14 STUDY OVERSIGHT

Oversight of IDCRC studies occurs at many levels, consistent with US and international regulations, policies, and guidelines applicable to human subjects research funded by the National Institutes of Health (NIH):

- At each clinical research site, the Site PI is responsible for continuous monitoring of participant safety as well as the quality of study conduct and study data.
- For each protocol, the protocol team are expected to provide continued scientific and operational management to identify emerging issues and address these with study sites as needed.
- When the Division of Microbiology and Infectious Diseases (DMID) as the regulatory sponsor of a trial, DMID will contract with clinical site monitors who conduct on-site monitoring activities and have established procedures to ensure that monitoring findings are addressed as needed at each site. FHI 360 works with sites to resolve action items identified by the monitors. When DMID is not the regulatory sponsor, IDCRC LG will be responsible for contracting with clinical site monitors.
- The IDCRC Clinical Operations Unit (COU) monitors protocol development and implementation through various mechanisms including regular communication with protocol teams and FHI 360, and by monthly review of study progress reports and protocol specific metrics.
- Similarly, the IDCRC Lab Operations Unit (LOU) oversees clinical and research laboratory services and quality management.
- An independent DMID Safety Monitoring Committee (SMC) or Data and Safety Monitoring Board (DSMB) may also review IDCRC studies when applicable.

Each of these levels of oversight is further described in this section.

14.1 On-Site Clinical Quality Management

Per DMID policy, all clinical sites conducting or participating in DMID-funded clinical research must develop and implement a Clinical Quality Management Plan (CQMP). The CQMP should “encompass quality control (QC) and quality assurance (QA) procedures, detailing the responsibility, scope, and frequency of these activities. Implementing the CQMP process enables site staff to verify data accuracy and completeness of data capture, protect human subjects’ rights and welfare, and ensure Good Clinical Practice (GCP) standards and regulatory requirements are met.” See Clinical Quality Management Plan (dmidcroms.com) for more details and Sections 12, 13 and 15 of this MOP (LINKS to be embedded)

All primary Vaccine Treatment and Evaluation Units (VTEUs) that are part of the IDCRC have a DMID-approved CQMP. To address protocol-specific sites and sub sites that do not have a current, DMID-approved CQMP, the COU will work with Protocol Chairs to customize the DMID protocol-specific CQMP (psCQMP) template for the protocol and then work with sites to complete the site specific psCQMP prior

to site activation.

14.2 Onsite Monitoring

DMID has a regulatory responsibility for oversight of all IDCRC studies under the US Code of Federal Regulations (CFR) Title 45, Parts 46, 160, and 164; Title 21, Parts 11, 50, 54, 56, and 312; and International Conference on Harmonisation (ICH) Guidelines E6.

To address part of these oversight responsibilities, DMID contracts with Clinical Site Monitors (CSM) to perform on-site monitoring at the IDCRC sites for which they are the regulatory sponsor. During site visits, the contracted CSM will conduct a variety of activities outlined in their approved Clinical Monitoring Plan.

The extent and frequency of monitoring will depend on the size, risk, and complexity of studies conducted at the site and may change over time depending on study status and performance of the site. The contracted CSM will describe the approach to monitoring a particular study in the approved protocol specific Monitoring Plan.

Site investigators must make study facilities and documents available for inspection by the monitors as requested by the CSM in the monitoring visit confirmation letter.

14.2.1 Site Monitoring Reports

Monitoring reports are prepared by the CSM following each visit and provided to the sponsor and the site; sites are required to respond to monitoring findings in a timely manner and in accordance with sponsor-specific procedures. The DMID Clinical Project Manager (CPM) or designee shares monitoring visit reports with the FHI 360 Protocol Specialist (PS) who then will follow up with sites as needed to address findings and action items, which will be tracked to resolution. Findings of significance will be escalated as appropriate to COU and DMID (OCRR/VTEU PI).

14.2.2 Quality Oversight Plan

DMID may determine that formal external monitoring will not be required. For these protocols, quality oversight may be conducted by FHI 360 in consultation with the COU, as described in a protocol specific Quality Oversight plan (QOP). During pre-implementation, FHI 360 will work with the COU, and protocol chair(s) as needed to develop the QOP and submit for review and approval by DMID prior to study implementation.

14.3 Protocol Team Oversight Responsibilities

IDCRC protocol teams are responsible for actively monitoring participant safety and the quality of study conduct, and for working with sites to address any issues or concerns that may arise.

