Division of AIDS (DAIDS) Site Clinical Operations and Research Essentials (SCORE) Manual: Screening, Enrollment/Randomization, and Unblinding of Participants

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Screening, Enrollment/Randomization, and Unblinding of Participants

The screening process evaluates potential participants for their eligibility to take part in a study.

The enrollment and randomization processes register participants into a clinical trial, assigning them to the appropriate treatment arm. Once participants are enrolled, they can receive the assigned study product/intervention.

In unblinded (open label) clinical trials, Clinical Research Site (CRS) staff and participants are all aware of the treatment/intervention assigned to each participant.

In blinded clinical trials, knowledge of a participant's treatment assignment is withheld from certain individuals. Examples of blinded clinical trials can include:

- Single-blinded - the Principal Investigator (PI)/Investigator of Record (IoR) and/or CRS staff is aware of a participant's treatment assignment, but not the participant.
- Double-blinded - the participant, PI/IoR, CRS staff, and study team are all equally unaware of a participant's treatment assignment.

Blinded studies may include unblinded teams, typically consisting of a Pharmacist of Record (PoR), biostatisticians, monitors, etc.

Unblinding of participants' treatment assignment may occur due to safety concerns or as a routine process at a specified visit in the protocol. The process of unblinding entails disclosure of the participant treatment assignment to the PI/IoR, CRS staff, and/or the participant.

Screening

Screening is the process (or period) of completing procedures/tests to assess potential participants' eligibility. The informed consent must be obtained prior to conducting any protocol-specified procedures. For more information, please refer to the Informed Consent of Participants section of this manual.

Once a potential participant consents to screening, a screening identification (ID) may be assigned depending on the network study. The CRS staff must conduct all protocol-specified screening procedures and tests, such as review of medical history, physical examination, and biospecimen collection. The CRSs must also implement a screening log that documents *all* participants that are screened for each trial, including participants ineligible for enrollment (screening failures) with the reason for ineligibility.

There are specific requirements for enrollment of minors in clinical trials. For more information, please refer to the appendix Clinical Research Site Requirements for Enrolling Minors into DAIDS Clinical Research of this manual.

Enrollment/Randomization

Participant eligibility must be verified by qualified, delegated (and preferably two) CRS staff members. It is the responsibility of each PI/IoR and their designated staff to ensure that only individuals who meet the eligibility criteria are enrolled.

Generally, once potential participants meet all protocol eligibility criteria, they can be enrolled. If a CRS uses separate screening and enrollment informed consent forms, the enrollment consent must be signed before proceeding with study-specified procedures. The enrollment log may be maintained separately from the screening log, or the two documents may be combined into one.

Randomization is the process by which participants are randomly assigned to a treatment/intervention per the protocol, after the PI/IoR has determined participant eligibility. Additional details regarding randomization will be included in each protocol and within the protocol Study Specific Procedures (SSP)/Manual of Operations/Procedures (MOP).

Age and Identity Verification

To maintain participant safety and study data integrity, DAIDS requires age and identity verification of clinical trial participants at all CRSs. Such verification ensures that only those who meet eligibility criteria can be enrolled and also that these same enrolled participants complete the assigned study procedures at each visit for the duration of the study. CRSs must do the following for potential participants:

- Determine their age and establish their identity before they take part in a CRS clinical trial.
- Verify their identity at each visit for the duration of the study before any study procedures take place.

To document this process, each CRS must develop, implement, and maintain a standard operating procedure (SOP). The SOP should describe how the CRS staff will determine the participants' age and establish/verify the participant's identity.

DAIDS has instituted this requirement to strengthen compliance with International Council for Harmonisation (ICH) Good Clinical Practice guidelines (ICH E6) and the United States (U.S.) Code of Federal Regulation (CFR) relating to the protection of human subjects in clinical trials. The following regulations and guidelines were considered in developing this requirement and may be referenced by CRS staff during development of their SOP:

- U.S. Department of Health and Human Services (HHS) regulations for the Protection of Human Subjects at 45 Code of Federal Regulations (CFR) part 46.
- U.S. Food and Drug Administration (FDA) regulations on Protection of Human Subjects at 21 CFR part 50.

