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# Division of AIDS (DAIDS) Site Clinical Operations and Research Essentials (SCORE) Manual: Premature Termination or Suspension of a Clinical Trial

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## Premature Termination or Suspension of a Clinical Trial

This section provides Clinical Research Sites (CRSs) with guidance on the premature termination or suspension of a clinical trial in its entirety or at a specific CRS and discusses what the Principal Investigator (PI)/Investigator of Record (IoR)/CRS should do in such cases.

Premature termination is when a study ends sooner than scheduled, as in the following examples:

- Determination that a study product's efficacy is better or worse than anticipated.
- Occurrence of unforeseen study drug safety issues or if data from preclinical studies indicate a presence of unanticipated toxicity risks that cannot be adequately quantified.
- Futility: Determination that a demonstrable difference in relevant therapy/treatment proves unlikely.
- Operational futility: the protocol is determined to no longer be able to meet study objectives (e.g., fails to enroll participants within a requisite time period, study drug no longer available or usable), and is ended.

Other situations may require suspension of some or all clinical trial activities for the study or at a specific CRS. Often during a suspension, the clinical trial and/or the CRS may not enroll new participants or receive additional study product. CRSs may, however, be required to continue follow up of previously enrolled participants for safety or other assessments.

When conducting a study, there are often different communication and process requirements for suspension or termination, and these are typically defined by the protocol itself, the Study-Specific Procedures (SSP) and/or the Network's Manual of Operations/Procedures (MOP).

### Who Can Terminate or Suspend a Clinical Trial?

Termination or suspension of a clinical trial, whether in its entirety or at a specific CRS may be implemented by any applicable Regulatory Entity (RE)/Regulatory Authority (RA), Institutional Review Board (IRB)/Ethics Committee (EC), or DAIDS. Additionally a PI/IoR may suspend enrollment in a clinical trial at their CRS if deemed necessary.

#### ***Regulatory Entity/Regulatory Authority***

An RE/RA may decide to terminate or suspend a clinical trial due to safety issues, noncompliance, significant concerns (e.g., complaints by a participant or any other party), or an inspection finding(s). The termination or suspension may apply to all clinical trials at a CRS or those specific to a PI/IoR.

If an RE/RA terminates or entirely suspends a clinical trial, DAIDS will communicate this to all participating CRSs. If the clinical trial is terminated or suspended at a particular CRS, then the RE/RA may contact the PI/IoR/CRS directly. They may also choose to conduct an inspection before making a final decision. If a PI/IoR or CRS is contacted directly by an RE/RA, they should immediately notify their IRB/EC and DAIDS.

For U.S. Health and Human Services (HHS)-funded studies, the Office of Human Research Protections (OHRP) may also be involved in decisions regarding termination or suspension of clinical trials at the CRS where there is a significant concern for participant safety, rights and/or data integrity.

### ***Institutional Review Board/Ethics Committee***

Per HHS regulation 45 Code of Federal Regulations (CFR) Part 46.113 and FDA regulation 21 CFR Part 56.113, the IRB/EC has the authority to terminate or suspend approval of a clinical trial and must report this to the PI/IoR, DAIDS, and the RE/RA, in accordance with their procedures and other local laws and regulations. The IRB/EC may terminate or suspend a clinical trial at a CRS when:

- It determines that the clinical trial is not being conducted in accordance with the IRB/EC requirements or local laws and regulations.
- The clinical trial has been associated with unexpected serious harm to participants.
- There is a lapse in IRB's/EC's continuing review.

If the suspension is due to a lapse in IRB/EC approval, the CRS must notify the Office of Clinical Site Oversight (OCSO) Program Officer (PO) and the Protocol Registration Office (PRO). The PI/IoR will communicate with the IRB/EC and OCSO PO to ensure participants' safety and obtain approval to continue following up with enrolled participants and collect their data during the lapse period.

### ***HIV/AIDS Networks***

An HIV/AIDS Network may decide to terminate or suspend a clinical trial due to safety issues, noncompliance, or other significant concerns (e.g., complaints by a participant or any other party). The termination or suspension may apply to all clinical trials at a CRS or those specific to a PI/IoR.

