13. Study Implementation

This section provides guidance on key components of the study implementation process: protocol team responsibilities and communication structure, screening and enrollment, study documentation, data management activities, and other implementation activities. For details regarding study monitoring and oversight, see IDCRC MOP Section 14 (Study Oversight).

For details regarding activities that must be completed before an IDCRC study can be opened to accrual, see IDCRC MOP Section 9 (Protocol Development) and Section 12 (Pre-Implementation).

13.1 Protocol Team Responsibilities

The protocol team (PT) is established during the protocol development period as defined in IDCRC MOP Section 9 (Protocol Development). Processes started during development (e.g., protocol team calls) continue throughout the life of the protocol; the frequency may be modified during implementation at the direction of the DMID Clinical Project Manager (CPM), protocol chair (PC), or co-chairs (PCs) and team.

During implementation, the PT will have standing meetings as detailed in Table 13-1 to facilitate management and oversight of study activities at the site(s), laboratories, and data coordinating center (either DMID SDCC[1] or IDCRC SDSU[2]):

Protocol Team management / oversight activities include the following. In general, these activities will be overseen by the PCs working closely with the protocol specialist (PS) and relevant partners (for example, data coordinating center; DMID partners):

- Engagement in standing and ad hoc protocol team meetings and other communication to ensure timely notification of decisions, completion of tasks, identification and resolution of protocol related issues
- Review of routine study metrics including screening, enrollment, AEs/SAEs, protocol deviations (PDs), data queries, lab data and sample quality, and other operational data though formal reports produced by data coordinating center (Emmes or SCHARP) as well as informal reporting through regular calls / meetings
- Review of External Monitoring Reports (produced by DMID contractor) and response to findings as indicated
- Escalation as needed of identified risks to data and sample quality, safety of subjects, timeline,

[1] The Emmes Company serves as DMID's Statistics and Data Coordinating Center (SDCC) for most IND studies conducted under the IDCRC.

[2] The Statistical Center for HIV/AIDS Research and Prevention (SCHARP) at the Fred Hutchinson Cancer Research Center is the Statistics and Data Sciences Unit (SDSU) for the IDCRC. The SDSU also serves as the data coordinating center on non-IND studies under the IDCRC and some IND studies when requested by DMID.

budget, and continuing non-compliance with DMID guidance, ICH GCP standards, etc.
- Drafting and implementation of protocol amendments following the review and approval process as described in IDCRC MOP Section 9 as modifications to the protocol and IC are identified
- Maintenance / revision of protocol-specific Manual of Procedures (MOP) using version control
- Maintenance of protocol timeline created during the development phase
- Maintenance of protocol decision log to document significant decisions and modifications
- Review and regulatory submission of safety data as appropriate

For a detailed description of study oversight activities such as external monitoring, see IDCRC MOP Section 14 (Study Oversight).

13.2 Protocol Team Communications

After initial release of a draft or final version study protocol, several types of study-related communications may be used to report on study progress or provide further clarification of protocol-specified procedures and study documentation requirements.

Table 13-1. Protocol Team Communications

Communication Type	Description
Protocol Team Calls	• Protocol teams (including site representatives) and Operating Unit representatives take part in routine virtual meetings/calls throughout study implementation; all members take part in scheduled calls or meetings as able. • Typically led by the PC or the FHI 360 PS as appropriate, scheduled and facilitated by PS. • Focus is status of protocol, overview of screening and enrollment, protocol deviations, serious or unexpected AEs, product needs (as appropriate), site-specific status/needs, site challenges, etc. • Agendas developed with PCs, PS, DMID representatives and shared with team in advance of call. • Call summaries are typically prepared and distributed by the FHI 360 team within 5 working days. Meeting and conference call summaries will list all participants and action items.
Management Team Calls	• For some protocols, there may be a need to have meetings of a smaller "management" team including PCs, DMID representatives, data managers, Laboratory Operations Unit (LOU) representative, Clinical Operations Unit (COU) representative, and PS to discuss higher level issues such as protocol revisions, team issues needing clarifications, PDs risks/challenges, etc. The decision of which sub-calls to have will be a decision by the PCs and CPM. • Similar to PT meetings, the PS will facilitate scheduling, development of the agendas, minutes, etc. Depending on the protocol, these may be standing or ad hoc.
Safety Meetings	• Safety Monitoring Committee (SMC) and Data Safety Monitoring Board (DSMB) may be convened per protocol and at the discretion of the sponsor (DMID or other sponsor); these are convened and coordinated by the study