14.3.1 Routine reports

Monitoring at the protocol team level is typically accomplished through review of study-specific reports generated by the data management group (The Emmes Company or SCHARP). During team calls, protocol teams will routinely review the following reports: screening, enrollment, AEs/SAEs, protocol deviations, data queries, and other operational data to track accrual and study progress, identify any problems or concerns with regards to study timeline, risks to patient safety or data quality,

etc.

14.3.2 Site Visits

The protocol chair, protocol team members, and representatives from the COU, Lab Operations Unit (LOU) or Statistics and Data Sciences Unit (SDSU) may conduct onsite or virtual site visits to assess study implementation and/or provide training and other technical assistance to site staff. As needed, issues or problems identified during such visits are brought to the attention of the protocol team for discussion and development of corrective and preventive action plans.

14.3.3 Escalation Process

If any clinical operations issues arise during the study that cannot be resolved at the protocol team level, or if the protocol team determines that corrective and preventive action plans may be warranted, the protocol chair or other protocol team members should refer the issues to the COU for further review, guidance, and decision-making. Similarly, if any lab related issues arise, the protocol team will work with the Lab Operations Unit (LOU) to escalate the issue as appropriate. For details regarding the LOU escalation process, See MOP Section 17.

14.3.4 Safety Monitoring

Each IDCRC protocol and corresponding Manual of Procedures (MOP) specifies the roles and responsibilities of protocol team members for monitoring participant safety.

Site staff are responsible for monitoring the safety of each study participant and entering clinical and laboratory data into eCRFs in a timely manner (as described in eCRF completion guidelines or form instructions), so that current data are available for review at the protocol team level. Site staff are also responsible for alerting the site investigator to any safety-related issues or concerns that may arise, consistent with protocol requirements, who will then bring those issues to the protocol chair or team as appropriate.

Data management team members also play a key role in monitoring participant safety, through their roles in reviewing and coding safety data, querying sites as needed to ensure that accurate and complete data are available for review, generating safety data reports for review, generating interim analysis reports for independent review committees, and identifying when study pause or stopping rules specified in the protocol have been met.

If at any time a safety issue or concern is identified, the DMID Medical Officer and/or Medical Monitor, safety data manager(s) and other designated protocol team members are responsible for taking appropriate action to address that concern. Such actions may include, for example, DMID requesting additional review of study data by the SMC or DSMB, pausing administration of study agents, and developing modifications/amendments to the protocol and its associated manuals once the safety review has occurred. The protocol team is also responsible for informing study sites if any changes in study conduct are required.

Safety data should be reviewed at least monthly, and more frequently if specified by the protocol, during conference calls, in-person meetings or by email. Reviews are documented in the form of call or meeting summaries. Documentation of these reviews is not typically provided to study sites. However, as noted above, sites are notified if a safety issue is identified that necessitates a change in study conduct; such notifications also address notification of IRBs/ECs and other relevant review bodies.

Should a study site require a safety-related summary to meet IRB/EC requirements for continuing review, this may be requested from the protocol team, with the request emailed to the PS. During the ongoing conduct of a study, available information will be limited.

14.4 IDCRC Clinical Operations Unit (COU)

The COU provides leadership on protocol development and implementation planning as well as operational support, management, and oversight of the IDCRC research portfolio. Along with its subcontractor partner, FHI 360, the COU oversees protocol teams, quality assurance and monitors progress towards study milestones and timelines.

14.4.1 Oversight of GCP / Regulatory compliance

As part of COU oversight responsibilities for assuring project-wide regulatory compliance, FHI 360 will review the monitoring reports produced by the DMID clinical site monitoring contractor to identify any problematic trends or issues related GCP and regulatory compliance, study product accountability, etc. The PS will flag any problematic trends or concerns for the DMID CPM or other DMID representative as appropriate, as requested by DMID. Any ongoing non-compliance or other issue of concern will be escalated to the COU and the designated DMID Project Officer who will then determine if a Corrective and Preventive Action Plan (CAPA) is needed, as described in Section 13.4.3.

The essential documents collected by FHI 360 during the pre-implementation phase will be continuously reviewed, updated, and maintained throughout the implementation phase to ensure site staff maintain necessary qualifications to conduct DMID funded studies. FHI 360 maintains a database of all staff actively engaging in research across VTEUs and sub sites along with dates of HSP, GCP and other required trainings and essential documents to facilitate ongoing oversight across VTEUs. As certifications are due for renewal, FHI 360 will notify sites as appropriate for updated training to be completed and certificates to be submitted.

