MTN Protocol Deviations Policy

(Excerpted from MTN 2017 Manual of Operational Procedures – Section 16.4)

Oversight of Reportable Protocol Deviations

The U.S. Food and Drug Administration's (FDA) Compliance Program Guidance Manual, Inspectional Chapter, Section D3, defines a protocol deviation (PD) as "generally an unplanned excursion from the protocol that is not implemented or intended as a systematic change." A PD can occur for many reasons, some of which are unforeseen. Every clinical researcher should anticipate that deviations will occur and have a policy in place to address them as they arise. A comprehensive MTN Protocol Deviation policy, in compliance with U.S. federal regulations, is a key component of study conduct oversight.

The DAIDS Policy on Source Documentation Requirements Appendix (https://www.niaid.nih.gov/sites/default/files/sourcedocappndx.pdf), Policy number DWD-POL-CL-04.00A1, states the following:

> *All protocol departures/deviations/violations must be recorded in the subject's research record. If pertinent, reasons for the departures and/or attempts to prevent or correct the departures are to be included in the documentation…. Examples of departures and appropriate documentation: a) a missed visit needs a note stating it is a missed visit and the site's attempts to locate the subject to request that he/she come in to make up that visit.… Departures from protocol also include incomplete laboratory evaluations, physical assessments, questionnaires, etc. If the vital status of a subject is known during the time period that a visit was missed, that information and the means by which it was obtained (e.g., telephone contact, conversation with relative, or other medical records, etc.) should be reflected in the subject's research record.*

Pervasive and persistent trends in PDs as well as other performance metrics could result in the temporary suspension of the study at the site by OCSO/DAIDS. (See *Office of Clinical Site Oversight Standard Operating Procedure for Temporary Suspension of Clinical Research Site Activities*, Number OCS-014 [https://www.hanc.info/resources/Documents/Forms/AllItems.aspx].) Persistent trends in PDs could also result in FDA or another regulatory body electing not to use site study data in its consideration of the product's approval. Early identification of PD trends allows for swift corrective and preventive actions and better ensures overall good study conduct and good quality data to support potential licensure of the product.

For each MTN study that opened to accrual on or after June 1, 2012, PDs will be reported to the SDMC via a CRF. Questions will be fielded by the study FHI 360 CRM and the MTN Regulatory Group, and the study management team will routinely review the reported PDs.

Central reporting of all PDs will provide:

- The ability to identify areas for retraining or other corrective and preventive actions
- The ability to identify areas of the protocol that may need to be clarified

- Information that will allow MTN to fulfill reporting obligations to Investigational New Drug (IND) sponsors for their submissions to FDA and other regulatory bodies

The PD policy stipulates the following:

1. All deviations from the protocol will be reported to the SDMC within the time frame and according to the specifications included in the Study Specific Procedures (SSP) Manual for that protocol. Most PDs will be reported on a PD CRF, but others (such as missed visits and study regimen non-adherence) may be reported on other specific CRFs. Any questions from sites about PDs should be sent to the FHI 360 CRM for the study, who will consult with the MTN Regulatory Group (mtnregulatory@mtnstopshiv.org) as needed.
2. Some, but not all PDs, may be considered critical events, per the DAIDS policy *Identification and Classification of Critical Events; Site Responsibilities* [https://www.niaid.nih.gov/sites/default/files/cesiteresp.pdf]. As per that policy, sites are required to promptly report critical events directly to DAIDS and to their local IRB/IEC.
3. Per the FDA and International Conference on Harmonisation (ICH) E6 Good Clinical Practice (GCP) regulations, PDs are allowed to occur without prior sponsor and Institutional Review Board (IRB)/Independent Ethics Committee (IEC) approval, *only when the need arises to eliminate apparent immediate hazards to study participants* (ICH GCP Guidance for Industry Section 4.5.2, 4.5.4; 21 CFR 312.66; 21 CFR 812.35[a] [2]). Although allowable, these PDs must be reported to both the study sponsor and the site's local IRB/IEC within a specified amount of time and per local institutional policies.
4. Questions regarding potential anticipated protocol deviations due to participant noncompliance, such as an upcoming study visit that a participant does not expect to be able to attend, should be referred to the MTN Regulatory Group unless directives for managing this have already been provided in the protocol or SSP Manual.
5. Sites are to follow local requirements regarding reporting PDs to local regulatory bodies.
6. Each site must maintain a central file of deviations and make it available to the MTN Leadership, DAIDS, protocol teams, the Network Evaluation Committee (NEC) and other MTN groups upon request. The SDMC will maintain on ATLAS (an online interface maintained by the SDMC that provides secure access to data, reports and analysis tools) a summary listing and table of PDs, including missed visits (reported on a separate CRF) for each study.
7. On at least a monthly basis, the study management team will review the ATLAS reports of PDs and related Corrective and Preventive Action plans (CAPAs). The study management team, Protocol Chairs or FHI 360 CRM will communicate with any site regarding suggested modifications to CAPAs, and will notify the study team of any trends identified.