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# Division of AIDS (DAIDS) Site Clinical Operations and Research Essentials (SCORE) Manual: Investigator Responsibilities

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## Investigator Responsibilities

Investigator responsibilities are based on applicable DAIDS requirements, International Council for Harmonisation (ICH) Good Clinical Practice (GCP) (“ICH E6”), and United States (U.S.) Code of Federal Regulations (CFR). Clinical Research Sites (CRSs) should consult applicable regulations, guidelines, and policies, such as 21 CFR Parts 11, 50, 54, 56, 312 (subpart D), and 812; 45 CFR Part 46; ICH E6 (section 4); and their Institutional Review Board (IRB)/Ethics Committee (EC) for a complete understanding of Investigator responsibilities.

The Principal Investigator/Investigator of Record (PI/IoR) is the qualified individual responsible and accountable for study conduct at their CRS. Each CRS may have more than one PI/IoR when conducting multiple clinical trials.

DAIDS holds these individuals responsible for:

- Ensuring DAIDS clinical trials are conducted according to the protocol and applicable local, IRB/EC, and/or other regulatory entity/regulatory authority (RE/RA) laws or requirements.
- Acting as signatory for U.S. Food and Drug Administration (FDA)’s Form FDA 1572 for clinical trials conducted under an Investigational New Drug (IND) application or the DAIDS IoR Form for non-IND studies.

PIs/IoRs must be qualified by education, training, and experience to assume responsibility for proper clinical trial conduct. These individuals must provide evidence of qualifications with a current curriculum vitae, licenses, and/or other relevant documentation requested by DAIDS, IRBs/ECs, and/or regulatory entities/regulatory authorities (REs/RAAs).

DAIDS has also defined two grant-specific leadership roles: CRS Leader and Clinical Trials Unit (CTU) PI. A PI/IoR may also serve in these grant-specific roles.

- CRS Leader: An onsite, senior research scientist responsible for CRS administrative and scientific components. Oversees overall CRS activities, including daily operations, performance, and compliance.
- CTU PI: Individual listed as the Grantee on the Notice of Award who is responsible for all CTU activities and performance. Because CTUs may include one or more CRSs, CTU PI responsibilities include communications, performance, and financial management of the CTU and its affiliated CRSs. This PI also provides CTU scientific and administrative representation to DAIDS Clinical Trials Network(s).

Because PIs/IoRs assume full responsibility and accountability for DAIDS clinical trials, they are essential to the conduct of high-quality studies. They may face challenges during clinical trials that are distinctly different from those encountered during routine medical practice. It is critical that the PI/IoR dedicates the time and effort necessary for proper conduct and supervision of the clinical trial.

## Protecting Clinical Trial Participants' Rights, Safety, and Welfare

PIs/loRs must ensure participants' rights, safety, and welfare are protected while participating in and after completing a clinical trial.

The PIs/loRs are responsible for ensuring CRSs properly follow all DAIDS requirements related to informed consent as outlined in the SCORE Manual's [Informed Consent of Participants](#) section, including:

- Obtaining IRB/EC/RE/RA approval of a protocol and any participant-facing study information (e.g., informed consent form [ICF], study advertisements, etc.) before CRSs present it to potential participants and/or their legally authorized representatives (LARs) (hereinafter referred to as participants/LARs).
- Ensuring potential participants/LARs receive adequate and complete clinical trial information before participating in a clinical trial.
- Ensuring participants/LARs are never coerced or unduly influenced to participate in a clinical trial.
- Ensuring ICFs are clearly worded and in a language participants/LARs understand.
- Ensuring participants/LARs have ample time to review ICF information and receive answers to all questions before consenting to participate.
- Ensuring CRSs provide additional safeguards to protect participants' rights and welfare if the study involves participants who may be vulnerable to coercion or undue influence (e.g., children, prisoners, individuals with impaired decision-making capacity, economically or educationally disadvantaged individuals, etc.), per 45 CFR Part 46.111(b) and 21 CFR Part 56.11(b).

PIs/loRs and CRS staff must provide participants with adequate clinical care for any adverse event (AE), including those related to clinically significant laboratory values that are definitively or possibly related to clinical trial participation. They must ensure participants who experience an AE receive the necessary clinical care/treatment from qualified CRS staff or a qualified clinician (45 CFR Part 46.116[b][d] and 21 CFR Part 50.25[a][6]). Industry guidance also recommends informing the participant's primary care physician about their clinical trial participation, when applicable and agreed upon by the participant/LAR.

