



Division of Acquired Immunodeficiency Syndrome Regulatory Affairs Branch Guidance for Determining the Appropriate Use of Full Version Protocol Amendments, Letters of Amendment, and Clarification Memos during the Lifecycle of a DAIDS- Approved Protocol

1.0 PURPOSE

This guidance document was developed to assist Protocol Teams, Division of Acquired Immunodeficiency Syndrome (DAIDS) staff, and other stakeholders, in choosing the appropriate method for clarifying or making changes to a DAIDS approved protocol. The three methods are Full Version Protocol Amendment, Letter of Amendment (LOA) and Clarification Memo (CM). This guidance document also includes information for when it is appropriate to use an Urgent Safety Notification.

2.0 SCOPE

The methods described in this guidance document for protocol changes and clarifications apply to all DAIDS supported and/or sponsored IND and Non-IND studies. Because these methods are DAIDS specific, they may not apply to clinical trials in which DAIDS is not the sponsor. The Sponsors Authorized Representative (SAR) within the DAIDS Regulatory Affairs Branch (RAB) should be consulted if there are any questions related to implementing any protocol clarifications or changes.

3.0 BACKGROUND

Due to the large portfolio of international trials supported and/or sponsored by DAIDS, a method has been established to expedite the process for implementing protocol modifications at both domestic and international sites. In 2000, DAIDS RAB developed an alternative to a Full Version Protocol Amendment for making protocol changes to streamline and expedite the protocol modification process. DAIDS RAB began utilizing the LOA to quickly implement protocol changes for both domestic and international trials. The LOA was initially utilized as a method to extend the protocol drug regimen for participants until the study drug was available. Since the introduction of this alternative to the Full Version Protocol Amendment, the LOA has been used to make changes in hundreds of protocols including those conducted outside the United States. Clarification memos have been successfully used for many years by protocol teams to provide additional detail to language already existing in the protocol.

4.0 DEFINITIONS

- 4.1 Full Version Protocol Amendment: Protocol modifications that result in a change in protocol version number. This new protocol version incorporates any currently proposed changes in addition to those made in all CMs and LOAs that have been approved since the finalization of the previous protocol version.

- 4.2 Letter of Amendment (LOA): A letter that makes a limited number of modifications to the protocol as an alternative to a Full Version Protocol Amendment. A LOA does not change the protocol version number and is considered part of the previously approved protocol version (e.g., Protocol Version 1.0, LOA #1, LOA #2, etc.). All LOAs are submitted to the FDA for IND studies.
- 4.3 Clarification Memo (CM): Document written by the Protocol Team, after a full version of a protocol (e.g. Version 1.0, 2.0, etc.) has been distributed to site(s), which provides further explanation or details to an area of the clinical research that is already present in the protocol.
- 4.4 Urgent Safety Notification: An expedited **DAIDS** letter used to alert investigators, IRBs/ECs and other Regulatory Entities (REs) as required, and study participants of a significant and immediate safety concern related to a study product.

5.0 RESPONSIBILITIES

- 5.1 DAIDS Medical Officer (MO): The DAIDS MO works with the Protocol Team to assess if proposed changes require a Full Version Protocol Amendment, LOA, or CM. The DAIDS MO is responsible for making the final determination regarding the use of a CM. The DAIDS RAB SAR is available for consultation if the DAIDS MO wishes to discuss if a CM is the appropriate method to make the proposed protocol clarification/change.
- 5.2 Sponsor's Authorized Representative (SAR): As a member of DAIDS RAB, the SAR is responsible for reviewing proposed changes and for making the final decision regarding the appropriate method to modify both IND and Non-IND protocols (e.g., LOA vs. Full Version Protocol Amendment).

