17 ANCILLARY STUDIES/INVESTIGATIONS 2

17.1 Ancillary Study Application 2

17.1.1 Management and Analysis of Ancillary Study Data 2

17.1.2 Additional Considerations for Ancillary Studies Using Stored Biological Specimens 2

17.1.3 Operational Management of Ancillary Studies and Completion of the Application Form 3

17.2 Ancillary Study Review and Approval Process 4

17.2.1 Protocol Chair and Team Approval 4

17.2.2 Executive Management Committee (EMC) Approval 4

17.2.3 Development of Ancillary Study Protocol 4

17.2.4 DAIDS Review and Approval of Ancillary Studies 4

17.2.5 IRB/EC Review of Ancillary Studies 5

17.2.6 Site-specific Registration to Ancillary Studies 5

17.3 Funding of Ancillary Studies 5

17.4 Monitoring of Ancillary Studies 5

17.5 Publication of Ancillary Study Results 5

17.6 Documentation of Ancillary Study Approval 5

17 ANCILLARY STUDIES/INVESTIGATIONS

Ancillary studies may involve collection of additional data and/or samples from study participants or use of existing data and/or samples for analyses or laboratory assessments that are not directly related to the specific objectives of the relevant HPTN study as defined in the protocol document.

Ancillary studies may involve HPTN investigators and/or non-HPTN investigators and may be initiated by the primary study team or by investigators inside or outside of the study team and the Central Resources staff of the HPTN. They may involve all sites participating in a primary HPTN study or a subset of sites. Ancillary studies may involve the use of data, biological specimens, or other information obtained through an HPTN study and/or additional procedures related to study participation and may be either prospective or retrospective in nature. Ancillary studies may include surveys or focus groups among primary study participants and laboratory-based investigations using specimens obtained from participants in a primary HPTN study or some combination of the above.

Investigators who are interested in performing an ancillary study must submit an Ancillary Study Application. The process for proposal, review, and approval of ancillary studies is described below.

Note that laboratory assessments performed at the HPTN Laboratory Center (LC) that are related to the specific study objectives defined in the protocol are not considered ancillary studies; this includes quality assurance/quality control (QA/QC) assessments. Use of HPTN specimens for other purposes beyond the protocol objectives requires submission and approval of an Ancillary Study Application.

Additional considerations for ancillary studies involving use of stored specimens are described in Section 17.1.2.

17.1 Ancillary Study Application

All investigators proposing an ancillary study, whether internal or external to the HPTN, must complete the HPTN Ancillary Study Application. The Leadership and Operations Center (LOC), LC and Statistical Data Management Center (SDMC) should be contacted for input prior to the application being submitted. The completed Ancillary Study Application may or may not be assigned a number by the HPTN Executive Committee (e.g., HPTN 074-01, HPTN 074-02, etc.) that relates the application to a primary HPTN study.

The application should provide the information needed for the protocol team and Network Leadership to assess the merit of pursuing the proposed ancillary study, taking into account its scientific value, accord with the aims of the primary study team and network, consistency with the study consent documents, resource requirements and feasibility.

17.1.1 Management and Analysis of Ancillary Study Data

Plans for handling data generated through an ancillary study must be specified in the Ancillary Study Application. Prior to submitting the application to the HPTN, the investigator is required to discuss with the SDMC plans for data management and analysis and clarify if any input by the SDMC and/or access to primary study data will be necessary. The SDMC may or may not assume responsibility for handling ancillary data.

17.1.2 Additional Considerations for Ancillary Studies Using Stored Biological Specimens

There are additional considerations and requirements for ancillary studies/investigations involving the use of stored biological specimens. These requirements apply to all HPTN organizations, investigators, and other staff members, as well as non-HPTN investigators. The priority commitment of study specimens is the completion of work needed to address the specific study objectives defined in the protocol document.

