APPENDIX I UNBLINDING PROCEDURES

I.1 Purpose

This document provides guidelines for unblinding participants enrolled in IMPAACT clinical trials.

I.2 Scope

This document defines the concepts of "blinding" and "unblinding" participants, provides guidelines for when to unblind, and delineates procedures for how to unblind when it is determined that such unblinding is appropriate. This document does not describe the procedures for unblinding of regulatory bodies or of individuals with the responsibility for Expedited Adverse Event reporting to regulatory bodies.

I.3 Definitions

I.3.1 Blinding

Knowledge of individual treatment assignments for participants enrolled in studies is withheld from certain individuals. These individuals may include participants enrolled in the trial, research staff at clinical sites, protocol chair(s), and other study team members.

- Single-blinded study: The treating physician is aware of which treatment the participant is receiving, but the participant is not, or vice versa
- Double-blinded study: The participant, treating physician, site staff, and study 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., ZDV + 3TC [open] plus nelfinavir or nelfinavir-placebo [blinded])

I.3.2 Unblinding

For purposes of this document, "unblinding" means revealing the arm or some component of an arm to which an individual participant has been assigned. This may include any or all site staff, participant, protocol chair(s), and/or other team members.

- Full unblinding at completion of the study: Under normal circumstances, all participants will be unblinded simultaneously once the data are complete per instructions in the protocol document. Full unblinding also occurs when sudden (or unplanned) unblinding of a study is required due to interim results of the study or results of another trial.
- 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 of some participants is still blinded.
- Urgent unblinding of individual participants during study conduct: Urgent, unplanned unblinding prior to the conventional unblinding date is done to protect participant safety, e.g., for drug identity during an acute reaction. The unblinding information is shared only on a need-to-know basis.

I.3.3 Open-label or Unblinded Study

Both the participant and the treating clinician responsible for the participant (including site staff) are aware of the participant's treatment assignment.

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	• Incorporates unblinding guidelines in the protocol document • Determines the unblinding date in advance along with the timetable for study closure • Prepares information for site personnel to communicate to study participants when their treatment assignment is discussed
Data and Safety Monitoring Board (DSMB) or Study Monitoring Committee (SMC)	• When relevant, reviews the study safety and efficacy data and may make recommendations to unblind all or part of a study prematurely
IMPAACT Management Oversight Group (MOG)	• Review DSMB or SMC recommendations to unblind all or part of the study prematurely • Aid the team in reaching a decision to unblind

Table I-1. Roles and Responsibilities for Unblinding

Team Member	Responsibility
Protocol Chair	*Individual Participant Unblinding* • Discusses the issue of urgent unblinding of an individual participant with the core study team members, usually on a conference call or through email • Communicates the team's decision in writing (email is sufficient) to the person who made the request, with a copy to the core team members • In consultation with the protocol statistician, approves the release of the treatment codes *Partial Unblinding Based on Interim Study Monitoring Review Recommendation* • If a recommendation has been made to unblind due to interim analysis results or results of another trial, the protocol chair makes the decision to unblind the relevant arms of an ongoing study in consultation with the core team and in conjunction with the MOG.
Protocol Statistician	*Full or Partial Study Unblinding* • Obtains treatment codes for the study prior to the initiation of planned analyses *Individual Participant Unblinding* • Takes an active role in discussing the details of urgent unblinding with the core team members • Along with the protocol chair approves the release of the treatment codes
Medical Officer (MO) or Medical Monitor (MM)	• Actively takes part in the discussions to unblind an individual participant
Investigational New Drug (IND) Holder	• Weighs in on the unblinding discussions and comments, as appropriate
Protocol Data Manager	• In all situations (i.e., individual unblinding, unblinding for pharmacology, study unblinding at the end of study) transmits unblinding request to the chief data manager or designee • Supplies a standard unblinding memo to the team to review, revised to include any study-specific language, and helps finalize the unblinding memo
Chief Data Manager or Designee	In all cases, this is the person responsible for revealing the treatment information. *Full or Partial Study Unblinding* • Prepares "unblinding" listings for each site and distributes to the sites along with the unblinding memo on the date the team has specified *Individual Unblinding* • Receives team-approved request for individual unblinding from the protocol data manager
Protocol Pharmacologist	• Requests approval from the protocol team to receive treatment codes required for pharmacokinetic (PK) analyses (e.g., to identify participants on a specific drug for targeted assay). This may not require full unblinding.

Table I-1. Roles and Responsibilities for Unblinding

Team Member	Responsibility
Clinical Research Site (CRS) Coordinator	• Does not reveal the participant's treatment assignment on an open-label study when contacting team members or the Data Management Center (DMC) • 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)

I.5 Reasons and Guidelines for Unblinding

Conventionally, full unblinding takes place when all data forms have been keyed into the database for all participants, data cleaning has been completed, and the team has declared the study data set to be complete. On a date predetermined by the study team, treatment assignments are provided to all participating sites for each participant entered into the study.

