

POLICY

Emergency Unblinding

Effective Date:

1 **1.0 PURPOSE**

2 This policy describes the National Institute of Allergy and Infectious Diseases (NIAID)
3 Division of AIDS (DAIDS) requirement for clinical research trials to have written
4 procedures to allow the Investigator of Record (IoR) at a research site to
5 independently unblind the investigational product assignment of an individual clinical
6 trial participant when the IoR deems that information to be necessary for determining
7 appropriate clinical management of a medical emergency.

8 **2.0 SCOPE**

9 This policy applies to all NIAID (DAIDS) supported or sponsored clinical trials in which
10 the IoR and the participant are both blinded to treatment assignment. Emergency
11 unblinding is limited to situations when the IoR has determined that appropriate
12 emergency medical care of a study participant requires access to the treatment
13 assignment.

14 This policy does not apply to routine unblinding upon study completion or unblinding
15 of entire arms of the study based on findings from interim review.

16 **3.0 BACKGROUND**

17 The Division of AIDS sponsors and supports clinical research that is compliant with the
18 U.S. Department of Health and Human Services (HHS) regulations for the Protection
19 of Human Subjects at 45 CFR 46, the U.S. Food and Drug Administration (FDA)
20 regulations at 21 CFR 50, 56, 312, & 812, when applicable, and the International
21 Council on Harmonization Guidelines on Good Clinical Practice (ICH E6 GCP). ICH E6 is
22 an international ethical and scientific quality standard for designing, conducting,
23 recording and reporting trials that involve the participation of human subjects. In
24 accordance with ICH E6 (R2) 5.1.1, the sponsor is responsible for implementing and
25 maintaining quality assurance and quality control systems with written procedures to
26 ensure that trials are conducted, and data are generated, documented (recorded),
27 and reported in compliance with the protocol, GCP, and the applicable regulatory
28 requirements. The IoR may implement a deviation from, or a change of, the protocol
29 to eliminate an immediate hazard(s) to trial subjects without prior Institutional Review
30 Board/Ethics Committee (IRB/EC) or any other study participant safety review
31 committee approval/favorable opinion (45 CFR 46.103(b)(4)(iii), 21 CFR 56.108(a)(4),
32 and ICH E6 (R2) 4.5.4). Each clinical trial should have risk management strategies in
33 place to reduce the risk of hazard to trial participants as described in ICH E6 (R2) 5.0.

POLICY

Emergency Unblinding

Effective Date:

The IoR is responsible for the medical care of individual trial participants (Declaration of Helsinki General Principle 3 and ICH E6 (R2) 4.3). This includes medical decisions about starting or stopping study treatment. One component of risk management in double-blind clinical trials is having procedures in place to allow the site IoR to access treatment codes to unblind the investigational product assignment of an individual participant in the case of a medical emergency where knowing the treatment assignment might impact medical care (ICH E6 (R2) 5.13.4). Some regulatory agencies have clarified that involvement of the sponsor in unblinding decisions is not acceptable in a medical-emergency situation and that the IoR must be able to request unblinding without permission from the sponsor or protocol team. It is the sole judgment of the IoR after careful consideration, to decide when a clinical situation is deemed a medical emergency that requires unblinding, since this decision may have serious consequences for trial integrity.

The coding system for randomization used in blinded trials should include a mechanism for rapid unblinding in case of emergency, which does not allow undetectable breaks of the blind (ICH E6 (R2) 5.13.4). Appropriate unblinding mechanisms may include: internet-based access methods, phone-based systems, use of the site pharmacist to access unblinding codes and access to sealed opaque envelopes maintained on-site. A back-up plan should be in place. The sponsor may be involved in providing the unblinding information but may not delay or reject unblinding requests from the site IoR.

4.0 DEFINITIONS

Blinding: A procedure in which one or more parties to the trial are kept unaware of the treatment assignment(s). Single-blinding usually refers to the subject(s) being unaware, and double-blinding usually refers to the subject(s), investigator(s), monitor, and, in some cases, data analyst(s) being unaware of the treatment assignment(s). (ICH GCP)

Clinical Trial: A research study in which one or more human subjects are prospectively assigned to one or more interventions (which may include placebo or other control) to evaluate the effects of those interventions on health-related biomedical or behavioral outcomes. (NIH)

Institutional Review Board/Ethics Committee (IRB/EC): The board, committee, or other group formally designated by an institution to review, to approve the initiation of, and to conduct periodic review of research involving human subjects. The primary

POLICY

Emergency Unblinding

Effective Date:

purpose of such review is to assure the protection of the rights and welfare of participants in research. IRB/EC reviewing HHS sponsored research must be registered with OHRP and identified on the institution's Federalwide Assurance (FWA). (DAIDS)

Investigator of Record (IoR): The individual at the clinical research site responsible for ensuring that a clinical trial is being conducted in accordance with the protocol, applicable U.S. federal regulations, in-country regulations and any provisions imposed by the reviewing IRB/EC/other regulatory entity. This person is the signatory for the Form FDA 1572 for studies conducted under an Investigational New Drug Application (IND) or the DAIDS Investigator of Record Agreement for non-IND studies. (DAIDS)

Quality Management: The overall system that includes all activities involved in Quality Assurance and Quality Control including the assignment of roles and responsibilities, the reporting of results and the resolution of issues identified during the review. (DAIDS)

Unblinding: Process of revealing previously blinded treatment assignment. (DAIDS)

For additional definitions, see [DAIDS glossary](#).

