Infectious Diseases Clinical Research Consortium

9a. Protocol Development and Review

9a.1 Development

Once a concept is approved for protocol development, protocol team (PT) formation begins. Each PT will include:

- Protocol Chair (PC) (and Co-Chair as appropriate)
- Protocol Specialist (PS) from FHI 360
- Research Assistant from FHI 360
- OCRR Program Officer
- DMID Clinical Project Manager (CPM)
- Data Manager and Biostatistician from Statistical and Data Science Unit (SDSU).
- Data Manager and Biostatistician from DMID Statistical Data Coordinating Center (SDCC) as appropriate (Both parties will work together on statistical design considerations; the SDSU may be tasked with full support responsibilities for low risk/ non interventional protocols).
- Site Investigators (SI)
- NIH representatives (Medical Officer, Medical Monitor, Regulatory Affairs Specialist, Clinical Affairs Specialist as appropriate)
- Representative from the LOU as appropriate

Other members of the PT may include:

- Scientific experts from the Expert Working Group (EWG) such as a pharmacologist, virologist, immunologist, behavioral scientist, ethicist, or other expertise
- Leading experts who may or may not be affiliated with an IDCRC or VTEU institution
- Junior investigator(s) participating in an investigator development program at one of the VTEUs (serving in a Co-Chair capacity, for example)

9a.2 Protocol review process

Protocols are developed through an iterative review and revision process. The PT communicates frequently via email, conference calls, and virtual meetings. Such meetings are generally expected to include team members with key writing responsibilities rather than all members. Additionally, at least one ½ day virtual meeting should be held with the entire team to resolve significant issues in real time and finalize sections of the protocol, with the appropriate timing agreed upon by the team. .

9a.3 Protocol Chair and Protocol Specialist Roles and Responsibilities

9a.3.1 Protocol Chair

The PC is usually the primary author/investigator of the IDCRC protocol. In addition to duties as a PT member, the PC (or designee) is responsible for:

- Providing overall leadership and guidance to the PT throughout the development of the protocol.

- Establishing and maintaining an efficient schedule of conference calls (documentation of calls and decisions via meetings minutes), and meetings involving all members of the PT to ensure appropriate development.
- Coordinating the establishment of assigned tasks to achieve efficiency in the development of the protocol.
- Facilitating final decision-making within the PT to achieve agreement on scientific or operational issues; if agreement cannot be reached, referring the issue to the Executive Management Team (EMT) for consideration.

9a.3.2 Protocol Specialist

The PS is provided by the Project Director, FHI 360, and will maintain the integrity of the Protocol, as well as document all key decisions made during protocol development. FHI 360 staff will adhere to DMID guidance on version control. The PS will work very closely with the PC to:

- edit protocol, ensuring all PT and other internal and external comments are tracked and resolved and incorporated.
- create and provide basic informed consent outline.
- facilitate and track all protocol and informed consent revisions.
- alert the study DM and study biostatistician to begin CRF question review.
- identify and maintain communication with protocol team members via email and/or conference call; other calls outside of the Protocol Team will be organized as needed.
- facilitate DM interaction with the PT.
- collaborate with the CPM to coordinate submission of protocol and other appropriate documents to the appropriate authorities(internal at DMID, to the FDA for example) for review and approval.

In addition to the routine protocol team calls, the PC and PS will have separate weekly calls together to prepare PT call agendas and minutes discuss document comments/edits ahead of calls to ensure team calls progress smoothly and efficiently, review action items and potential issues and barriers. The PS may also have separate and individual calls with the assigned CPM to discuss timeline ,review schedules and other protocol development processes as needed. .

9a.4.0 Process

Following approval to develop an Expanded Concept Plan (ECP) into a protocol, the following actions will take place:

- The PS populates the NIAID-DMID eCTD protocol template with the information from the approved concept.
- The PS will insert and/or complete logistical sections of the protocol.
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- The PS will send the updated version (v0.1) of the protocol to the PCs for review and discussion prior to team call.
- The PC will lead a discussion on writing assignments (sections of the protocol may be assigned to team members for efficiency. Such as the SDSU Lead Protocol Statistician assigned to write the statistical section and the interim monitoring plan).
- Draft sections will be reviewed on team calls; changes incorporated by the PS either pre- or post- call depending on team preference.