Any unblinding prior to the conventional unblinding date can result in bias in both the site and the patient community, making the results of the study less objective. Routine (i.e., frequent) unblinding of individual participants and site personnel as participants come off protocols or as they reach study endpoints will result in potentially large numbers of participants being unblinded and may severely compromise the integrity or objectivity of the trial. Unplanned unblinding prior to the conventional unblinding date should be undertaken only to protect participant safety or to fulfill regulatory obligations to unblind for adverse events being submitted as safety reports; e.g., for drug identity during an acute reaction, such as one involving compromise of the airway. Unblinding procedures or plans which deviate from this document should be presented to the relevant Scientific Committee (SC) and to the protocol statistician at the Statistical and Data Analysis Center (SDAC) for approval.

I.5.1 Guidelines for Unblinding Individual Participants During a Study

Unblinding information should be shared with as few individuals as possible. This document designates the primary care physician as the recipient of the unblinding information (treatment assignment). The memo from the Chief Data Manager or designee will indicate to whom the team has given authorization to transmit this information. These individuals may include:

- Attending IMPAACT clinician
- CRS coordinator and/or study nurse
- CRS pharmacist
- Participant

Unblinding while a study is ongoing should be considered only:

- As protocol directed (e.g., at week 16)
- On a case-by-case basis by the protocol chair(s) and only after discussion with the senior protocol statistician and the MO or MM

Unblinding should not occur until all primary endpoint data (clinical, virologic, or laboratory-based as mandated by the protocol) and toxicity data for each participant have been entered and cleaned, all outstanding data problems resolved, and any clinical endpoints reviewed by the protocol chair(s). In urgent situations, this requirement will be waived.

Unblinding of participants must be implemented through the DMC (as described in Section I.6).

Participants who have died during the course of a study should not be unblinded at that time, because the criteria per Section I.5 would not be met, and it could affect future decisions of the site investigator in the treatment of other participants.

When some degree of unblinding must occur, this should be limited to the fewest number of people on a need-to-know basis. In some instances, only the participant's primary clinician needs to be unblinded. Team members, including the protocol chair(s) and the data manager, should not be privy to treatment assignments.

At times, partial unblinding may be necessary and is preferable to complete unblinding. "Partial" unblinding of an individual participant refers to unblinding to only one aspect of the treatment arm on a study when the same drug is used in more than one arm; thus, some aspects of the participant's treatment are still unknown. All endpoint and toxicity data for the participant must generally be entered and cleaned prior to partial unblinding.

It is critical to the objectives of any blinded study that the objectivity of the investigators and participants be maintained until the necessary data are collected and verified. Any participant or site unblinding before the team has completed a review of all primary endpoint and toxicity data on ALL participants allows for the possibility of bias. A guiding principle is:

> *A participant's attending IMPAACT clinician should be unblinded only if the treatment information is critical for making immediate therapeutic decisions for the participant (e.g., if withholding the treatment information would put the participant at risk of serious adverse events or death.)*

This guideline applies to all participants including:

- Participants who "fail" a study, either by reaching an endpoint or experiencing a toxicity
- Participants who complete their follow-up while others are still in follow-up
- Participants who have completed follow-up but whose data are not complete

If meeting the eligibility criteria for participation in a new study requires unblinding the participant's 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 them for the duration of their participation in the trial.

Unblinding a participant simply 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. In the case of IMPAACT studies, the randomization system can provide blinded treatment information internally to inform assignment to subsequent steps of the same study and to prespecified rollover studies.

I.5.2 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 drafts a memo**,** and the chief data manager or designee sends the instructions along with the memo to the sites.

Many aspects of data entry specified in Section I.5.3, below, may need to be completed prior to unblinding and this will be specified in the memo.

I.5.3 Unblinding after the Study Closed to Follow-Up

Unblinding a study may consist of:

- The chief data manager informing the sites of the blinding codes for their participants
- The site personnel informing participants of their blinded treatment codes
- Protocol team informing protocol chair(s) or other medical investigators of the study results
- Some combination of the above

When a study has been closed to follow-up, either naturally at the scheduled closure or following the recommendation of an IMPAACT SMC or the DSMB, the conditions outlined below must exist before unblinding participants, 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 taken, but laboratory data or results are not required to be finalized or keyed. The time necessary to finalize the data can be up to three months or more after study closure.

I.6 Procedures

I.6.1 Unblinding Individual Participants

Requests can be made to unblind participants, on a case-by-case basis immediately for emergencies or urgent situations.