- Stored specimens may not be used for ancillary studies until the study team leadership has confirmed that all laboratory assessments related to the specific study objectives as well as quality assurance/quality control (QA/QC) assessments have been completed, and that any associated data queries have been resolved. An exception may be granted to allow for release of specimens for ancillary studies prior to completion of this work, if the study team leadership determines that the specimens requested are not needed to complete this work.
- Prior to shipping or using specimens for an ancillary study, the protocol team must confirm that consent was provided for the proposed assays or the proposed work is consistent with the purpose indicated in the consent with regards to the use of stored specimens.

Requests for obtaining stored specimens are included in the ancillary study application process.

If an ancillary study that includes use of biological specimens is approved, the HPTN LC and SDMC will work with the investigators to determine the availability and location of the requested specimens and the procedures needed to transfer the specimens to the appropriate laboratory(ies). For studies that require shipment of specimens to a laboratory other than the HPTN LC, or shipment of samples to the HPTN LC for testing not specified in an existing Material Transfer Agreement, the investigator and/or LC must arrange for the appropriate documentation to be prepared and approved. Any costs related to specimen transfer to a laboratory outside of the HPTN LC will be the responsibility of the investigator proposing the study. In some cases, the ancillary study may require additional testing at the HPTN LC. In those cases, the HPTN LC Principal Investigator (PI) will determine whether the LC is able to do the requested testing, and whether additional funds would be needed for sample shipping or testing. If LC resources are required, this must be indicated on the Ancillary Study Application. Funding issues must be resolved before the ancillary study is approved. If an ancillary study is approved that includes biological specimens, non-HPTN investigators must also complete a Material Transfer Agreement before specimens can be provided. If applicable, a copy of the signed agreement must be attached to the ancillary study application.

17.1.3 Operational Management of Ancillary Studies and Completion of the Application Form

The operational support budgeted for completion of the primary study does not apply to ancillary studies. It is expected that the investigator proposing an ancillary study will be responsible for scheduling conference calls, coordinating study design and protocol development (if necessary), writing informed consent forms (if necessary), obtaining all required approvals (local Institutional Review Board/Ethics Committee (IRB/EC), Ministry of Health (MoH), etc.), handling all budgeting procedures, coordinating implementation at involved sites, etc. If the investigator would like to request that any of these functions be performed by the HPTN LOC, this must be made clear in the ancillary study application along with appropriate budgeting.

The Ancillary Study Application must include details as to what type of Central Resources and budgets are required to complete the proposed ancillary study (if any). If resources are needed at any of these groups, the Ancillary Study Application should specify the relevant Resources needed. Examples of operational elements are processing of samples or data, scheduling conference calls, case report form (CRF) development, protocol development, etc.

These required application elements are described in the Ancillary Study Application form.

17.2 Ancillary Study Review and Approval Process

All ancillary studies are subject to HPTN Network approval and, if applicable, DAIDS approval, as described in sub-sections below. The purpose of the review and approval process is to ensure that site and Central Resources are being used appropriately and that the rights and well-being of human subjects are protected in accordance with United States (US) Code of Federal Regulations (CFR) 45 CFR 46.

17.2.1 Protocol Chair and Team Approval

Ancillary study applications must first receive review and approval from the following before submission to the HPTN EC for review:

- The main study Protocol Chair(s), on behalf of protocol team members
- Representatives of the Central Resources (SDMC protocol statistician, LC and LOC), and DAIDS Medical Officer for the primary HPTN study. (Note: if Central Resources are being requested, the relevant protocol representative should obtain approval for use of these resources from their respective leadership as part of this review step).
- The study product manufacturer (where applicable)

Note: It is the proposing Investigator's responsibility to ensure that all approvals listed above have been obtained. Typically, approvals are communicated via email. Additionally, if study sites will be involved in or affected by the ancillary study, the proposing Investigator should work with the Protocol Chair(s) and Central Resources to determine site needs and the best process for obtaining site agreement.