6.0 PROCEDURE

6.1. Determining the appropriate method for implementing protocol changes or clarifications

- 6.1.1 The three DAIDS approved methods for making clarifications or changes to a protocol are mutually exclusive and apply to both IND and Non-IND protocols. A Full Version Protocol Amendment must incorporate the clarifications and changes included in all previous CMs and LOAs that have been implemented since the last finalized version of a protocol.
- 6.1.2 DAIDS MOs are encouraged to consult with DAIDS RAB if there are any questions related to the appropriate method for making protocol clarifications and/or changes. DAIDS RAB will make a preliminary determination based on a review of the protocol team's draft proposal and the extent to which the changes affect the protocol and sample informed consent.

- 6.1.3 An accurate determination as to the appropriate method used to make changes to a protocol is made by DAIDS RAB once the protocol team has submitted a formal request (e.g., LOA vs. Full Version Protocol Amendment).
- 6.1.4 The final decision to utilize a CM is the responsibility of the DAIDS MO.
- 6.1.5 A protocol must be a final, DAIDS approved protocol (e.g., Version 1.0, Version 2.0, etc.) prior to the approval and implementation of a Full Version Protocol Amendment, LOA, or CM.

6.2 Full Version Protocol Amendment

- 6.2.1 A full version protocol amendment is utilized when required changes to a protocol are substantive in number and/or nature.
- 6.2.2 A full version protocol amendment results in a new protocol version number (e.g., Version 2.0, 3.0, etc.).
- 6.2.3 Protocol changes made via a Full Version Protocol Amendment are incorporated directly into the protocol document. A Full Version Protocol Amendment must incorporate all CMs and LOAs previously implemented since the last DAIDS approved version of the protocol.
- 6.2.4 In order to maintain GCP, at the time of LOA review and approval, the DAIDS RAB SAR may determine that any future changes to the protocol must be made via a Full Version Protocol Amendment. This requirement may result due to the number of LOAs that have been implemented under the current protocol version.
- 6.2.5 The following examples require a Full Version Protocol Amendment:
 - 6.2.5.1 The protocol has identified major issues that require changes to the protocol.
 - 6.2.5.2 An increase or decrease of more than 10% of the total number of participants to be enrolled.
 - 6.2.5.3 Any change which results in a change to the protocol design that includes but is not limited to:
 - 6.2.5.3.1 Inclusion of a new study arm.
 - 6.2.5.3.2 Inclusion of a new sub-study.
 - 6.2.5.3.3 Inclusion of a new informed consent form or significant changes to the existing form.

- 6.2.5.3.4 A change in the schedule of study product dosing which results in a higher dosage being given in the study or frequency in which study product is given.
- 6.2.5.3.5 The introduction of a new study product or study product formulation.
- 6.2.5.3.6 If the FDA requires significant protocol changes during the 30-day review period to avoid a clinical hold, a Full Version Protocol Amendment is required before initiating a study.

6.3 Letter of Amendment (LOA)

- 6.3.1 A LOA can be used when there are specific changes to the protocol that result in the addition of new information or the deletion of incorrect or unnecessary information.
- 6.3.2 A LOA must be submitted to the site's IRB/EC and other REs as required for review and approval prior to its implementation.
- 6.3.3 A LOA may result in minor changes to the SIC.
- 6.3.4 If the collective changes being requested by the protocol team are extensive and cannot be implemented easily and immediately, the DAIDS RAB may require the protocol team to develop a Full Version Protocol Amendment.
- 6.3.5 If multiple LOAs have been implemented for a single version of the protocol and additional changes are requested by the team, DAIDS RAB may require the protocol team to develop a Full Version Protocol Amendment to maintain Good Clinical Practice (GCP).
- 6.3.6 The following examples are instances in which a LOA would be the appropriate method to make changes to a protocol:
 - 6.3.6.1 Changes to the volume of blood or number of samples that will be collected at a specific study visit.
 - 6.3.6.2 Changes to the procedures or lab tests that will be conducted at a specific study visit. Any new lab test or procedure should not increase the risk to the participants. The addition of a blood draw would be acceptable while the addition of a lumbar puncture would require a Full Version Protocol Amendment.
 - 6.3.6.3 A change to the inclusion/exclusion criteria that results in slightly broadening parameters to help increase enrollment (e.g., reducing the CD4 count from 350/mm³ to 300/mm³ or increasing the upper age limit from 13 to 17 years of age).