There are two requirements that must be met for unblinding:

- Case report forms that contain subjective data (e.g., signs/symptoms, diagnoses) or self-reported data (e.g., adherence, quality of life) must be completed and keyed. In the event of an emergency or urgent situation, this requirement may be waived.
- The Unblinding Request Program must be completed:
    - Requests to unblind a participant should be made by using the Unblinding Request Program on the DMC website. The purpose of this program is to provide a structured way to collect information that study teams and the DMC need to promptly and efficiently process requests for unblinding individual participants. All the fields on the screen should be completed, including the study number, participant identifier, step number, site number, information about the primary care physician, date the information is needed, and a detailed reason for the unblinding. Once the "Send Mail Message" is submitted, an e-mail message will be automatically sent to the core study team and will provide site staff with a copy in the appropriate e-mail account. Considering

the study is done in many different time zones, it may take several hours for the team to respond. The protocol data manager may be contacted by telephone if the site staff has reason to believe that this method of communication has failed or in life-threatening situations. 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 primary care physician via fax or email within 24 hours of the team's approval.

- The protocol chair(s) should discuss the case with the other core study team members, usually on a conference call or through e-mail. Specifically, the protocol senior statistician and the appropriate MO or MM must be included in the discussion. The IND holder should be provided an opportunity to comment.
- The protocol chair(s) must communicate the team's decision in writing (e-mail is sufficient) to the person who made the request, with a copy to the other members of the study team. This documentation of the decision is important for tracking purposes.

NOTE: Planning to unblind ALL participants individually as they come off study is unconventional, as the potential for bias in the reporting of results for other participants at a site is substantial. If a study team plans to perform unblinding in this fashion, this procedure must be indicated in the protocol so that it can be reviewed and approved by the IMPAACT Multidisciplinary Protocol Review Group (MPRG) and the SDAC Design Review Committee. In this circumstance, the procedures in Section I.6.2, Procedure to unblind all participants, below, should be followed on an individual basis.

I.6.2 Unblinding All Participants for a Study

Under normal circumstances, participants will be unblinded at one time once the data are complete, as outlined in Section I.5.3. Any "special" circumstances under which all participants will be unblinded, such as in the NOTE in Section I.6.1 above, must be included in the protocol document.

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

Unplanned or sudden closure unblinding
The following standard language will be included in all new protocols. Any changes to this standard will be protocol-specific and will be included in the review by the MPRG and the SDAC Design Review Committee.

- 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. This can occur based on a recommendation from the DSMB or an SMC or the results of another trial.
- Participant contact: If the decision is made to unblind, participants 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 who have completed follow-up 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 must 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) are at a minimum partially unblinded **in most cases**.

I.6.3 Unblinding of Individuals Outside of IMPAACT for a Special Request

On rare occasions, an outside body such as the National Institute of Allergy and Infectious Diseases or US Food and Drug Administration may request that certain information from a study be unblinded. Such requests must be approved by the study team, the appropriate SC 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.

I.9 Examples of Common Requests to Unblind Individual Participants

Example 1: When a toxicity occurs, the site may request to know the actual treatment received to manage the participant.

Appropriateness to unblind: This is determined by the protocol chair in consultation with the protocol senior statistician and MO depending upon the type and grade of the toxicity and the availability of therapeutic options. A participant's attending physician should be unblinded only if the treatment information is critical for making immediate therapeutic decisions for the participant.

Example 2: When a participant is co-enrolled in another study and a toxicity occurs, the investigator of the co-enrolled study may request to unblind the treatment on the original study.

Appropriateness to unblind: This is determined by the protocol chair in consultation with the protocol senior statistician and MO depending upon the type and grade of the toxicity and the availability of therapeutic options. A participant's attending physician should be unblinded only if the treatment information is critical for making immediate therapeutic decisions for the participant.

Example 3: When a clinical endpoint occurs, the site may request to know the actual treatment received to manage the participant.

Appropriateness to unblind: It is only appropriate to unblind a participant after all clinical endpoints have been verified by the protocol chair and toxicity information has been submitted. A participant's attending physician should be unblinded only if the treatment information is critical for making immediate therapeutic decisions for the participant.

Example 4: When a participant request to have the actual treatment revealed to act in his/her own best interest.

Appropriateness to unblind: This is determined by the protocol chair in consultation with the protocol senior statistician and MO.

Example 5: When a non-IMPAACT physician has taken over the care of a participant and requests to know the participant's treatment history to plan future treatment strategy.

Appropriateness to unblind: This is determined by the protocol chair in consultation with the protocol senior statistician and MO.

Example 6: When a medical investigator requests treatment codes for auxiliary analyses of PK data or sensitivity data.

Appropriateness to unblind: Once such a request is approved, the DMC may unblind the laboratory investigator, but there should be a clear strategy not to unblind the site personnel or the protocol chair.