OFFICE OF BIODEFENSE, RESEARCH RESOURCES,
AND TRANSLATIONAL RESEARCH (OBRRTR)

INSTRUCTIONS FOR THE CONDUCT OF CONTRACTOR-HELD IND CLINICAL TRIALS PERFORMED UNDER A CONTRACT

Clinical trials funded with Federal monies receive special scrutiny from the funding institutions in order to ensure the protection of Human Subjects and compliance with all applicable laws and regulations.

Within DMID, the Office of Clinical Research Affairs (OCRA), the Office of Regulatory Affairs (ORA), and the Office of Clinical Research Resources (OCRR) are responsible for oversight of all clinical studies funded by DMID. This document will outline the oversight mechanisms and interactions you will have during the conduct of clinical studies if you are awarded a contract with DMID. Your proposed work plan should incorporate all elements of these instructions.

Communication

- Your first point of contact within DMID will be your Contracting Officer's Representative (COR).
- DMID also assigns a Clinical Project Manager (CPM) who will manage the clinical trial-related activities within DMID. Back-Up CPM(s) will also be assigned. Your COR will provide contact information and appropriate formats for communication with the DMID CPM for your clinical trial, approximately 6 months prior to the anticipated IND filing in order to facilitate the timely execution of the clinical work.
- A DMID Study Team is established to oversee the development and conduct of each protocol. The Study Team usually consists of the CPM, a Medical Officer, Medical Monitor (in addition to IND Sponsor's Medical Monitor), Contracting Officer's Representative/Scientific Lead/Program Officer, Regulatory Affairs Manager, and Pharmacist. The DMID Study Team responsibilities include review, comment and approval of all clinical trial protocols, informed consent forms, Investigator's Brochure and protocol related documents as well as continuous oversight over protocol execution. The DMID study team will collaborate with you in discussing the major components of the protocol and request that you submit a protocol synopsis early in the protocol development process.
- DMID will not communicate directly with your sub-contractors. You and your sub-contractors must have a communication plan that gives you, as the Primary Contractor, responsibility for communication with DMID. Your sub-contractors should not communicate with DMID unless the Primary Contractor is included.
- As your contract nears protocol development, we suggest separate biweekly meetings with the clinical personnel to address any issues.

DMID would like an agenda and an email of minutes with bulleted action items.

Clinical Science Review

- This review needs to occur concurrently with the protocol team review. It is usually conducted when the protocol synopsis has been agreed upon by the protocol team. It must be done prior to the protocol team approval of the protocol.
- The purpose of the DMID Clinical Science Review is to collaboratively develop the best protocol for clinical trials funded by DMID: best design, feasibility, with optimal sample size.
- The following is a description of the DMID process for these meetings.
- The meeting is a weekly, 60-90 minute review of a single synopsis, open to DMID staff, with the following minimum requirements:
    - The CPM submits documents 9 calendar days prior to meeting (additional time may be needed for complex review at the discretion of the Associate Director, Clinical Research (ADCR))
        - Documents to be submitted:
            - Completed DMID Protocol Synopsis template
            - Investigator's Brochure (IB)
                - If no IB, a summary document of pre-clinical toxicity, efficacy, immunogenicity, pharmacokinetics (as applicable), CMC, and any human data (do not submit set of original pre-clinical reports)
            - Send references if available that would help with understanding the background (e.g., if unusual pathogen/diseases or if there are trial results involving the study product or related products)
        - ADCR determines completeness of documents and pre-clinical data for review
        - Additional time may be needed for complex review or outside reviewers
    - Meeting
        - Participants:
            - Presenter:
                - Sponsor Company Medical Director if company-held IND
            - Independent NIAID Reviewers, not associated with the study (coordinated by ADCR/designee):
                - MO or PO (knowledgeable in field if possible) to serve as primary reviewer

- Statistical review: Division of Clinical Research, Biostatics Research Branch
- Clinical operations: CPM, Nurse Consultant, or COR (familiar with field)
- Medical Monitor - OCRA
- Regulatory Affairs Specialist - ORA
- Resource utilization - OCRR
- ADCR
- Ad hoc expertise based on protocol: Product reviewer, pre-clinical animal model, pediatrics, HSP, ethics, PK, etc.

