Appendix VI: Emergency Unblinding by CRS IoR for Medical Reasons

Introduction

Participant treatment assignments are accessible only to

- Clinical Research Site (CRS) pharmacists preparing or managing, but not administering, study products,
- Protocol pharmacists, (e.g. DAIDS Pharmaceutical Affairs Branch (PAB),
- Statistical and Data Management Center (SDMC) staff who need to know treatment assignments, and
- Data and Safety Monitoring Board (DSMB).

Emergency unblinding is expected to be extremely rare. It should only occur in the setting of a potentially life threatening clinical event, and if knowing the participant's treatment assignment would affect decisions regarding the participant's immediate medical management. Both conditions must be satisfied.

Other study staff should only be unblinded in emergency situations as described below. Such events are expected to be extremely rare. During routine protocol conduct, unblinded staff should not be involved in AE attribution or any assessments of participants for whom they know the treatment assignment.

Except in these rare cases, blinding of treatment assignments for individual participants (i.e., by PTID) must also be preserved until the trial is formally unblinded.

If, in the judgment of the IoR or designee, or in the judgment of the participant's medical provider and the IoR or designee, a medical event is of sufficient extreme severity that it requires the immediate unblinding of a participant, the IoR or designee may use the unblinding feature in the Medidata system to perform emergency unblinding of a participant. If this feature is not available or the IoR or designee is unable to perform this for any reason, the IoR or designee may ask the site pharmacist to unblind the participant.

The IoR and the person assigned to be the IoR designee for this specific purpose must complete the unblinding training module in the MediData Rave system. Documentation of this training must be maintained in the HPTN 083 regulatory file.

In all other cases potentially requiring unblinding except those described above, the Clinical Management Committee and DAIDS Medical Officers must be involved in decisions to unblind a participant's provider and/or the IoR or designee. In all cases, the minimum number of personnel required for the immediate management of the participant should be unblinded to the treatment assignment. Staff who become unblinded may no longer be involved in the attribution of adverse events or other participant assessments for study-related purposes.

Refer to Table 1 for details of Emergency Unblinding. Participant-level unblinding information should be shared on a need-to-know basis. Care should be taken to prevent additional unblinding to maintain study integrity. The IoR/IoR designee or pharmacist are responsible for preventing additional unblinding beyond those who need to know and for protecting information that may identify the participant, including PTID.

Table 1. Unblinding related to medical/safety events

	Emergency Unblinding by CRS IoR
Initiates Unblinding	IoR/IoR designee or participant's medical provider - *This situation is expected to be extremely rare*
Requests Unblinding	If time permits, the Clinical Management Committee (CMC), which includes representation from the DAIDS Medical Officers should be included in the unblinding decision.
Approves Unblinding *(Consensus)*	n/a
Provides Treatment Information	**Primary plan**: IoR or designee uses unblinding feature in Medidata to perform emergency unblinding of a participant. **Back-up plan**: Site pharmacist
Becomes Unblinded *(need to know basis)*	IoR (or clinician providing care) Participant
Receives Notification	**Primary plan**: The Medidata system will document the request, including PTID, user, date, time, and reason for unblinding, and will be captured within the system itself. *IoR or designee notifies:* SDMC Clinical Data Manager, LOC Clinical Research Manager (CRM), IRB/EC *HPTN CRM notifies*: Protocol Chair/Co-chair, DAIDS protocol pharmacist, DAIDS Medical Officers, SDMC Statistician *SDMC Statistician notifies*: DSMB Chair **Back-up plan**: The IoR or designee provides a written request to unblind the participant's treatment assignment to the pharmacist. The pharmacist then provides the participant's treatment assignment in writing directly to the requesting IoR or designee. If there is no time for a written request due to the urgency of the situation, the IoR or designee may verbally request the pharmacist to

	unblind a participant's treatment assignment. However, in such cases, the verbal request must be followed by a written request to the pharmacist within 24 hours of the verbal request and must include a reason why the request to unblind participant's treatment assignment could not be provided to the pharmacist in writing initially. The written request to unblind the participant's treatment assignment from the IoR or designee and a copy of the written participant's treatment assignment provided by the pharmacist to the IoR or designee must be filed in pharmacy records. The IoR or designee must email the following protocol team members within 24 hours of the event, copying the pharmacist: - HPTN 083 Protocol Chairs - HPTN 083 SDMC Protocol Statisticians and Clinical Data Manager - HPTN LOC Clinical Research Managers - HPTN 083 DAIDS protocol pharmacist - HPTN DAIDS Medical Officers The pharmacist must email the DAIDS PAB protocol pharmacist regarding the participant's emergency unblinding within 24 hours of the event. The IoR or designee notifies the IRB/EC. The SDMC Statistician notifies the DSMB Chair.
Contacts	SDMC statistician contacts the IoR or designee to obtain PTID and details as needed