Because CRS staff may identify new conditions and/or diagnoses in study participants unrelated to clinical trial participation, PIs/loRs must inform the participant/LAR of the new conditions/diagnoses and advise them on seeking appropriate clinical care/treatment.

During clinical trials, PIs/loRs must ensure qualified staff are reasonably available to provide clinical care to the study participants. They must also confirm the CRS provides contact information/instructions to participants/LARs for use in the event of a medical emergency. If any identified AE qualifies as an expedited AE (EAE) or serious AE (SAE)

that requires expedited reporting to DAIDS and the IRB/EC, PIs/IoRs must ensure the EAE is reported within the required timelines, even if all details regarding the event are not available.

## **Managing Protocol Deviations**

PIs/IoRs are required to adhere to approved protocols and have established processes to avoid protocol deviations to the extent possible. They must explain, document, and report any protocol deviations to the Protocol Team per applicable DAIDS Clinical Trials Network, protocol, and/or IRB/EC requirements. Depending on the circumstances, some deviations may require CRSs to implement corrective and preventative actions (CAPAs).

DAIDS does NOT permit planned deviations, and CRSs are not allowed to implement planned deviations unless the deviation would shield participants from an immediate hazard. Similarly, there are instances when failing to comply with the protocol is necessary and acceptable to protect participant rights, safety, and well-being.

## **Maintaining the Study Blind**

PI/IoR must have a written unblinding process that aligns with the protocol and DAIDS requirements for blinded clinical trials. Any premature unblinding, either accidental or to ensure participant safety, must be documented and reported accordingly by the delegated CRS staff member. For further guidance on unblinding, refer to the SCORE Manual's [Screening, Enrollment/Randomization and Unblinding of Participants](#) section.

## **Managing Early Participant Withdrawals/Early Study Endings**

When a participant withdraws prematurely from a clinical trial, the PI/IoR must make a reasonable effort to understand the reasons they withdrew, explain the consequences of withdrawing early, and inform the participant that the CRS may follow them (if they consent) for safety reasons.

In the event that a study is suspended or terminated early, the PI/IoR must ensure participants are informed and receive adequate treatment and follow-up, and where applicable, notify the RE/RA.

## **Study Product Responsibilities**

To ensure participant safety and proper clinical trial conduct, PIs/IoRs and CRS staff must be thoroughly familiar with the appropriate use of the study product(s) as described in the protocol, the current Investigator's Brochure (IB), the product package insert, and any other DAIDS-provided sources. PIs/IoRs must also:

- Ensure study products are only provided to individuals authorized to receive it.
- Provide oversight of Pharmacist of Record who ensures study products are stored according to clinical trial documents (e.g., the protocol, the Study-specific

Procedures, Manual of Procedures/Operations (MOP), and/or any applicable requirement) in order to maintain product stability.

- Ensure participants receive continuous guidance on correctly using study products before first dose and throughout the clinical trial.
- Maintain complete and accurate accountability logs documenting study product dispensation, return, and disposal.

## Ensuring Clinical Trial Data Quality and Integrity

Essential documents such as source documents, required communications, and/or IRB/EC and RE/RA approvals serve to substantiate a clinical trial's data integrity, confirm the existence of participants, and permit DAIDS, their representatives and/or representatives of any regulatory agency, IRB or EC to evaluate a clinical trial's conduct.

PIs/IoRs must ensure source documents are Attributable, Legible, Contemporaneous, Original, Accurate, and Complete (ALCOA-C), which includes: source data changes are traceable (i.e., system audit trail for changes to electronic records, initials/date for changes to paper records), original entries are legible (not obscured), and any changes to source documents can be explained (e.g., validate source document changes using an audit trail). PIs/IORs are responsible for maintaining copies of completed, signed and dated essential documents (as applicable); and must ensure source documentation including completed, signed and dated Case Report Forms (CRFs) (if applicable) in paper or electronic format according to all policies, guidelines and regulations are available to DAIDS, their representatives and/or representatives of any regulatory agency, IRB or EC. Please see the SCORE Manual's [Essential Documents](#) and [Source Documentation](#) sections for details.

### eCRF Sign-Off

The investigator must review and sign-off protocol eCRF data prior to interim analyses and prior to the final analysis.

The investigator may delegate responsibility for sign-off on protocol eCRF data. The following criteria must be met for delegation:

- The individual must be delegated the task of signing casebooks on the Delegation of Duties Log; and
- The individual must be listed on the Form FDA 1572 or DAIDS IoR Form; and
- The individual must be a clinician (i.e., medical doctor or nurse); and
- The individual must be substantively involved in the protocol research, making a direct and significant contribution to the data.

