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 or intervention assignment is withheld from one or more individuals participating or involved in the study. These individuals may include study participants (and/or their parents/guardians), study site staff, and protocol team members.

- **Single-blinded study:** The site investigator, other site staff, protocol team members, and/or sponsor staff involved in treatment evaluation are 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, protocol team members, and sponsor staff involved in treatment evaluation are unaware of the treatment assignment
- **Partial-blinded study:** Within a study arm, some of the study products are blinded and others are open-label (e.g., known active drugs [open] plus active drug or placebo [blinded])

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, site investigator, other study site staff, primary care physician, protocol team members, Network, and/or sponsor members.

- **Full unblinding at completion of the study:** Under typical circumstances, all assignments of all participants are unblinded after the final clinical database lock has occurred, per instructions in the protocol. Full unblinding may also occur before the final clinical database lock has occurred if warranted based on interim results of the study or results of another study.
- **Partial unblinding:** Partial unblinding occurs when one or more study products or arms are unblinded, but others remain blinded. Thus, some aspect of the assignment of some participants remains blinded.
- **Emergency unblinding of an individual participant's assignment for medical reasons:** Urgent, unplanned unblinding prior to full study unblinding may be performed to protect participant safety when, as determined by the site Investigator of Record (IoR) or designee, knowing the participant's 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 assignment for non-urgent medical reasons:** Unplanned unblinding of a participant's assignment before full study unblinding may be 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. Examples include:
  - A participant becomes pregnant or contracts an illness before full study unblinding, and the participant or the participant's medical care provider requests the assignment because this information might affect decisions regarding the participant's medical management.
  - A participant with HIV wants to enroll in another study for which knowledge of the assignment is required for eligibility determination.
  - A participant wants to donate an organ or stem cells to a relative, and documentation of assignment would facilitate evaluation of the participant 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 • Determines the planned unblinding date in advance, along with the timeline for study closure • Prepares information for site staff to communicate to study participants (and/or their parents/guardians) when their assignment is discussed
Data and Safety Monitoring Board (DSMB) or Study Monitoring Committee (SMC)	• Reviews safety/efficacy data and may make recommendations to unblind all or part of a study prematurely (i.e., prior to the planned unblinding date)

Table I-1. Roles and Responsibilities for Unblinding

Team Member	Responsibility
Data Management Center (DMC) User Support	• Provides emergency unblinding information to the IoR or designee when the site pharmacist of record (PoR) is otherwise unavailable to provide this information and the IoR or designee cannot access the Emergency Unblinding Utility on the DMC portal • Available 24 hours a day, seven days a week, except for five US holidays (New Year's Day, Memorial Day, Independence Day, Thanksgiving Day, and Christmas Day) • Grants access to the Emergency Unblinding Utility to IoR. Grants access to the Emergency Unblinding Utility to designees, with approval of the IoR
Division of AIDS at the National Institute of Allergy and Infectious Disease (DAIDS/NIAID)	• 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 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 Assignment for Medical Reasons* • If consulted by a site IoR, may provide input on the need for unblinding of an individual participant (neither consultation nor approval are required) *Early (Non-Urgent) Unblinding of Individual Participant's Assignment for Medical Reasons* • Discusses early unblinding of an individual participant with the site IoR and relevant protocol team members, e.g., via conference call or 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 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, IMPAACT Network leadership, and study sponsor
Protocol Statistician (if protocol statistician is blinded, the Unblinded Statistician)	*Full or Partial Study Unblinding* • Obtains assignments for a study prior to initiation of planned analyses *Early (Non-Urgent) Unblinding of Individual Participant's Assignment for Medical Reasons* • Actively takes part in discussing early unblinding with other relevant protocol team members • Along with the protocol chair, approves the release of assignments

Table I-1. Roles and Responsibilities for Unblinding

Team Member	Responsibility
DAIDS Medical Officer (DAIDS MO)	*Emergency Unblinding of Individual Participant's Assignment for Medical Reasons* • If consulted by a site IoR, may provide input on the need for unblinding of an individual participant (neither consultation nor approval is required) *Early (Non-Urgent) Unblinding of Individual Participant's Assignment for Medical 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 Assignment for Medical Reasons* • Provides input in unblinding discussions, as appropriate
Protocol Data Manager (PDM)	• In all situations except emergency unblinding of an individual participant's assignment, transmits unblinding request to the Chief Data Manager or designee • Prepares unblinding memorandum(s) for team review and finalizes memorandum(s) incorporating team input
Chief Data Manager or Designee	• In all situations except emergency unblinding of an individual participant's assignment, is responsible for providing unblinded treatment assignments *Full or Partial Study Unblinding* • Prepares unblinded listings of assignments for each site and distributes these to the sites along with the unblinding memorandum on the date specified by the team *Early (Non-Urgent) Unblinding of Individual Participant's Assignment for Medical Reasons* • Receives team-approved request for individual unblinding from the PDM and provides assignment to site IoR or designee
Protocol Pharmacologist and/or Testing Laboratory	*Full or Partial Study Unblinding* • Requests approval from the protocol team to receive assignments required for pharmacokinetic 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 manual of procedures) with respect to inclusion of assignment information when contacting protocol team members and/or the 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 memorandum