### ***DAIDS***

As sponsor, DAIDS can terminate or suspend a clinical trial at all sites or at one specific CRS for the following reasons:

- The study product presents a significant risk to participants, and DAIDS decides to eliminate the immediate hazard(s) to protect participants' physical well-being.
- Interim analysis reveals:

- Significant safety concerns
- One treatment arm has superior results
- Evidence that a demonstrably significant difference in treatment is unlikely.
- The clinical trial scientific question is no longer relevant, or the objectives will not be met (i.e., slow accrual)
- Serious, persistent noncompliance is detected, such as during monitoring, auditing, or data analysis, at the CRS for one or multiple DAIDS clinical trials.
- Data analysis indicates a trend of a potential safety issue for the local study population.
- Research misconduct such as fabrication and falsification of data. For example: Altering or omitting exam results to make a participant meet eligibility criteria

Per the International Council for Harmonisation (ICH) Good Clinical Practice (GCP) (“ICH E6”) guidelines and FDA regulations, a sponsor shall promptly secure compliance, discontinue shipments of study product, or end the CRS participation in the investigation when discovering that the PI/loR is not in compliance with the signed agreement (Form FDA 1572 or similar), general investigational plan, or other applicable requirements.

DAIDS must communicate termination or suspension to the PI/loR and when applicable, the IRB/EC, and RE/RA. DAIDS communications and interactions with CRSs are discussed later in this section.

### ***PI/loR or CRS***

The CRS leadership and/or the PI/loR may decide to terminate or suspend the clinical trial at their CRS for the following reasons:

- The CRS has a trend of noncompliance across protocols and has self-imposed an institution-wide corrective and preventive action (CAPA), which has resulted in suspension of all studies until CAPA implementation.  
**Note:** For guidance on developing and implementing a CAPA process, please refer to the CAPA training module in the DAIDS Learning Portal (DLP).
- The PI/loR has ongoing safety concerns for their study population.
- The CRS has chosen to stop participating in a specific clinical trial or any clinical trial.
- The CRS temporarily lacks an adequate number of qualified staff or facilities to conduct a study in a safe and compliant manner (as in the case of a natural disaster).

The PI/loR must communicate a study’s termination or suspension at their CRS to DAIDS, IRB/EC, and RE/RA, as applicable.

## **CRS Responsibilities for When the Entire Clinical Trial is Terminated or Suspended by Another Responsible Entity**

In the event of premature termination or suspension of a clinical trial by a RE/RA, IRB/EC, the HIV/AIDS Network, or DAIDS, the PI/loR and/or the CRS will receive notification from DAIDS and/or the HIV/AIDS Network to terminate or suspend related activities at their site.

The PI/loR and/or the CRS must notify participants, IRB/EC, any RE/RA, community stakeholders, and other stakeholders, as appropriate, of the termination or suspension of the clinical trial and ensure that participants receive adequate follow-up and alternate therapy/treatments for their condition. Risks to participants' therapy/treatment interruption must be evaluated and discussed with all involved parties.

In the event of a suspension, DAIDS and/or the HIV/AIDS Network will notify the CRS when clinical trial activities can resume at their facility.

For FDA Investigational New Drug (IND) studies, suspension and termination of the entire study is discussed further in 21 CFR Part 312.42 and 21 CFR Part 312.44.

## **CRS Responsibilities for When the Clinical Trial is Terminated or Suspended Only at Their Facility by DAIDS or Responsible Entity**

If the clinical trial at a CRS is terminated or suspended by a RE/RA, IRB/EC, the HIV/AIDS Network, or DAIDS, the PI/loR will receive a letter of termination or suspension giving the reasons for the decision and/or the requirements for lifting the pause. The PO/loR will follow the guidance provided by the PO in the suspension letter.

In the event of a suspension, if the CRS has met the requirements and conditions to resume trial activities, then the RE/RA, IRB/EC, the HIV/AIDS Network and/or DAIDS may lift the suspension per their procedures.

## 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. [DAIDS Protocol Registration Manual](#)

## Version History

V1.0	1/19/2021	Original Version
V2.0	10/2/2023	Pg 3, 5 - Added language to include Network initiated suspensions.  Simplified CRS instructions with notification of suspension/pause; instructions will be included with the notification memo.