	sponsor.
All-site email messages	• Protocol teams often provide key study-related updates or milestones to site representatives via email (e.g., participant accrual, closure of follow-up).
Memoranda	• When protocol-specified or other important study implementation decisions require communication to sites (e.g., study drug dose-finding or cohort progression decisions), these may be communicated in a memorandum that is reviewed by the protocol team and then distributed to all sites via email. • Prior to distribution of any such communication, agreement must be obtained from at least one protocol chair (chair, co-chair, or vice chair), one protocol statistician, one protocol data manager, and the DMID medical officer. • The process of preparing, obtaining review and consensus, and distributing this type of communication is coordinated by the PS.
Weekly Status Updates and Monthly Protocol Progress Reports	• FHI 360 provides a high-level summary of weekly progress for active protocols to the COU, LOC and DMID. Additionally, the FHI 360 PS drafts protocol progress reports documenting important dates and milestones, accomplishments and study progress, issues and resolutions, timelines, accrual and completion reports, which are shared with the COU, LOC and DMID on a monthly basis.
Protocol amendments with an attendant summary of revisions	• These documents are developed and issued as described in IDCRC MOP Section 9. Development of these documents is coordinated by the PS with DMID, and final versions are distributed to all protocol team members and study sites. Final versions are also posted on the appropriate site (FHI 360 SharePoint / EMMES website).
Study-specific MOP updates	• As with the initial MOP version, development of the updated version is coordinated by the PS and final versions are posted on the study SharePoint (SP) site, as described in IDCRC MOP Section 12 (Study Pre-Implementation Activities). • For MOPs created and managed by EMMES, updates will be managed by the appropriate data manager and be posted to the Emmes CRID website.
Accrual / Retention, Data Quality Reports	• Data reports on study progress, protocol adherence, data quality, etc., are developed and issued by the data coordinating center (EMMES or SCHARP)
Refresher trainings / conference calls with site staff	• Refresher trainings and conference calls for study coordinators and other site staff with the PS, data manager, laboratory representative and other PT members are held as needed, and for some studies on a routine basis. • These sessions provide a forum for discussion of study implementation challenges, clarification of operational aspects, review of protocol updates (i.e., associated with amendments and clarification memoranda) and other topics suggested by site staff.

13.3 Protocol Team Meeting Guidelines

Protocol team members should attend standing calls to contribute their perspective or expertise to discussions and decisions as well as to stay abreast of study progress and team decisions. Typically, within a week following the standing call, the PS, with the approval of the PC(s), will disseminate a summary of the call or meeting, listing all participants (noting attendance) and highlighting decisions

and actions items.

The PC or the protocol co-chair/vice-chair should attend all calls as able. If one or both chairs are going to be absent for a standing meeting, they should notify the other chair and the PS ahead of absence to allow time for the agenda to be modified accordingly. For some PTs, the DMID CPM or Medical Officer may be able to stand in for PCs during a team call; however, this should be coordinated ahead of time. In the absence of both chairs, the agenda should be modified to defer key decisions or voting to a later date while still meeting protocol requirements for timeliness and frequency of review; in particular, safety data reviews should occur within protocol-specified timelines.

For calls where the team members input is deemed necessary, the PS will request that absent members reply via email to confirm their review of the call minutes and indicate whether they concur with the discussion that took place in their absence (copied to the PS). If the absent member does not concur, the PC or co-chairs will determine next steps (e.g., further email communication, convening an ad hoc conference call, deferral to the next scheduled conference call). Once a decision is achieved, the PS will inform all relevant team members of the outcome.