- If, during the revision process, the PC wishes to make modifications to the approved concept proposal components, the PS must inform the FHI 360 Project Director who will discuss with the Clinical Operations Unit (COU). The COU leadership will determine if these are substantive or not.
- The COU will inform the EMT about substantive changes and appropriate communication with the PC and/or PS will be initiated.
- Non-substantive edits can be made by the PS (edits that do not change objectives and/or endpoints and do not impact overall sense of originally approved protocol and/or lead to budget increases).
- The PS will keep track of all changes in meetings minutes (the discussion points should be noted; rationale for changes maintained; impact on timelines; product needs etc.).
- The PC and PS will draft an informed consent (IC) form based on the agreed-upon template that complies with sIRB, DMID policies, FDA, and ICH requirements. IC forms will include those sections required in the DMID Informed Consent Master Checklist.
- The PS will begin (and maintain) a protocol timeline (standard or fast-track; see below).

For efficiency, the PT should prioritize development of the study schema, which includes the study objectives, design, and eligibility criteria first, followed by the schedule of evaluations. Development of other sections of the protocol (e.g., background and rationale) may proceed concurrently with work on the schema, design, and eligibility criteria. Once such agreement is achieved, these sections should generally not be re-visited. . All other sections should then be developed based on the agreed-upon content of these sections. Each study objective should be clearly associated with one or more study outcome measure, and all outcome measures should correspond with at least one study objective, and should take into consideration requirements for submitting study results of primary and secondary objectives to ClinicalTrials.gov.

The team will continue to expand and refine the draft protocol and other appropriate documents. These documents will include but not be limited to the ICs, a timeline and any others as deemed necessary by the team and the CPM and/or outlined in the relevant award.

Throughout the process of development, the PS will discuss any needed DMID reviews with the CPM. Up to two DMID-CROMS Quality Crosswalk Reviews per protocol may be conducted, as appropriate and per DMID request received. The first review occurs late in protocol development and includes the late draft protocol, Investigator's Brochure or current package insert, and informed consent form template(s). During the first quality review:

- Protocol is reviewed against the Investigator's Brochure or package insert to verify that all relevant information is present
- Protocol sections are reviewed for consistency and completeness
- Informed consent form template is reviewed against the protocol document to verify all relevant information is present
- Informed consent form template is reviewed for required elements and text.

Reviewers complete the CROMS Quality Crosswalk Review Form. Crosswalk Review comments are non-binding recommendations; however, the issues identified should be carefully considered for potential to disrupt or undermine study conduct. The CPM routes the completed form to the PS who is responsible for summarizing comments in a table, circulating to the PT and collating feedback, and incorporating any agreed upon edits into the protocol and informed consent form template.

A second review may be requested even if a first quality review was not conducted. A second quality review may occur after the final protocol and associated study documents are available and includes the following documents: the final protocol (version 1.0 or higher), Investigator's Brochure or current package insert, informed consent form templates, MOP, Case Report Forms (CRFs), and Study Product Accountability Logs and/or Pharmacy worksheets or forms. If requested, the second review involves the same activities as the first review plus verifying CRFs, the MOP, and any other associated documents are consistent with the protocol. The process for receiving, disseminating, and incorporating Crosswalk Review comments is identical to procedures outlined for the first quality review.

DMID will be responsible for preparing and submitting an IND for any studies sponsored by the NIAID. The PS will work closely with the CPM to assist with content from the PT that is required for preparation of the IND.