## Facilitating Study Closure

When a clinical trial is complete, PIs/IoRs must, at minimum:

- Notify the institution of study closure, when applicable.
- Summarize the clinical trial's outcome and submit this outcome to the IRB/EC, per IRB/EC policies.
- Provide any required reports to applicable REs/RAs.
- Ensure all essential documents are filed and stored according to the SCORE Manual's "Essential Documents" section, ICH E6 (section 8.0), applicable regulations, and institutional requirements.

## Supervising Clinical Trial Conduct

The U.S. FDA's guidance document, *Investigator Responsibilities - Protecting the Rights, Safety, and Welfare of Study Subjects*, focuses on four major areas when assessing whether a PI/IoR supervised a clinical trial adequately:

1. Whether PIs/IoRs delegated tasks to appropriately qualified individuals.
2. Whether study staff received adequate training on how to conduct the delegated tasks and were provided with an adequate understanding of the study before performing applicable delegated tasks.
3. Whether PIs/IoRs supervised study staff adequately and remained involved throughout study conduct.
4. Whether PIs/IoRs adequately supervised/oversaw third parties involved in study conduct to the extent possible.

PIs/IoRs must select an adequate number of staff members to assist with clinical trial conduct and must review their qualifications before delegating any clinical trial-specific duties/tasks. When selecting personnel to support clinical trial implementation and perform study-specific duties/tasks, PIs/IoRs must consider the individual's level of education, previous clinical trial experience, and required credentials/licensing. If PIs/IoRs plan to delegate any task that requires medical training in advance (i.e., study-related tasks involve medical decisions and participant care), they must delegate such tasks to a qualified individual.

## Responsibilities when Delegating Duties

If a PI/loR plans to delegate any clinical trial-related duties to qualified CRS staff, they must create and maintain (i.e., document changes to delegated duties in a timely manner) a Delegation of Duties (DoD) log listing clinical trial-related duties:

- This log must delineate delegated responsibilities, name assigned personnel, and include signatures, initials, and start and stop dates, as applicable.
- CRS staff must receive (and document) training on the protocol, protocol-related documents, clinical trial risks, and appropriate use of study product, as applicable to their roles.

Before a CRS staff member can perform any study-related tasks, they must be added to the DoD log, with all required information completed.

PIs/loRs are responsible and accountable for supervising all clinical trial-related activities delegated to qualified individuals. The level of supervision required for staff may vary by their experience level, the nature of the study, and the participant population. The PI/loR must dedicate sufficient time to properly conduct and supervise the clinical trial and must maintain documented evidence of this oversight at the CRS.

While no specific rules define what level of PI/loR oversight is acceptable, the *FDA Guidance for Industry—Investigator Responsibilities* guides investigators on developing a plan to supervise and oversee the clinical trial. Assessment of a PI's/loR's clinical trial involvement and oversight will be performed using some of the examples below; however, evidence of only one of the examples may not sufficiently prove PIs/loRs have provided adequate oversight.

- Documentation that the PI/loR performed clinical trial-related duties (e.g., obtained informed consent, reviewed participant eligibility criteria, evaluated AEs [grading, significance, seriousness]).
- Documented attendance at monitoring visits.
- Frequent, documented study-related communication with CRS staff, DAIDS, and other stakeholders.

Documentation such as meeting minutes, agendas, and/or attendance records that proves PI/loR involvement in study-related CRS meetings to review clinical trial progress, serious and expedited AEs, changes to an approved protocol, deviations, and other topics.

If the PI/IoR needs to delegate duties/functions to a third party, they must implement procedures to ensure the third party is qualified to perform the delegated tasks and must supervise third-party activities to ensure compliance with applicable requirements. For example, Study X requires biospecimen analyses that require the engagement of a third-party specialty laboratory. The PI/IoR must determine applicable credentials and certifications and ensure the third party keeps them current.

As sponsor, DAIDS is responsible for overseeing clinical trials and fulfills this responsibility using a qualified monitoring contractor, based on considerations such as a clinical trial's objective, purpose, design, complexity, blinding, size, and endpoints. PIs/IoRs must facilitate and permit DAIDS, DAIDS representatives and/or RE/RA inspectors to monitor and inspect the CRS and all study-related files.

Please refer to the SCORE Manual's [Clinical Research Site Personnel Qualifications, Training and Responsibilities](#) section for more information on the DoD Log and CRS staff qualification/training requirements.