Should any team or sub-group note that call attendance is frequently low, action should be taken by the PCs to address this; when resolution cannot be achieved within the team, action may be taken by the IDCRC Clinical Operations Unit (COU). Low call frequency will be escalated to the COU by the FHI 360 Project Director during routine COU calls

Some concerns or issues will be addressed via email only. In these cases, all protocol team or subgroup members ideally will provide input via email; an email response must be obtained from members of the management team or applicable team members as appropriate. A protocol chair will coordinate with the PS to confirm the outcome of the decision or the review and, if consensus is not reached, to determine next steps. Once a resolution is identified, the PS will inform all relevant team members of the outcome.

13.4 Participant Accrual and Retention

This section briefly describes establishment of study enrollment targets, screening and enrollment and procedures for IDCRC protocol sites.

13.5 Enrollment

For multi-site IDCRC studies, the COU will specify an estimated number of participants to be enrolled at each participating study site; this allocation across sites will typically be determined at the completion of the site selection process based on information contained in Site Interest Forms. Sites will be notified of these allocations in their Intent-to-Fund memos.

Typically, changes in the sample size of the overall study and/or the length of the participant's study involvement should be reported by protocol and informed consent form (ICF) amendment to the requisite Single and/or Institutional Review Boards/Independent Ethics Committees (IRB/IEC) for approval prior to initiating the change. In some cases, the PT may determine that an amendment is not required if the change does not impact the minimum sample size needed for primary or secondary aims of the study for instance. For more information about study modifications, see IDCRC MOP Section 9.

13.6 Screening and Enrollment

Screening and enrollment visit procedures will be described in the study protocol and the protocol-specific MOP.

13.6.1 Screening and Enrollment Logs

Study sites will be asked to document study screening and enrollment activities on screening and enrollment logs.

13.6.2 Study Enrollment Period

Unless otherwise specified, the study-specific enrollment period begins on the first day of participant enrollment at any participating study site. For most studies, participant accrual is tracked throughout the screening and enrollment period to identify any barriers or risks to the overall study schedule.

13.6.3 Definition of Enrollment

The definition of enrolled may be found at https://prsinfo.clinicaltrials.gov/definitions.html

13.7 Obtaining Informed Consent

Written informed consent must be obtained from all IDCRC study participants or their legal guardians prior to the performance of any protocol-specified screening or enrollment procedures, unless written informed consent is not necessary per the responsible IRB. See IDCRC MOP Section 11 (Human Subjects Considerations) for additional information on the informed consent process.

13.8 Tracking Accrual and Retention

Protocol teams are responsible for closely monitoring accrual (and retention) on an ongoing basis and taking appropriate action as necessary to ensure that targets are met. For instance, screening data should be monitored closely to identify specific barriers to enrollment (based on reasons for exclusion) and to monitor the pipeline of potential participants at participating sites, both of which inform study feasibility. Any issues or challenges will be brought to the attention of the COU via the FHI 360 PD during routine COU calls. Study accrual and retention reports are run on a regular basis by the data coordinating center and will be made available to PCs, PS, DMID and other team members via the data coordinating center's web portal[3]. These reports are typically shared and reviewed during protocol team calls.

13.9 Follow-Up Visits

For each IDCRC study, the expected duration of participant follow-up, as well as the number and type of follow-up study visits or contacts that are scheduled to take place during the course of the study, are specified in the study protocol.

Each protocol-specific MOP will contain details of visit windows and

[3] For SDCC/Emmes studies, the data system portal is the Clinical Research in Infectious Diseases (CRID) (https://emmescrid.com). For SDSU/SCHARP studies, the data system portal is Atlas Science (https://atlas.scharp.org).

unscheduled/supplemental/interim visits

13.10 Investigator-Initiated Early Termination of Participants

Investigator-initiated termination of an individual's IDCRC study participation prior to the protocol-specified completion of follow-up should occur only under extraordinary circumstances. For instance, termination may be considered if there is potential for harm to study participants or significant disruption of study operations.

Prior to terminating a participant from an IDCRC study, the Site Investigator may seek input from certain members of the PT, and discuss operational, and statistical implications of the termination.

Site staff must always record reasons for termination in participant study records.

13.11 Data Collection and Documentation

Study site staff are responsible for the collection, storage, timely submission, and quality assurance of study data collected at their site, as outlined in their site Data Management SOP.
Additionally, throughout the study, sites must maintain and keep administrative and regulatory documents up to date as well as adequate and accurate study participant case histories per applicable U.S. Code of Federal Regulations (21 CFR parts 50 and 312, and 45 CFR Part 46), guidelines published by the Food and Drug Administration (FDA), and GCP.

