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1.0 PURPOSE

1.1 The purpose of this policy is to describe the DAIDS' protocol change and clarification methods for National Institute of Allergy and Infectious Diseases (NIAID) Division of AIDS (DAIDS) sponsored and/or funded clinical research.

2.0 SCOPE

2.1 This policy applies to all clinical trials (IND and Non-IND) for which DAIDS serves as the regulatory sponsor and/or funder. Because these protocol change and clarification methods are DAIDS specific, they may not apply to clinical trials in which DAIDS is not the regulatory sponsor.

3.0 DEFINITIONS

For additional definitions, see DAIDS glossary

3.1 Full Version Protocol Amendment: A full version protocol amendment is utilized when changes to a protocol are substantive in number and/or nature. A full version protocol amendment includes any changes to the protocol including the sample informed consent and incorporates information in clarification memos (CMs) and Letters of Amendment (LOAs) that have been issued since the finalization of the previous version of the protocol. All full version amendments result in a change in protocol version number. All full version amendments are submitted to Institutional Review Boards (IRBs)/Ethics Committees (ECs) and other Regulatory Entities (REs). All full version amendments are submitted to the U.S. Food and Drug Administration (FDA) for studies being conducted under an Investigational New Drug (IND) application.

3.2 **Letter of Amendment (LOA):** A letter that makes a limited number of modifications to the protocol on an expedited timeline as an alternative to a Full Version Protocol Amendment revision process. An 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 IRBs/ECs/REs. All LOAs are submitted to the U.S FDA for studies being conducted under an IND.

3.3 **Clarification Memo (CM):** A document that provides further explanation or details on information already present in the full version of a protocol. A CM does not change the protocol version number and is considered part of the previously approved protocol version (e.g., Protocol Version 1.0, CM#1, CM #2, etc.). CMs do not require submission to IRB/EC/RE unless required by institutional and/or IRB/EC policies. Clinical Research Sites (CRS) must follow local IRB/EC/RE review requirements for CMs prior to implementation at a site. CMs are not submitted to the U.S. FDA.

4.0 RESPONSIBILITIES

4.1 **DAIDS Medical Officer (MO):** The DAIDS MO works with the Protocol Team/Protocol Principal Investigator to assess if proposed modifications require a Full Version Protocol Amendment, LOA, or CM. The DAIDS MO approval and sign-off is required for a Full Version Protocol Amendment, LOA, or CM.

4.2 **DAIDS Regulatory Affairs Branch (RAB) Sponsor's Authorized Representative (SAR):** The RAB SAR is responsible for reviewing the proposed modification and for making the final decision regarding the appropriate method to change or clarify the protocol. The RAB SAR approval and sign-off is required for Full Version Protocol Amendments, and LOAs. For CMs, the RAB SAR provides a determination if a CM is appropriate, however the RAB SAR does not provide final approval or sign-off on CMs.

5.0 POLICY

5.1 This policy has been created to ensure that all protocol changes are done in accordance with U.S. regulation 21 CFR 321.20 and ICH Good Clinical Practice (GCP) E6(R2), 4.5 Compliance with Protocol.

5.2 The Protocol Team/Protocol Principal Investigator should conduct the clinical trial in compliance with the protocol approved by DAIDS as the sponsor and that has been given approval/favorable opinion by the IRB/EC/RE. The CRS Investigator of Record (IoR) must sign the protocol signature page to confirm agreement.

5.3 The Protocol Team/Protocol Principal Investigator and CRS IoRs should not implement any deviation from, or changes to the protocol without approval from DAIDS as the sponsor and without prior review and documented approval/favorable opinion from the IRB/EC/RE.

5.4 The Protocol Team/Protocol Principal Investigator must use a DAIDS' protocol change or clarification method outlined in this policy for all DAIDS sponsored clinical trials.

5.5 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.

6.0 REFERENCES

6.1 21 CFR 312.30, Code of Federal Regulations Title 21

6.2 ICH Guideline for Good Clinical Practice E6(R2) 4.5 Compliance with Protoco

7.0 APPENDICES

7.1 DAIDS-OPC-A15-GUD-00008,Protocol Change Process Job Aid

8.0 REVISION SUMMARY

8.1 POL-A15-OPC-018.00 is the original version of this policy. The policy had been in effect since March 2000 (updated in May 2012, Version 2.0 and updated in May 2018, Version 3.0) in the form of a guidance document.

8.2 DAIDS-OPC-A15-POL-00018 rev 01 is the first revision of this Policy in MasterControl. The document format and numbering were updated to reflect current requirements.