- FDA regulations on Institutional Review Boards at 21 CFR part 56.
- FDA regulations on Investigational New Drug Application at 21 CFR part 312.
- ICH E6.

Additionally, an Age and Identity Verification SOP Template and a CRS Guidance for Developing an Age and Identity Verification SOP are available as appendices to this section. These documents are meant to assist the CRSs in the development of the required SOP, and they include additional details on the type of essential information to be considered for inclusion in the site's SOP.

Each CRS should seek the approval of their local Institutional Review Board (IRB)/ Ethics Committee (EC) before implementing the SOP. This requirement for IRB/EC submission was implemented to help ensure the proposed process is acceptable for local populations and conforms with all applicable laws and regulations.

An Explanatory letter to IRB/EC is also included as an appendix to this section and may be used by the CRS when submitting the SOP to the IRB/EC. If the IRB/EC declines to review and approve the SOP, CRSs must request a letter documenting this decision and the rationale. This documentation is to be kept in the CRS regulatory files. At the discretion of the CRS and associated institution, the SOP may be reviewed and approved by another institutional office in lieu of the IRB/EC. Examples include the office of research integrity, institutional ethics office, etc.

If required by the reviewing/approving entity, the CRS should update all applicable informed consent form(s) with the Age and Identity Verification process and obtain IRB/EC approval before reconsenting the participants.

CRS staff are to follow their written SOP(s) and any stricter protocol-specific requirements to determine and verify the age and identity of each participant and document this process in the participant research records.

The CRS must maintain communications with all entities that review the SOP, all version(s) of the approved SOP, and their IRB/institutional approvals as part of their regulatory file, and make these available to DAIDS, its representatives, and regulatory agencies upon request.

For additional guidance on this topic please refer to the Frequently Asked Questions (FAQ), or contact your Office of Clinical Site Oversight (OCSO) Program Officer (PO).

Co-Enrollment Prevention

Sponsors and IRBs/ECs often consider simultaneous participation of individuals in multiple clinical trials exclusionary, despite there being no regulatory prohibition on co-enrollment in

most countries. Co-enrollment can be defined as enrollment of a participant in more than one clinical trial or in the same trial at multiple locations. Specifically, for the purposes of this manual, the term refers to co-enrollment that is prohibited by the eligibility criteria of a protocol. Where prohibited, co-enrollment can cause harm to the participant and can adversely impact the integrity of the study data.

Prohibition of co-enrollment may be warranted due to (but not limited to):

- Participant study burden
- Participant safety concerns posed by exposure to more than one study product, making it impossible to assess causality of Adverse Events (AE)
- American Red Cross-standards or country-specific limitations on blood-draw volumes within a set period of time
- Individual interventions interfering with each other
- Potential unblinding of studies

Individual protocols may outline exceptions that allow participants to co-enroll in related trials. The PI/IoR should consult with their IRB/EC and the Protocol Team for exceptions.

Due to increased participant risk from co-enrollment, DAIDS will require clinical research sites (CRSs) participating in DAIDS-sponsored research within the DAIDS Clinical Trial Networks to identify and prevent participant co-enrollment, where it is prohibited by protocol eligibility criteria. Each CRS will develop, implement, and maintain a robust SOP that describes how the CRS will identify and prevent co-enrollment in DAIDS clinical trials and other non-DAIDS clinical trials to the extent possible. The type of prevention process will vary based on the level of co-enrollment risk at the CRS. Please reference the CRS Guidance for Developing a Co-Enrollment Prevention SOP for a series of questions that will help sites determine their level of risk. The processes developed for preventing and identifying co-enrollment must follow all applicable, local, US, and International laws and regulations – the most stringent should always be followed. In addition to the CRS Guidance document, DAIDS has provided a Co-Enrollment Prevention SOP Template as an appendix to this section. These documents are meant to assist the CRSs in the development of the required SOP, and they include additional details on the type of essential information to be considered for inclusion in the site's SOP.

