assignment must be requested using the Unblinding Request Program on the DMC website:

- The purpose of this program is to collect information that protocol teams and the DMC need to promptly and efficiently process unblinding requests. All fields on the screen should be completed, including the study number, participant identifier, step number, site number, information about the IoR or designee, date the information is needed, and a detailed reason for the unblinding. Once the "Send Mail Message" is submitted, an email message will be automatically sent to the group designated in the study protocol and will provide site staff with a copy in the appropriate email account. It may take one or more days for the team to respond.
- The protocol chair will communicate the team's decision in writing (e-mail is sufficient) to the person who made the request, with a copy to the group or individuals designated in the study protocol.
- After the team approves the unblinding request, the protocol data manager informs the chief data manager of the approval. The chief data manager (or designee) will send the treatment information to the IoR or designee via fax or email within 24 hours of the team's approval.
- Documentation of the communication is to be maintained by both the site and the DMC.

I.6.2 Unblinding the Treatment Assignments of All Participants for a Study

Under normal circumstances, the treatment assignments of all study participants will be unblinded once the data are complete, as outlined in Section I.5.3.

Procedure to unblind the treatment assignments of all participants
During preparation of the closure timeline, the protocol team should confirm plans for unblinding. The unblinding date is usually determined in advance by study team along with the timetable for study closure. The team prepares any information it wishes site personnel to communicate to study participants (and/or their parents/guardians) when their treatment assignment is discussed. The DMC supplies a standard unblinding memorandum to the team for review and for the addition of any study-specific language the team wishes to include. The chief data manager (or designee) prepares unblinding listings for each site with the unblinding memorandum on the date the team has specified.

Unplanned or sudden closure unblinding
The following standard approach will be followed. Any changes to this standard will be protocol-specific and will be specified in the protocol and reviewed by the IMPAACT Multidisciplinary Protocol Review Group.

- Sudden (or unplanned) unblinding of one or more arms due to *interim analysis results or results of another trial*: The decision to unblind one or more arms of an ongoing study is made by the team in conjunction with the MOG (which includes NIH representatives and network leadership). This can occur based on a recommendation from the DSMB/SMC or the results of another trial.
- Participant contact: If the decision is made to unblind, participants (and/or their parents/guardians) should be unblinded as soon as possible. Unblinding is conducted through the DMC, which sends treatment assignments to the sites soon after the unblinding decision. Every effort should be made by the sites to contact participants (and/or their parents/guardians) who have completed follow-up (and/or their parents/guardians) in order to explain the study results.

- Implications of unblinding on study data: When a treatment comparison is unblinded based on an interim analysis, the results of that interim analysis are expected to be reported in publications. Data from visits that occurred before the interim review but that were not in the database at the data cutoff date have little potential for bias and may be reported with a comment. Data from visits that occurred after unblinding are potentially biased and must not be used if the intent is to claim that all the data are from a blinded study. In unblinding due to both "interim analysis" and the "other trial results" situations, if analyses are reported on clinical data or samples taken after the unblinding date, the conditions under which these data were gathered must be made clear in any publication.

It is important to note that, if all arms are not unblinded, participants on the remaining arm(s) (and/or their parents/guardians) are at a minimum partially unblinded **in most cases**.

I.6.3 Unblinding of External Entities for a Special Request

On rare occasions, an outside body such as the US Food and Drug Administration may request that certain information from a study be unblinded. Such requests must be approved by the study team and the MOG.

I.7 References

- DSMB or SMC guidelines (Section 13)
- Unblinding Request Program

I.8 Questions

Questions and comments regarding this policy may be directed to IMPAACT.OperationsCenter@fstrf.org.