13.12 Administrative and Regulatory Documentation

DMID specifies the administrative and regulatory documents that sites must maintain in a regulatory binder or file on site. As modifications or updates to required documents occur, site staff should also send the modified/updated versions to FHI 360 PS. The original and modified/updated versions of these documents should be available for inspection at any time

13.12.1 Maintenance of Essential Documents

The essential documents collected by FHI 360 during the pre-implementation phase will be continuously reviewed, updated, and maintained throughout the implementation phase. The same steps for collection and review will be followed. A training tracker will be maintained at FHI 360 and requests will be made to sites as appropriate for updated training to be completed and certificates to be submitted.

> For more details regarding essential documents, see IDCRC MOP Section 12 (Pre-Implementation Activities) and the DMID Essential Document Review Worksheet and DMID Regulatory File Document Guidelines.

13.12.2 Source Data and Source Documentation

IDCRC study sites must adhere to the standards of source documentation specified in the DMID policy on Requirements for Source Documentation in DMID Funded and/or Sponsored Trials. This policy contains both requirements and recommendations. Study sites must comply with all requirements and

are advised to comply with all recommendations. For more information, please refer to the **Source Documentation Standards for DMID Clinical Studies** posted on the DMID-CROMS website.

For IDCRC studies, source data and source documents will be defined in the protocol and the protocol-specific MOP.

13.12.3 Participant Research Record Contents and Storage

To comply with federal regulations, site(s) should maintain adequate and accurate participant files containing all information pertinent to the study for each study participant. Participant files should be kept in a safe, locked storage area with limited access at the study site. The protocol-specific MOP will contain specifications regarding what study related documents should be kept in participant files.

13.12.4 Study Visit Information

The protocol and/or MOP typically will include an overview of study procedures by visits to guide the staff performing procedures at each study visit (in accordance with the protocol).

13.12.5 Documentation of Study Product Accountability and Dispensing

Designated pharmacy staff must document the receipt, dispensing and final disposition of all study product and study supplies that are used in IDCRC studies. This documentation must comply and be maintained in accordance with guidelines provided in the study protocol and/or protocol-specific MOP.

13.12.6 Record-Retention Requirements

Study staff will retain all records on-site throughout the study's period of performance per the guidance within the protocol. DMID will provide the site with instructions for long-term storage of records after the study is completed. Site staff should not destroy any study documents without written permission from NIAID/DMID. See IDCRC MOP Section 15 in this Manual for additional details regarding record retention requirements and study close out activities.

13.13 Data Management Procedures

Data managers from Emmes or SCHARP will be actively involved in the PT throughout the implementation phase.

13.13.1 Electronic Case Report Forms (eCRFs)

Once the study is implemented, site study staff will enter study data directly into the eCRFs via the electronic data capture (EDC) system[4] developed and maintained by the data coordinating center as the central study database. Instructions for use of these systems and detailed guidance on completion of the electronic case report forms (eCRFs) for each study are included in that system's User Guide or Training Manual and the eCRF Completion Guidelines / Instructions included as an Appendix to the

[4] Emmes uses Advantage eClinical for electronic data capture. SCHARP will use Medidata Rave for most studies; however, SCHARP sometimes may use choose to use a different data capture system such as REDCap depending on the study parameters.

protocol-specific MOP.

13.13.2 Data Collection Forms / Source Documents

Data collection forms may be derived from the eCRF may be provided for studies by Emmes and FHI 360 on behalf of SCHARP to be used as source documents (these would only be used if the electronic system was not available).

Source documents are original documents/data/records from which information is abstracted and collected in the study database. Examples include medical records, participant diaries, lab results, notes, paper copies of study case report forms. When the data is directly entered into the database (e.g. during a participant interview) the electronic record in the database is the source document. Any hard copy source documents should be kept in a secure location following confidentiality guidelines outlined in the study protocol.