- Process:
  - Presentation in meeting by Sponsor Medical Director (15 min)
    - Slides, template available, to include: background, rationale, hypothesis, safety info, objectives, design, inclusion/exclusion, study product, study visits, statistical consideration
      - Do not need to duplicate all elements of the synopsis, rather main points to ensure everyone present can start with similar knowledge
  - Review / discussion by primary reviewer (10 min - no formal presentation)
  - Other reviewers (20 min)
  - Closed session (10 min)
  - Output:
    - Written comments with major (must change) / minor (consider), and summary of scientific value
    - Major comments must be addressed in revised synopsis
    - Sent to all reviewers
    - Once major concerns are addressed - approval
      - Can ask for re-review if significant deficits

Protocol Development

- All clinical trial protocols and amendments must be provided to DMID for review and approval before submission to the FDA.
- You do not need to use the DMID protocol template. However, DMID will need to review and ensure that all the DMID protocol template elements are included. You must address all the elements identified by the protocol template. For FDA submission, your protocol must be in eCTD format.

- The Common Toxicity Criteria (CTC) toxicity grading scales are not acceptable for DMID healthy volunteer studies.
- The FDA Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventative Vaccine Clinical Trials may be considered. They may be modified with DMID approval. In any case, toxicity scales must be used to evaluate safety, including laboratory measurements. These will be used when evaluating pausing rules.
- Any toxicity grading scales you use must be approved by the DMID Medical Officer and Medical Monitor. The normal ranges of the laboratory used in the clinical trial must be aligned with the toxicity grading scales so that a participant does not have a normal lab measurement per the laboratory but a grade 1 per the scales or vice versa.
- Inclusion/Exclusion Criteria: Clinical Laboratories – The protocol must state which clinical laboratories must be within normal range at screening and/or baseline to be eligible for enrollment in the clinical trial. If additional laboratories are collected, the protocol must indicate how these laboratories will be evaluated. Typically, DMID will not allow any additional screening laboratory value to be above a Grade 1 toxicity. DMID does not allow subjects into the study in which the PI determined out of range laboratory values as "not clinically significant." Please see the NIAID policy: Development of Criteria for Volunteer Participation in DMID Clinical Research (shared by CPM post-award).
- All treatment-emergent events (including laboratory values) should be graded per the toxicity scales and need to be captured as adverse events. This does not necessarily mean that they must be recorded on an adverse event case report form, but they do need to be counted as an adverse event to the drug or vaccine in safety reports and CSR.
- Relatedness to the investigational product must be determined for out of range laboratory values.
- Regarding the determination of the SAE/adverse event's relatedness to the investigational product, DMID uses the categories of Related/Not Related. If the Sponsor prefers to use multiple categories, this will need to be approved by the DMID Medical Officer and Medical Monitor. If they are accepted, please keep in mind that for the pausing rules, all categories other than "not related," including "doubtfully related," will be considered "related" unless the Medical Monitor approves otherwise.
- The protocol may require multiple reviews by DMID. Following each review, you will receive a protocol with tracked changes and comments embedded or a separate list of comments that must be addressed either in writing or in a discussion with the protocol team. A new version with tracked changes will need to be submitted to the DMID team for review. DMID typically uses 0.1, 0.2, etc. with a change in date for the draft versions. When we've agreed that the protocol is ready for FDA submission, the version number is changed to a whole number, 1.0, 2.0, etc. However, you may use your own versioning system.