Table I-1. Roles and Responsibilities for Unblinding

Team Member	Responsibility
Site Investigator of Record (IoR) or designee	*Emergency Unblinding of Individual Participant's Assignment for Medical Reasons* • Determines need for emergency unblinding (input of study sponsor or protocol team not required) • Requests assignment for individual participant from the site PoR or, if the PoR is not available, uses the Emergency Unblinding Utility on the DMC portal. Access to the Utility is granted to IoRs listed in the NIAID Clinical Research Management System (CRMS). If cannot access the Emergency Unblinding Utility, contacts the DMC User Support Department. • Approves DMC User Support requests for designees' access to the Emergency Unblinding Utility on the DMC portal • Documents the unblinding and notifies individuals or groups designated in the protocol (copying the PoR) • Ensures that relevant institutional review boards/ethics committees (IRBs/ECs) and regulatory entities are notified • Ensures that assignments are shared only with persons who need to know the assignments and that no other unblinding occurs *Early (Non-Urgent) Unblinding of Individual Participant's Assignment for Medical Reasons* • Determines need for early unblinding in consultation with the group or individuals designated in the protocol • Requests assignment using the Unblinding Request Program on the DMC website • If request is approved, receives assignment memorandum from the Chief Data Manager or designee at the DMC • Ensures that relevant IRBs/ECs and regulatory entities are notified • Ensures that assignments are shared only with persons who need to know the assignments and that no other unblinding occurs
Site Pharmacist of Record (PoR)	*Emergency Unblinding of Individual Participant's Assignment for Medical Reasons* • Provides assignment for individual participant to site IoR or designee upon request • Files the unblinding request and the assignment provided in the pharmacy records for the study • Notifies the DAIDS Pharmaceutical Affairs Branch (PAB) protocol pharmacist of the unblinding • Ensures that the requested assignment is shared only with the IoR or designee and that no other unblinding occurs

I.5 Reasons and Guidelines for Unblinding

Conventionally, full unblinding takes place after the final clinical database lock has occurred, which happens 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 the protocol), and the protocol team has declared the study dataset to be complete. On a date pre-determined by the protocol team, 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

final clinical database lock can result in bias and should therefore be avoided. Unblinding of individual participant assignments as participants reach study endpoints or come off study may severely compromise the integrity or objectivity of the study. Unplanned unblinding prior to the final clinical database lock 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 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 Study Enrollment System (SES) can provide blinded assignment 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 Assignments for Medical Reasons

The need for emergency unblinding of individual participant 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 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 assignment, also independent of the study sponsor or protocol team, from the DMC. In this case, the IoR or designee should use the Emergency Unblinding Utility on the DMC portal (www.frontierscience.org). IoRs listed in the NIAID CRMS are given access to this utility. Designees must request Emergency Unblinding Utility access through DMC User Support and will be granted access upon approval by the IoR. If the IoR or designee does not have access to the Emergency Unblinding Utility, they may obtain the assignment from the DMC's User Support Department, which is available 24 hours a day, seven days a week (**+716-834-0900, ext. 7302; user.support@fstrf.org**), except for five US holidays (New Year's Day, Memorial Day, Independence Day, Thanksgiving Day, and Christmas Day).

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

Requests for unblinding should be made by the IoR or designee to the PoR in writing, and the PoR should provide the participant's 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 to the PoR within 24 hours, including the reason why the request could not initially be made in writing. The PoR is responsible for documenting the unblinding in the pharmacy records for the study.

In cases of extreme emergency when the PoR is unavailable, the IoR or designee may perform the unblinding via the Emergency Unblinding Utility on the DMC portal.

In cases of extreme emergency when the PoR is unavailable and it is not possible for the assignment to be obtained via the Emergency Unblinding Utility, the IoR or designee may request the unblinded assignment from the DMC in writing by emailing DMC User Support (user.support@fstrf.org) and alerting them of the request via phone. In cases of extreme emergency in which it is not possible for the unblinding request to be made in writing to the DMC, the IoR or designee may make the request orally but must provide a written statement of the request within 24 hours to the DMC, including the reason why the request could not initially be made in writing.

In these cases of extreme emergency when the DMC receives an oral or written unblinding request from the IoR or designee, the DMC will provide the unblinded assignment in writing. In cases of extreme emergency when requested by the IoR or designee, when it is not possible for the assignment to be delivered by the DMC in writing, it should be provided orally by the DMC. The DMC will provide a written confirmation of the unblinded assignment within 24 hours and document the unblinding in the study database.

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

Unblinded 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 Assignments for Medical Reasons

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

Site IoRs or designees may request a participant's 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. Examples are provided in Section I.3.2.