During the development phase the EWG will regularly review the progress of the PT via summary reports provided by the PS. The EWG may also review interim versions and provide guidance to the team. These protocol reviews will be conducted during a routine meeting of the EWG. Typically, two reviewers will be assigned to review the draft protocol. The EWG may invite the protocol Chair (or Co-Chairs) to present updates on the progress of the protocol and key decision points yet to be finalized. The EWG members will ask questions of the protocol Chair (or Co-Chairs) in this open session. Next a closed session of the EWG will occur where the two reviewers will address confidential comments to the EWG. The EWG will provide guidance to the PT regarding required changes to the protocol document within three working days of the EWG conference call. Since the EWG meets monthly, the team will have three weeks to reply to the EWG with a revised version of the protocol

For protocols on fast track for approval the EWG Co-Chairs will review and comment in lieu of a full EWG review. Should an EWG Co-Chair be a member of the protocol team another member of the EWG will be selected to conduct the review. These reviews should be expedited and completed within a minimum of one working week from receipt. For protocols that have undergone any form of expert review prior to EWG review, a review by only one Co-Chair, or one EWG member may be considered.

DMID standard version control will be maintained.

9a4.1.1 Distribution of Protocol Version 1.0

Upon receipt of the final DMID CPM approval notification, the PS electronically distributes the final approved protocol Version 1.0 to the PT and participating study sites, or works with the Study sponsor to distribute if the trial is not under a DMID IND. For protocols under IND the main study documents will be controlled by the SDCC and housed on their website.

For studies not under IND study documents will be housed on the study SharePoint portal.

Many pre-implementation activities begin during the protocol development process, while others are dependent upon the distribution of the final, IRB approved protocol. See Section 13 of this manual for details regarding pre-implementation activities.

9a.4.1.2 Timeline for Study Development

There will be studies proposed that follow a standard pathway to development approval, and studies that will be proposed for rapid development and approval, i.e. fast-track protocol.

9a.4.1.3 Standard Development Process

In general, for a standard (i.e., non-emergent) protocol, the team will have reviewed and agreed upon the following by the end of the first month of performance:

- Baseline draft version of the protocol,
- Study implementation timeline, and
- Safety assessments and other plans as appropriate.

The PS and CPM will work together to ensure that a full review of the protocol and supporting documents are ready for final review by end of the fifth month of development. This will include a final review by the full protocol team.

9a.4.1.4 Fast Track Development Process

For a fast-track protocol, the timeline from approval of the concept to near-final version of the protocol will be approximately four weeks. DMID representatives will work closely with the IDCRC appointed team to ensure the appropriate reviews are completed (for example a Clinical Science Review may occur at the early stage, and in parallel with, protocol development). Exclusive of FDA review, this accelerated timeline will produce a DMID-approved protocol version 1.0 within eight weeks of approval of the concept.

For non-interventional protocols, a report by the VTEU PIs may be substituted as a Clinical Study Report.

9a.4.1.5 Study Timeline

As protocols are developed, the PS and CPM will establish a study timeline. This includes timeframes for protocol development plus IND submission if needed, Data Collection Form and database development, regulatory reviews, and approvals (FDA and IRBs), acquisition of study materials, study site activation, enrollment projections, enrollment completion, data analysis, and completion of a clinical study report (CSR) as applicable.

9a.5.0 Protocol Development Oversight

While protocol development is the responsibility of the PC and PT, the COU will receive regular updates on progress from FHI 360. The COU will provide routine reports to the EMT. For protocols that are not meeting established timelines the COU will discuss with the PCs and PS what barriers or processes need to be addressed. If necessary, the COU will recommend that the PC be invited to join an EMT call to discuss progress and remediation plans.

9a.6.0 Protocol Modifications

Protocol amendments may be required for a variety of reasons: changing knowledge about the rationale for the study, new safety information, and possibly modifications to inclusion or exclusion criteria, for example. Modifications made via a full version protocol amendment are incorporated directly into the protocol document and result in a new protocol version number. The PS is responsible for working the with PC and team to develop the amendment for both IND and non-IND protocols. The PT will also consider the need to make corresponding modifications to the informed consents and discuss any potential reconsent requirements. The protocol amendment process should include a recommendation for re-consent need, and the logistical requirements required to re-consent subjects, prior to IRB submission, however it is understood that institutional IRB guidance will always be followed. The final IRB-approved clean and tracked change protocol amendment and master informed consent template (if applicable) as well as a table summary of changes are submitted to the CPM for DMID review and approval.

Protocol modifications may only be implemented after the documents have been moved forward for review by DMID (Sponsor) and IRB (sIRB) and been fully approved.