5.0 RESPONSIBILITIES

Investigator of Record

The *IoR* is responsible for identifying a qualified sub-investigator (with appropriate education and training) who will serve as the designee and be responsible for fulfilling the requirements of the *IoR* should the *IoR* not be able to meet his/her requirement for any given reason. See the [Protocol Registration Manual](#) for additional information on completing the Form FDA 1572/DAIDS *IoR* Form with this information.

The *IoR* or designee is responsible for 1) identifying situations where the emergency medical care of a study participant requires knowledge of their blinded treatment assignment, 2) implementing the documented emergency unblinding procedures including associated communication pathways, 3) documenting the reasons for unblinding and which parties were unblinded in the appropriate protocol documents, and 4) informing their local IRB and/or EC and the sponsor of all subjects whose assignment was unblinded.

Note: All references to *IoR* in this policy also apply to the *IoR* designee.

POLICY

Emergency Unblinding

Effective Date:

99 Protocol Team

100 The *protocol team* is responsible for having written procedures in place before the
101 trial starts documenting how, in case of an emergency, identity of blinded
102 investigational product can be revealed without breaking the blind for the remaining
103 subjects. These procedures should allow the IoR to independently unblind individual
104 participants in case of a medical emergency (without having to seek permission from
105 the sponsor or the protocol team). Emergency unblinding plans should be
106 acknowledged in the protocol but may be documented in greater detail in the Manual
107 of Operating Procedures (MOP), Study-Specific Procedures (SSPs), Standard
108 Operating Procedures (SOPs) or other study-related documents. The Protocol Team
109 may be involved in communication of an unblinding event to the sponsor or DAIDS
110 staff.

111 Site Pharmacist

112 The *site pharmacist* may serve as a source of emergency unblinding information. If
113 so, the site pharmacist is responsible for 1) providing unblinding information to the
114 site IoR in a timely fashion, 2) documenting the provision of unblinding information
115 in the pharmacy records and 3) notifying the DAIDS Pharmaceutical Affairs Branch
116 (PAB) protocol pharmacist, if applicable.

117 Data Center

118 The *data center* may be responsible for providing emergency unblinding information.
119 If so, the data center is responsible for 1) having a 24-hour phone or internet-based
120 system in place to provide emergency unblinding information to the site IoR upon
121 request or providing sealed emergency unblinding envelopes to be stored at the site,
122 2) documenting the unblinding event in the protocol database and 3) implementing
123 their portion (if any) of the communication plan documented in the emergency
124 unblinding procedures.

125 Sponsor

126 The study *sponsor* is responsible for allowing the IoR to independently perform
127 emergency unblinding (without involvement of the sponsor) and for providing any
128 necessary documentation to the FDA or other regulatory authorities. The sponsor
129 may require the IoR (or protocol team) to inform them in a timely manner after the
130 unblinding event.

POLICY

Emergency Unblinding

Effective Date:

DAIDS Staff

DAIDS staff are responsible for assuring that all DAIDS supported or sponsored blinded clinical trials have emergency unblinding procedures in place that are compatible with this policy and international guidance. Program Officers (POs) and Medical Officers (MOs) should work together to review emergency unblinding plans and verify compliance with this policy prior to study initiation. PAB staff (if assigned) should be involved in review/verification of unblinding plans that involve pharmacy staff. DAIDS staff should work with the IoR and protocol team to assure that communication to the sponsor and appropriate regulatory authorities is completed in a timely manner.

6.0 POLICY

6.1 Each DAIDS supported or sponsored blinded clinical trial will have documented procedures in place to allow the site IoR to independently unblind trial participants in case of a medical emergency.

6.2 The emergency unblinding procedures must be acknowledged in the protocol and may include additional detail in the MOP, SSP, SOP or other study-related documents.

6.3 Emergency unblinding procedures must include the following elements:

6.3.1 Ability of the site IoR or designee to unblind individual study participants in a timely manner without seeking approval from anyone else (including the sponsor or protocol team) and without inadvertently unblinding any other participants

6.3.2 A primary unblinding plan and a back-up plan in case the primary is unavailable (e.g. 24-hour phone system and site pharmacist)

6.3.3 A description of the steps to be undertaken by the IoR to access unblinding information for both the primary and back-up plans

6.3.4 A communication plan describing the pathways for communication with the appropriate entities below and time lines for each:

- a. Data Center
- b. Protocol Leadership

POLICY

Emergency Unblinding

Effective Date:

- c. DAIDS staff (e.g. MO, PO, PAB representative)
- d. Sponsor (e.g. DAIDS Regulatory Affairs Branch (RAB) representative or external sponsor)
- e. Local IRB/EC
- f. Regulatory authorities (FDA, European Medicines Agency (EMA) and in-country authorities)

6.3.5 A documentation plan for an unblinding event which should include the following components:

- a. Identification of participant unblinded
- b. Reason for unblinding
- c. Date and time of unblinding
- d. How unblinding information was obtained (primary or back-up plan implemented)
- e. Which team members have been unblinded

6.3.6 A description of how the event will be documented in the study database

7.0 REFERENCES

[HHS regulations for the Protection of Human Subjects at 45 CFR 46](#)
[FDA regulations on Protection of Human Subjects at 21 CFR 50](#)
[FDA regulations on Institutional Review Boards at 21 CFR 56](#)
[FDA regulations on Investigational New Drug Application at 21 CFR 312](#)
[FDA regulations on Devices at 21 CFR 800-892](#)
[E6 \(R2\) Good Clinical Practice: Integrated Addendum to International Conference of Harmonization \(ICH\) E6 \(R1\)](#)
[EMA Human Regulatory Q&A: Good clinical practice](#)
[World Medical Association Declaration of Helsinki](#)
[DAIDS Protocol Registration Manual](#)