13.13.3 Quality Control

Site staff will use form completion guides developed and distributed by either Emmes or SCHARP. These guides provide the framework for collecting the necessary study data based on the schedules of evaluation in the study protocol and aid in scheduling participant visits and specimen collection.

Additionally, each site will have a Clinical Quality Management Plan (CQMP) or protocol-specific Clinical Quality Management Plan (pCQMP) that will outline the Quality Control (QC) review steps, especially for source documents, prior to their data entry into the EDC system / central study database.

13.13.4 Form Submission Schedule

An eCRF / DCF completion schedule will typically be included in the protocol-specific MOP. Additionally, the schedule of forms will be included in the eCRF completion guide produced by either Emmes or SCHARP for that protocol.

13.13.5 Assignment of Subject IDs

The approach to assignment of subject IDs will be outlined in the protocol-specific MOP as well as in the form completion guidelines provided by the Emmes or SCHARP.

13.13.6 Data Queries

The protocol data manager and designated Emmes or SCHARP staff review eCRF data submitted to the EDC system / central study database and items that need verification or further clarification are sent as queries to the site data management staff.

For Emmes studies using Advantage eClinical, on a frequency agreed upon with the PT, the data manager sends a number of QA/QC reports to site staff to identify data that are inconsistent, missing, or contain out-of-range values. Additionally, QA/QC reports are available on the CRID portal and may be run as needed by site staff. Site staff should review and respond to QC reports sent by the data coordinating center in a timely manner.

For studies that SCHARP is managing, reports to review queries, overdue forms, and other quality assurance issues are available through the EDC system and may be run as needed by sites. Within Medidata Rave, sites can manage queries through the Medidata Rave Task Summary or the Query Management module. Data management staff at the sites should routinely review the task summary or available reports to correct or clarify the data items in question. Site staff should also utilize reports within Medidata Rave to address delinquencies. Reports for quality review of participant data, productivity, and administrative reports, are available to sites. For all SCHARP studies, queries may also be placed within Medidata Rave in preparation for interim analyses and these should be addressed as soon as possible. If the site has questions about any queried items that show up repeatedly, they should contact the protocol data manager for further explanation. Any issues should be addressed as soon as possible, generally within seven to ten working days of receipt.

13.14 Unblinding Requests

Unblinding may be required for emergency purposes during the course of a protocol. Unblinding procedures should be found in the protocol or MOP.

13.15 Participant Transfers

In the case of a participant that moves from one study location to another, the participant can be reassigned from the old site to the new site. Requests for participant transfers to new sites are sent to the protocol data manager for processing and reallocation (See Section 9 SOP Participant Transfer).

13.16 Reporting

Both Emmes and SCHARP have a standard set of reports for tracking study progress and site performance including screening and enrollment reports, retention reports, missed visit listings, QC reports, data management quality reports, Safety reports, SAE listings, protocol deviation listings, specimen monitoring reports.

Emmes routinely generates reports on site-specific and protocol-specific data management performance. These reports will be compiled by FHI 360 and shared with the COU on a quarterly basis.

Reports Per Protocol:
Accrual enrollment
Accrual report
Adv Event Listing
Birth control listing
Clinical Lab results
Early/ Determination and/Discontinuation
Global Trace Inventory
Global Trace Specimen summary
Medical History listing
Performance Metrix Report(monthly)
Protocol deviations
Screen failures
Screening Summary
Solicited Local Event listing

Solicited Systemic Event Listing
Study Completion List
Visit Compliance report

For SCHARP studies (using Medidata Rave or another EDC system), the reports include:

- Enrollment
- Data Management Quality
    - Timeliness of submitted data
    - Query responsiveness
    - Error responsiveness Retention and Visit Completion
    - Data completeness
- Protocol Deviations Summary
- Secure Reports upon study team request

If there are concerns about a site's data management quality, the data manager and protocol team work with the site to help develop strategies for improving performance.

13.17 Confidentiality of Study Data

The disclosure of study end points during an ongoing study should be limited to designated committees (e.g., closed SMC, DSMB) to avoid bias in study conduct and/or interpretation of data. If early disclosure of study endpoints is planned prior to study completion (such as presentation at a meeting or publication of preliminary results), the plan for such disclosures should be addressed in the protocol.