17.2.2 Executive Management Committee (EMC) Approval

If the Protocol Team approves the Ancillary Study Application, it will be reviewed for approval by the HPTN EMC.

17.2.3 Development of Ancillary Study Protocol

Ancillary studies may require development of a separate protocol, potentially including a separate informed consent form. Depending on the nature of the ancillary study, a protocol number may be assigned at this stage. A separate informed consent requirement is dependent on the nature and scope of the investigation and the language included in the consent forms for the primary study. For example, if the ancillary study involves additional procedures, specimens, or visits and/or involves different risks and benefits than those described in the primary study informed consent form, separate informed consent for the sub-study would be required. Investigators will work with the HPTN LOC and DAIDS to determine whether a separate protocol and written informed consent are needed. If needed, these documents must be developed and then reviewed and approved by the Protocol Team prior to undergoing the DAIDS review process. The ancillary study protocol chair will work with the LOC CRM to determine timeline and development process.

17.2.4 DAIDS Review and Approval of Ancillary Studies

After EMC approval, ancillary studies may be subject to additional DAIDS review and approval. The necessary DAIDS approval steps for ancillary studies may vary depending on the scope and nature of the activity/investigation and whether it is prospective or retrospective. Investigators will work with the LOC and DAIDS to determine the necessary steps for each specific investigation. The DAIDS Medical Officer for the primary study will work with the DAIDS Prevention Science Review Committee (PSRC) Chair to determine if a proposed ancillary study requires PSRC review based on the description of the proposed activity in the ancillary study application.

17.2.5 IRB/EC Review of Ancillary Studies

It is the responsibility of each participating site investigator or record of the ancillary study to ensure all approvals or exemptions are documented. If the study will take place at multiple US sites, it may be appropriate to utilize the HPTN single IRB (sIRB), or another contracted sIRB. The LOC will work with the proposing investigator to make this determination. Resources for use of an sIRB, if required, must be included in the ancillary study budget. If the ancillary study requires separate written informed consent, the consent form must be reviewed by the DAIDS Regulatory Affairs Branch (RAB) or its Regulatory Support Center (RSC) prior to finalization and submission to the responsible Institutional Review Boards/Ethics Committees (IRBs/ECs) or written confirmation from DAIDS RAB/RSC that review is not required must be obtained. Informed consent forms for ancillary studies must adhere to United States (US) federal requirements for inclusion of the essential elements outlined in 45 CFR 46, and the informed consent template followed for HPTN studies should serve as a guide in the development of the form.

17.2.6 Site-specific Registration to Ancillary Studies

Registration of the sites to the ancillary study may be required. The procedures and requirements for registration are detailed in the DAIDS Protocol Registration Manual (also see Section 10.10).

For ancillary studies requiring protocol registration with the RSC, no study-specific activities can begin until the site has received written notification from DAIDS that all registration requirements have been completed.

17.3 Funding of Ancillary Studies

Ancillary studies may be performed with HPTN funding, with funding from other sources, or a combination. The proposed source of funding will be specified in the application. If HPTN funding is in excess of that allocated for a primary HPTN study is needed to conduct an ancillary study, the HPTN EC will determine how these funds may be made available, if warranted.

17.4 Monitoring of Ancillary Studies

If funded by the HPTN, an ancillary study may be monitored by the Clinical Site Monitor, if specifically requested by DAIDS.

17.5 Publication of Ancillary Study Results

All data analyses, presentations, and publications resulting from ancillary studies will be prepared and reviewed in accordance with relevant DAIDS and HPTN policies (see Section 21). Acknowledgement of HPTN should be done as per HPTN policies and procedures.

17.6 Documentation of Ancillary Study Approval

Copies of all HPTN, regulatory, and IRB/EC and/or sIRB approvals (if applicable) must be maintained on file by the study site, and the lead Investigator, designee, or the LOC, as applicable.