Developing a process to identify and prevent prohibited co-enrollment among clinical research sites within the recruitment area may necessitate sharing of Personally Identifiable Information (PII) between sites. Data sharing procedures must be implemented in such a way that participants' confidentiality is maintained. Please reference the HIPAA (Health Insurance Portability and Accountability Act) section of the Frequently Asked Questions (FAQ) on Co-enrollment Prevention for more details. Although HIPAA is only applicable to US sites, there is also some additional information on privacy and confidentiality within the FAQ.

Each CRS will submit their SOP to their local IRB, EC, or other relevant CRS institutional office to ensure that the proposed process is acceptable for local populations and conforms with all applicable laws and regulations. IRB/EC or other relevant approval should be obtained before implementing the initial version of the SOP. A template letter explaining why IRB/EC review is important is included as an appendix to this section and may be used by the CRS when submitting the SOP to the IRB/EC or other relevant body. At the discretion of the CRS and associated institution, the SOP may be reviewed and approved by another institutional office in lieu of the IRB/EC. Examples include the office of research integrity, institutional ethics office, human research protections office, etc. CRSs should document communications with all offices or institutions that review the SOP.

If the IRB/EC declines to review and approve the SOP, CRSs must request a letter documenting this decision and the rationale. This documentation is to be kept in the CRS regulatory files. DAIDS would also encourage sites to seek out another institutional office concerned with human research protections or research integrity to review the SOP if the IRB/EC will not review.

In addition, if required by the reviewing IRB or EC, the CRS will update all applicable informed consent form(s) with the Co-enrollment Prevention process and obtain IRB or EC approval before reconsenting the participants as necessary.

The CRS will maintain all versions of the approved SOP(s) as part of the CRS's Essential Documents and make them available to DAIDS, monitors and regulatory agencies upon request.

For additional guidance on this topic please refer to the FAQ on Co-enrollment Prevention or contact your Office of Clinical Site Oversight (OCSO) Program Officer (PO).

The CRS Staff are to follow the CRS's written SOP and any stricter protocol-specific requirements to identify and prevent participant co-enrollment in protocols where it is prohibited within the CRS and the geographic region as possible.

If a CRS identifies prohibited co-enrollment/s, they should contact the protocol team or teams (if more than one protocol is involved), the OCSO PO, and their IRB/EC to report it as a significant protocol deviation at time of site awareness. When applicable, the protocol team/s, in collaboration with the OCSO PO, will provide further guidance on next steps regarding participant safety, continued participation in the clinical trial, and appropriate corrective and preventative actions.

Note: CRS staff should inform participants of the potential risks associated with unauthorized co-enrollment and reiterate these risks over the course of the study. To avoid unauthorized co-enrollment, a CRS may choose to use various methods, including participant education, crosschecking of protocol enrollment logs within the CRS, or collaboration with other CRSs in the area. CRSs can also choose to use a real-time detection system with web- and/or biometric technology for participant identification, where

these systems are available to them. Please reference the CRS Guidance for Developing a Co-Enrollment Prevention SOP for more information. If an electronic system is used to prevent co-enrollment, the CRS staff should consult the Electronic Information Systems (EIS) policy to determine if it applies to the system.

Unblinding Participants' Treatment

Unblinding of participant treatment assignment may refer to planned unblinding of the full or partial study, early unblinding by the PI/IoR, or emergency unblinding for medical or safety reasons. On rare occasions, accidental unblinding may occur, in which case treatment assignment information is revealed to CRS staff and/or participants prematurely, unintentionally, or otherwise outside of the standard process.

ICH E6 Section 4.7 states: *"*The investigator should follow the trial's randomization procedures, if any, and should ensure that the code is broken only in accordance with the protocol. If the trial is blinded, the investigator should promptly document and explain to the sponsor any premature unblinding (e.g., accidental unblinding, unblinding due to a serious adverse event) of the investigational product(s)*".*

Planned Unblinding

Partial Planned Unblinding

Partial planned unblinding can be performed for operational reasons where the treatment assignments for a subset of participants are disclosed to the CRS staff (and participant if the protocol allows).