The site IoR or designee will consult with the individuals or group specified in the protocol regarding the need for unblinding (e.g., via email or conference call) and then submit the request for unblinding using the Unblinding Request Program on the DMC portal. Decisions will be made by the group or individuals designated in the 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. When earlier knowledge of a participant's assignment may affect the participant's medical care and/or would otherwise be in the participant's best interest, this requirement can be waived by the group or individuals designated in the protocol.

When this type of unblinding is approved, the knowledge of the participant's assignment should be

limited to the fewest number of people possible on a need-to-know basis. The PDM will inform the Chief Data Manager or designee of the team's decision and the Chief Data Manager or designee will prepare a memorandum that provides the 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 PDM, should not be unblinded.

If eligibility determination for a new study requires unblinding of an 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 after final clinical database lock. If the participant is on-study, the participant will be interacting with the community and site personnel still involved in the study, possibly biasing the site staff for the duration of the participant's involvement in the study.

I.5.3 Partial Unblinding for a Continuing Study

On occasion, a decision may be made to partially unblind one arm or one aspect of several arms due to the publication of interim study results. In cases such as these, the protocol team prepares a memorandum that includes guidance on the aspects of data entry specified in Section I.5.4 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 Final Clinical Database Lock

Unblinding a study may consist of:

- Informing study participants (and/or their parents/guardians) of their assignments
- Informing the sites of the assignments for their study participants
- Informing study chairs or other protocol team members of the study results
- Informing study chairs or other protocol team members of assignments
- 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 protocol team members.

Data must be entered and cleaned for primary outcome measures. Endpoint verification, if applicable, must be complete. Secondary outcome measure data should ideally be cleaned as well, but this requirement can be relaxed when unblinding is deemed a more immediate necessity by the protocol team. Laboratory samples must have been collected, but laboratory test results are not required to be finalized or entered into the study database. The time necessary to finalize and lock the clinical database can be six months or more after the last participant's last visit.

I.6 Procedures

I.6.1 Unblinding Individual Participant Assignments

Requests can be made to unblind individual participant assignments on a case-by-case basis as described in Sections I.5.1 and I.5.2.

When the site IoR or designee determines that an individual participant's assignment is urgently needed for immediate medical management, the assignment should 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 an individual participant's assignment for medical 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 assignment sooner is determined to be in the best interest of the participant.
- After initially conferring with the group or individuals designated in the protocol (e.g., via email or conference call), the participant's assignment must be requested using the Unblinding Request Program on the DMC website:
  - The purpose of this program is to collect information that the protocol team and DMC need to promptly and efficiently process unblinding requests. All fields on the screen should be completed, including the study number, PID, step number, site number, information about the IoR or designee, date the information is needed, and a detailed reason for the unblinding. Once the request is submitted, an email message will be automatically sent to the group designated in the 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 via email to the person who made the request, with a copy to the group or individuals designated in the protocol.
  - After the team approves the unblinding request, the PDM informs the Chief Data Manager or designee of the approval. The Chief Data Manager or designee sends the assignment information to the IoR or designee via encrypted email within 24 hours of the team's approval.
  - Documentation of the communication is maintained by both the site and the DMC.

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

Under typical circumstances, the assignments of all study participants will be unblinded after final clinical database lock, as outlined in Section I.5.4.

Procedure to unblind the assignments of all participants
During preparation for study closure, the protocol team should establish plans and timelines for unblinding. The team should also prepare any information needed to support site personnel in communicating assignments to study participants (and/or their parents/guardians). 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 specified by the team.

Unplanned or sudden unblinding
The following standard approach will be followed. Any deviations from this standard must be specified in the protocol and reviewed and approved by the IMPAACT MPRG.

- Sudden (or unplanned) unblinding of one or more arms due to *interim analysis results or results of another study*: The decision to unblind one or more arms of an ongoing study is made by the team in conjunction with the MOG (which includes National Institutes of Health representatives and Network leadership). This can occur based on a recommendation from the DSMB or SMC or the results of another study.
- Participant contact: if a decision is made to unblind, participants (and/or their parents/guardians) should be unblinded as soon as possible following the relevant procedure from Section I.5. Every effort should be made by the sites to contact participants (and/or their parents/guardians) who are currently on-study and who have completed follow-up in order to provide and explain the assignments in the context of the relevant study results.
- Implications of unblinding on study data: when assignments are 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 for the interim analysis report 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 the context of unblinding due to either interim analysis results or other study results, if analyses are reported on clinical data or samples collected after the unblinding date, the conditions under which these data were collected 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 external 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

- DAIDS Emergency Unblinding Policy, https://www.niaid.nih.gov/research/daids-clinical-research-event-reporting-safety-monitoring
- DSMB or SMC guidelines (Section 13)
- Unblinding Request Program
- Emergency Unblinding Utility

I.8 Questions

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