14.4.2 Site Clinical Quality Management Plans (CQMPs)

FHI 360 reviews the CQMPs and psCQMPs to ensure that the CQMPs and psCQMPs are current and approved by the Office of Clinical Affairs (OCRA) within DMID prior to site activation. The COU will also verify that the CQMPs and psCQMPs are maintained on an annual basis. The COU may request CQMP / psCQMP Quality Management Summary reports from VTEUs, and other clinical research sites involved in IDCRC research periodically as part of quality oversight activities.

14.4.3 Protocol Quality Oversight Plans (QOPs)

As noted in Section 13.2.2, for low resource and/or non-interventional protocols that will not be monitored by the DMID contracted clinical site monitor, the COU and FHI 360 will perform oversight activities as described in the protocol Quality Oversight Plan. For example, sites may be required to share their QM Summary reports with the COU on a monthly or quarterly basis. The COU will work with FHI 360 to review these summary reports to identify any problematic issues or trends at a site or across sites.

14.4.4 Study Progress Reports

As part of routine oversight of active protocols, FHI 360 produces a monthly Study Progress Report for each active protocol which outlines study sites, status of the (S)IRB approval, site activation, first enrollments at each site, participant accrual and retention, any issues or challenges and their resolution.

The report is shared with the COU, LG and DMID monthly.

FHI 360 also produces a weekly "snapshot" report of protocol activities (in which FHI 360 is involved), along with a timeline of protocol milestones that enables more timely review and tracking of site performance and study progress.

14.4.5 Protocol Specific Metrics

Additionally, protocol-specific metrics (domains below) will be tracked monthly by FHI 360 and provided to COU along with the monthly Study Progress Report.

- Protocol Implementation
- Regulatory Approval
- Site Preparation / Launch
- Participant Recruitment / Enrollment
- Retention / Completion
- Clinical Data Management
- Lab Data and Specimen Management
- Laboratory QA
- Timely submission of AEs
- Protocol Deviations/Violations
- Response to Queries from Site Monitoring reports
- Frequency and responsiveness to CAPAs

14.4.6 Site Performance and CAPA plans

As noted in Section 13.3.3, protocol chair(s) or the FHI 360 PS will escalate problematic issues or trends to the COU. The COU will review and intervene as appropriate, working with the Protocol Chair. A COU chair and the Protocol chair may reach out directly to a site investigator via email or call to investigate an issue. If the Protocol Chair and COU determine that a CAPA plan is warranted, the COU will involve the DMID Program Officer for that site, who will then work with the site to issue CAPA. The protocol chair and COU will have an opportunity to review and provide input on the CAPA parameters and will be apprised of updates by the DMID PO. CAPAs may also be requested by OCRR/VTEU PO; in this instance they will inform the COU.

Based on progress reports, protocol-specific metrics, CAPAs, and other communication channels, the COU will advise the LOC regarding enrollment slot re-allocation and performance improvement plans. In the event of site inability to enroll, or failure to complete a performance improvement plan, the LOC will advise DMID regarding site study closure and re-allocation of resources.

14.4.7 Protocol Modifications

The Principal Investigator/Protocol Chair(s) must notify the COU of modifications to approved protocols to enable the IDCRC to maintain effective oversight of its research portfolio.

See MOP Sections 9 and 15 for more details.

14.5 IDCRC Laboratory Operations Unit (LOU)

The IDCRCLG Laboratory Operations Unit will oversee clinical and research laboratory services which

include pharmacokinetics, bioanalyses, and specimen characterization; laboratory quality management; monitoring and evaluation of all LG specialized laboratories; sharing of specimens; and harmonization of laboratory activities of the LG and the VTEU- identified laboratories. See MOP Section 17 for more details regarding LOU oversight activities.

14.6 Study Oversight by the Sponsor

DMID has regulatory responsibility for oversight and monitoring of appropriate IDCRC studies. DMID staff members are active in overseeing and supporting the IDCRC from concept development through study implementation, analysis, reporting and publications as members of the IDCRC Executive Management Team (EMT), Expert Working Groups, Key Function Committees, and protocol teams. DMID staff members participate in meetings across all levels and operational units of the IDCRC to stay abreast of IDCRC progress towards study milestones, providing guidance as appropriate.