Early unblinding occurs when the CRS, on behalf of a participant, may request their treatment assignment before the study is formally unblinded. For example, a participant becomes pregnant before study unblinding, and she and her primary care provider require this information to aid in her clinical care.

Full Planned Unblinding

Full planned unblinding may occur where participants and CRS staff are unblinded after the last scheduled clinic visit or as per protocol.

Emergency Unblinding

Emergency unblinding by the site PI/IoR for medical reasons occurs when, in the judgment of the PI/IoR, the immediate information is needed to determine appropriate care for the participant after a medical event.

Emergency unblinding by the PI/IoR is extremely rare and requested only when a participant's treatment assignment would affect decisions regarding their immediate medical care; therefore, it is encouraged that the PI/IoR maintain the blind as much as

possible. Emergency unblinding does not require the Protocol Team's permission before the PI/IoR unblinds a participant's treatment assignment. However, the PI/IoR must report any emergency unblinding that has occurred to the Protocol Team, DAIDS, and the IRB/EC as soon as possible. To maintain study integrity, every effort should be made to prevent the unblinding of a participant's treatment assignment information to additional study staff (beyond those who need to know). The protocol team and the CRS must have written procedures for emergency unblinding in place before a clinical trial begins.

The requirements for emergency unblinding are described in the DAIDS Emergency Unblinding Policy (POL-A15-OPC-006), located on the National Institute of Allergy and Infectious Diseases (NIAID) website.

Accidental Unblinding

Accidental unblinding occurs when treatment assignment information is revealed to CRS staff and/or participants prematurely, unintentionally, or otherwise outside of the standard process (e.g., verbal or written accidental disclosure of participant's treatment assignment, identification of the blinded study product based on its appearance, study product labelling error, and/or laboratory testing conducted outside of the trial procedures). The PI/IoR must report any accidental unblinding that has occurred to the Protocol Team, DAIDS, and the IRB/EC as soon as possible.

Appendices

1. Clinical Research Site Guidance for Developing an Age and Identity Verification Standard Operating Procedure
2. Age and Identity Verification Standard Operating Procedure Template
3. Age and Identity Verification Explanatory Letter to the Institutional Review Board/Ethics Committee (IRB/EC)
4. Clinical Research Site Guidance for Developing a Co-Enrollment Prevention Standard Operating Procedure
5. Co-Enrollment Prevention SOP Template
6. Co-enrollment Prevention Explanatory Letter to the IRB/EC

References

1. U.S. Code of Federal Regulations, Title 21, Parts 11, 50, 54, 56, and 312
2. U.S. Code of Federal Regulations, Title 45, Part 46 and Subparts
3. International Council for Harmonisation Good Clinical Practice (ICH E6)
4. FDA E6(R2) Good Clinical Practice: Integrated Addendum to ICH E6(R1) Guidance for Industry
5. FDA Guidance: Investigator Responsibilities - Protecting the Rights, Safety, and Welfare of Study Subjects [Oct 2009]
6. Office for Human Research Protections
7. Glossary of Terms on Clinical Trials for Patient Engagement Advisory Committee Meeting
8. ICH-E11: Addendum to ICH E11: Clinical Investigation of Medicinal Products in the Pediatric Population
9. Age and Identify Verification SOP Requirements Frequently Asked Questions (FAQ)
10. Co-Enrollment Prevention SOP Requirements Frequently Asked Questions (FAQ)
11. DAIDS Emergency Unblinding Policy (POL-A15-OPC-006)
12. DAIDS Policy, Use of Electronic Information Systems in Clinical Research

Version History

V1.0	1/19/2021	Original Version
V2.0	8/27/2021	Added information and requirements to the Co-Enrollment Prevention section on page 5 – 7, three new appendices, and additional links in the appendices and references section. Updated the required SOPs appendix to include Co-Enrollment Prevention.