## **Investigator Agreements and Disclosures**

### **Signed Agreement Between Involved Parties**

As required by ICH E6 (8.2.6) as part of the essential documents, agreements between parties involved in clinical trial must be in place. These agreements include a contract between the CTU/CRS and other applicable parties providing the funds to the CRS to conduct clinical trial. These contracts should be protocol specific and document the financial aspects of the clinical trial.

### **Protocol Signature Page**

DAIDS requires PIs/IoRs to sign the protocol signature page (PSP) for the initial protocol and any amendment/Letter of Amendment to document PIs'/IoRs' commitment to conducting the clinical trial in compliance with the approved protocol, related documents, and any applicable laws and regulations. All DAIDS PSPs include standard language PIs/IoRs may not change; however, they may add any required language (e.g., institutional requirements) when applicable.

### **Form FDA 1572**

PIs/IoRs must sign an FDA Statement of Investigator, Form FDA 1572, when conducting a clinical trial that collects data as part of an IND application. Form FDA 1572 is a legally binding document designed to inform clinical investigators (PIs/IoRs) of their research obligations and secure their commitment to follow pertinent FDA regulations. By signing the form, they affirm they will conduct the clinical trial according to the approved protocol, applicable federal regulations, and ICH E6.



Form FDA 1572, Section 9, lists the commitments PIs/IoRs are agreeing to by completing the form. PIs/IoRs need to be certain they uphold all commitments on every clinical trial for which they are responsible and must complete a Form FDA 1572 for each. They must ensure all study-related responsibilities are appropriately fulfilled, even if they delegate certain tasks.

Please note that this section of the manual instructs PIs/IoRs and their appropriately delegated staff; and it does not include all parties who must be documented on this form. Please reference *Form FDA 1572 guidance with frequently asked questions* and the [DAIDS Protocol Registration Manual](#) for additional information on completing and submitting the form.

### **DAIDS Investigator of Record Form**

The [DAIDS IoR Form](#) is an agreement PIs/IoRs must sign for non-IND clinical trial. In signing, they affirm to DAIDS their commitment to comply with local laws and required regulations (listed in Section 8 of the form) throughout a clinical trial and accept full responsibility for study conduct at their CRS, even if they delegate certain tasks.

Please reference the *DAIDS Protocol Registration Manual* for details on completing and submitting these forms to DAIDS.

## Financial Disclosure Form/Statement

For all DAIDS clinical trials where DAIDS is the IND holder, PIs/IoRs must ensure CRS staff listed on the Form FDA 1572 complete a financial disclosure form/statement. The financial disclosure form/statement is an FDA regulation (21 CFR part 54) requirement that:

- Certifies the absence of certain financial interests (e.g., ensures PIs/IoRs are not receiving compensation that could affect a clinical trial's outcome).
- Certifies the absence of arrangements that could affect the reliability of data submitted to the FDA (e.g., ensures PIs/IoRs do not have a proprietary interest in the study product, including a patent, trademark, copyright, or licensing agreement).

Or

- Discloses financial interests/arrangements and identifies steps taken to minimize the potential for bias (e.g., determines whether PIs/IoRs have any equity interest [such as stock options] invested in any sponsor of the covered clinical trial).

The [DAIDS Regulatory Support Center](#) website stores generic financial disclosure forms/statements (and guidelines for completing the forms) for all DAIDS clinical trials. PIs/IoRs should use these forms unless DAIDS or the Protocol Team provides CRSs with a different form/statement.

The FDA guidance, *Financial Disclosure by Clinical Investigators*, provides additional information on the requirements.

## References

1. [U.S. Code of Federal Regulations, Title 21, Parts 11, 50, 54, 56, 312 and 812](#)
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 Guidance: Investigator Responsibilities - Protecting the Rights, Safety, and Welfare of Study Subjects \[Oct 2009\]](#)
5. [FDA Information Sheet Guidance for Sponsors, Clinical Investigators, and IRBs Frequently Asked Questions – Statement of Investigator \(Form FDA 1572\) \[May 2010\]](#)
6. [FDA Guidance for Clinical Investigators, Industry, and FDA Staff - Financial Disclosure by Clinical Investigators](#)
7. [DAIDS Protocol Registration Manual](#)

## Version History

V1.0	1/19/2021	Original Version
V2.0	5/4/2022	Pg 5 - Added information about the IoR's responsibility to have a copy of the eCRFs.
V2.1	10/2/2023	Pg 7 – Corrected hyperlink to <a href="#">Clinical Research Site Personnel Qualifications, Training and Responsibilities section.</a>
V3.0	11/4/2024	Pg 5 – Clarified requirements for timing of eCRF sign-off by the IoR.