- Be sure to allocate time for protocol review and revision when establishing your clinical timeline. It may require 3-6 months depending on the quality of the protocol and its alignment with DMID policies.
- The Clinical Project Manager will review the protocol materials and with the agreement of the team, determine when it is ready for DMID protocol approval.
- The ICF and protocol needs to have the NIH Certificate of Confidentiality information included, see https://www.era.nih.gov/erahelp/CoC_Ext/Content/A-Introduction/Introduction.htm.
- When a protocol or protocol amendment is submitted for review, it must include all supporting documents:
    - sample Informed Consent Form,
    - current Clinical Investigator Brochure and/or draft reports of study findings,
    - Package Insert (if applicable).

    The following documents (if applicable) must be reviewed and approved prior to enrollment:
    - Enrollment plan (may be included in the protocol)
    - Data Management Plan
    - Manual of Procedures (only needed if there are procedures not covered in the protocol)
    - Pharmacy Manual
    - Laboratory Manual
    - Specimen Handling Manual
    - Quality Management Plan
    - Safety Monitoring Committee template reports
    - Communication Plan
    - Safety Management Plan
    - Clinical Monitoring Plan with template reports

    The following documents must be reviewed and approved prior to database lock:
    - Statistical Analysis Plan
    - Clinical Study Report Template

- The DMID COR's written approval of the protocol based on the CPM agreement and all amendments is required prior to FDA submission.
- The DMID requires copies of the IRB approval letter for the protocol, informed consent form and any subsequent amendments.

Requirements for the Contractor to Hold the IND

- IND Sponsorship:

  - DMID will not make the final decision as to the contractor's ability to hold the IND until after protocol development and review. The contractor may proceed as if they will be the IND Sponsor until such determination is made.
  - Contractors that request to hold the IND must have the expertise and sufficient staff (Medical Officer, Clinical Project Manager, Regulatory Affairs Specialist, Medical Monitor) to fulfill all IND-related obligations and manage/oversee the conduct of the clinical trial.
  - It is important that the contractor does not turn over all responsibility to the clinical site or the CRO. The contractor must be able to manage the CRO/site's performance.
  - The clinical site must be willing to comply with all the FAR clauses and NIAID/DMID policies; FAR clauses flow down from the contractor to the sub-contractor.
  - The DMID-ORA-002 Request Form (Request to Sponsor an IND/IDE for a DMID-Funded Clinical Trial) must be completed and submitted to the CPM, copying the COR. The CPM will review and submit it to the DMID Office of Regulatory Affairs for review and approval. The CPM will send you this form to complete when appropriate post-award.

- DMID must review and approve all IND materials prior to submission to the FDA by the Contractor. DMID review requires at least ten business days. Given the coordination among four offices within DMID, it is not a guarantee that the review will be completed within this timeframe. The CPM will collate the comments after the internal review.
- Within a reasonable timeframe, DMID must receive all correspondence to and from FDA relating to the IND, including all materials referenced.
- Even if the study is conducted internationally, it must be conducted under an IND/IDE and follow US regulations, in addition to the international regulatory authorities.
- Federal Wide Assurance (FWA) is required for the IND sponsor and each participating site(s). The FWA numbers must be forwarded to DMID prior to the initiation of the study. These numbers must be included on the DMID-ORA-002 Request to Sponsor an IND/IDE form. The protocol must be registered with a single IRB. Form OMB No. 0990-0263 must be completed and submitted to the CPM and CO/COR. Instructions can be found on the HHS.gov/OHRP site.

ClinicalTrials.gov Protocol Registration

- All DMID supported protocols must be posted on clinicaltrials.gov by the IND Sponsor within 21 days of enrollment and updated as required. Note that DMID is only responsible for posting those trials for which DMID holds the IND. When the contractor holds the IND, the contractor must complete the posting. The NCT number must be received prior to enrollment.