- 6.3.6.4 Allowing a drug treatment substitution or the addition/deletion in background therapy.
- 6.3.6.5 The dropping of a protocol arm based on the recommendation of the Data Safety Monitoring Board (DSMB).

6.4 Clarification Memo

- 6.4.1 A CM provides additional detail or further explanation to information that is already included in the protocol.
- 6.4.2 DAIDS does not require CMs to be submitted to a site's IRB/EC and other REs, and DAIDS does not submit CMs to the FDA for IND protocols. However, sites must follow local IRB/EC review requirements for CMs prior to implementation at a site.
- 6.4.3 The decision to use a CM is the responsibility of the DAIDS MO and does not require DAIDS RAB approval or sign off. DAIDS MOs can consult with DAIDS RAB if there are questions related to the content proposed in a CM prior to making a final determination.
- 6.4.4 A CM does not affect participant safety or the risk assessment of the protocol.
- 6.4.5 A CM does not change the Sample Informed Consent (SIC).
- 6.4.6 The following examples are instances in which a CM would be the appropriate method for implementing a clarification to a protocol:
 - 6.4.6.1 Updates or corrections to phone numbers and/or addresses for protocol team members/laboratories already listed in the protocol.
 - 6.4.6.2 To correct inconsistent information in the protocol (e.g., The schedule of events specifies a lab test or blood volume to be collected at a specific study visit and conflicting information is included in the corresponding section of the protocol document.).
 - 6.4.6.3 To specify a specific type of collection tube to be used for drawing a lab specimen.

6.5 Urgent Safety Notifications

- 6.5.1 This type of notification is used when there is/are significant and immediate participant safety concerns related to a study product, and sites, participants, investigators, and IRB/ECs and other REs as required must be notified in an expedited manner.
- 6.5.2 Urgent Safety Notifications are written as Dear Investigator and Dear Participant Letters.

6.5.3 Urgent Safety Notifications are submitted to the FDA for IND studies and to the participating sites for submission to their IRB/EC and other REs as required for both IND and Non-IND studies.

6.5.4 The IRB/EC is responsible for determining the appropriate method for informing the participants of the information and for determining the appropriate methods for consenting participants. It will be determined at the time of the Urgent Safety Notification if a Full Version Protocol Amendment will be required (see Section 6.2 Full Version Protocol Amendments).

6.6 Summary of Operational Requirements for Protocol Modification

	Full Version Protocol Amendment	Letter of Amendment	Clarification Memo
IRB/EC Approval Required	YES	YES	NO*
Submitted to FDA (IND studies)	YES	YES	NO
Protocol Registration Required	YES	YES	NO
Copy Sent to Drug Company Collaborator	YES	YES	NO
RAB Makes Final Determination	YES	YES	NO
Change in Protocol Version Number	YES	NO	NO

* DAIDS does not require IRB/EC or other RE approval of CMs. Each site must follow the requirements of their IRB/EC and other REs as required prior to implementation.

7.0 INQUIRES

Questions and comments regarding this guidance document can be directed to the DAIDS Regulatory Affairs Branch at DAIDSRAB@niaid.nih.gov.

8.0 DOCUMENT HISTORY

Version Number	Approval Date	Approved By	Document Author
Version 3.0	May 31, 2018	Mary Anne Luzar, Ph.D. RAB Branch Chief	Mary Anne Luzar, Ph.D.
Version 2.0	May 1, 2012	Mary Anne Luzar, Ph.D. RAB Branch Chief	Mark Mishkin, M.P.H.
Original / Version 1.0	March 31, 2000	Mary Anne Luzar, Ph.D. RAB Branch Chief	Mary Anne Luzar, Ph.D.

9.0 REFERENCES

- 9.1 21 CFR 312.30 – Protocol Amendments
- 9.2 ICH Guideline for Good Clinical Practice E6(R2) 4.5 – Compliance with Protocol

10.0 SIGNATURE



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