- As described in Sections 13.1 and 13.2, DMID works with IDCRC VTEUS to develop and implement clinical quality management plans (CQMPs) and contracts with clinical site monitors to perform on-site monitoring at the IDCRC-affiliated sites that they fund.

- As noted in Section 13.3.4, DMID assigns a Medical Monitor / Medical Officer to each protocol as appropriate to monitor the safety and efficacy of the intervention(s) for both in-development and ongoing studies. Additionally, each protocol will have a DMID Clinical Project Manager as member of the protocol team to serve as the DMID primary point of contact, responsible for the coordination and management of DMID-supported clinical research throughout the life cycle of the protocol.

- As described in Section 13.4.3, DMID is a point of escalation for determining need for and implementation of corrective and preventive action plans for the VTEUs and subsites.

When necessary, NIAID may suspend or terminate site participation in an IDCRC study, for example in response to serious and/or persistent non-compliance with protocol, regulatory, and/or contract or grant requirements.

For some IDCRC studies, NIAID convenes a Safety Monitoring Committee (SMC) or Data Safety Monitoring Board (DSMB) as part of its study oversight responsibilities, as described in Section 13.7 below. DMID monitors the progress of studies through review of DSMB reports.

14.7 Data and Safety Monitoring Board (DSMB) / Safety Monitoring Committees (SMCs)

Data and Safety Monitoring Boards (DSMBs) are convened by DMID to review study conduct and safety and efficacy data for clinical trials involving interventions that entail greater than minimal risk to participants; however, other types of IDCRC studies may be subject to DSMB review. For Phase I and smaller Phase II trials, DMID convenes a Safety Monitoring Committee (SMC) to monitor participant safety and to advise DMID and study investigators, when it is determined that the DSMB is not required. Data Safety and Monitoring Boards (DSMBs) review both interim safety and other clinical endpoint data (e.g., surrogate markers). Safety Monitoring Committees (SMCs) review safety data.

The members of the DSMB and SMCs are independent investigators with no financial interest in the outcomes of the studies reviewed. Members include experts in the fields of biostatistics and medical

ethics, clinicians, and Infectious Disease / Vaccine experts, plus ad hoc members. Appointments to the DSMB and SMCs are made by DMID. DMID coordinates all DSMB and SMC activities.

For studies that are subject to DSMB or SMC review, reviews are conducted at least annually and in accordance with relevant NIAID standard operating procedures, which can be found at https://www.niaid.nih.gov/research/safety-oversight-clinical-research.

14.7.1 Preparation for and Participation in Reviews

The data management team (either The Emmes Company or SCHARP) prepares data reports for DSMB or SMC reviews; other materials may also be prepared by the protocol team (e.g., memos, slide presentations). Protocol chairs and other key protocol team members including medical officers as designated in the study MOP to receive open DSMB data reports are provided an opportunity to review drafts of data reports and other materials planned to be discussed in open review sessions.

The protocol chairs and other designated team members typically attend open review sessions to discuss study progress and respond to questions. Statisticians, blinded or unblinded as appropriate, attend closed review sessions to present data by coded randomization arm and respond to additional questions from the DSMB.

14.7.2 Review Findings and Recommendations

Findings and recommendations from the DSMB or SMC are communicated within DMID, with DMID leadership having ultimate responsibility for determining whether to accept the recommendations. Recommendations may involve continuing a study as currently designed or may involve modifications of a study.

The DSMB or SMC provides a summary report of the review to DMID. The written report is shared with the protocol team and site investigators. A subset of the protocol team (i.e., Protocol Chair, Statistician, Medical Officer) will provide a written response to the DSMB / SMC written report, if required, as soon as possible.

All study sites must submit a copy of the summary review report to their IRBs/ECs and other relevant review bodies; protocol teams may also provide supplemental materials for submission along with the summary report.

14.7.3 Response to Significant Recommendations

If the DSMB or SMC recommends significant modifications of a study (e.g., early termination, closure of one or more randomized groups), this information will be immediately communicated to DMID leadership, who will determine whether to accept the recommendations. IDCRC leadership and protocol team members will be informed of the recommendations and the DMID decision. Communications among the protocol team and with study sites will generally be coordinated by the COU in close collaboration with the protocol chair; however, DMID will assume primary responsibility for any public statements or press release associated with the DSMB or SMC recommendations.

If a press release is planned, DSMB or SMC review findings and recommendations should remain confidential prior to the public release. Priority should be given to informing study participants and other community stakeholders as soon as possible.