Clinical Data Management Plan (DMP)

- The DMP must be provided for the DMID review and approval prior to study initiation.
- The DMP must include the process for sharing of data with the DMID.
- The specifics of data sharing will differ from protocol to protocol but at a minimum, you will need to provide to the DMID staff the following:
    1. Timely safety data reports (blinded and unblinded) for the safety oversight review, the format of which must be approved by the DMID and Safety Oversight team members (SMC, DSMB). The DMID will review and approve all reports for the safety oversight committee meetings.
    2. Plans for interim data analysis and report format or data table shells to be used in such analysis.
    3. Statistical analysis plan/template of Clinical Study Report (Can be submitted prior to database lock).
- Plan for keeping data blinded for the sponsor, Safety Review Committee (if applicable), DMID and the Safety Monitoring Committee (SMC) members during the study (the SMC has the option of requesting unblinding for a specific subject or study as needed.)
- The DMP will include the eCRFs.
- The DMP will include how the data will be reviewed to determine if any pausing rules have been met.
- The format and programming of the database must be completed prior to enrollment.
- Data Sharing Plan provided to the COR.

Clinical Monitoring Plan and Monitoring the Clinical Trial

- Prior to site initiation, the following documents must be sent to the DMID for review and approval:
    - Protocol-specific clinical monitoring plan
    - Monitoring trip report templates
    - Completed DMID site assessment questionnaire and all other site qualification and assessment visit reports and/or pre-visit questionnaires used to determine site suitability for participation
    - Copies of any Form FDA 483 citations issued to the site(s) along with the corrective action plans
- You must conduct a site Study Initiation Visit and provide adequate clinical monitoring for the clinical trial. DMID personnel may attend this visit via telephone or in person.
- All monitoring visit trip reports must be forwarded to the DMID within 21 days following the monitoring visit. Trip reports must include all action items that have been identified, addressed or communicated to the DMID.
- Any findings, issues or discrepancies identified by the monitors must be addressed and followed to resolution by the IND Sponsor.

- The DMID must approve the use of the clinical site. If significant issues or discrepancies are identified, the DMID can withhold funding of your trial until they are corrected.
- The DMID reserves the right to audit any clinical site, the monitoring activities and your clinical processes at any time during the trial.
- Monitors must verify site personnel compliance with the NIH Human Subjects Protection training requirements. The training must occur within a year of study start and then be renewed according to the SOP's of the site and IRB.

Pharmacovigilance

Under the Clinical Terms of Award, the awardee must submit copies to the responsible DMID contracting officer's representative as follows:

- Expedited safety reports of unexpected or life-threatening experience or death.
- Expedited safety reports of serious and unexpected adverse experiences
- Expedited safety reports

Other adverse events documented during the course of the trial should be included in the annual IND report and reported to the DMID annually.

- As the IND Sponsor, you must have a Medical Monitor who will assess all SAEs.
- All SAE reports are reviewed by a DMID medical monitor who can request further clarifications or information if he or she deems it necessary.
- The sponsor is responsible for submitting all safety reports (CIOMS, SUSARs etc.) to the FDA. The DMID must be copied on all safety submissions.
- You must present the details of your safety reporting process in advance with the DMID OCRA Safety Coordinator and Medical Monitor. The Safety Monitoring plan must be reviewed and approved by DMID, but a signature from a DMID employee is not required on the plan. Provided that the Contractor has a Medical Monitor, the DMID Medical Monitor might only be required to review the Safety Management Plan.

Safety Oversight

- All DMID sponsored studies must have DMID agreed upon safety oversight mechanisms. You will need to submit your safety oversight plan for approval to the COR and Clinical team. Either you or DMID will handle this task.
- All NIH-funded clinical trials have either a Safety Monitoring Committee (SMC) or Data Safety Monitoring Board (DSMB) that will provide recommendations regarding the study to the DMID.
    - All clinical trials of 100 or more subjects will require a DSMB, rather than an SMC.

  - You may suggest individuals to serve as members on the SMC or DSMB; however, the DMID has the final right of approval for all members.
  - The IND Sponsor may elect to establish and manage the SMC/DSMB according to DMID policies
    - If you prefer for DMID to arrange this, then DMID's contractor will compose the SMC/DSMB charter. They will use an approved template for drafting the SMC/DSMB charter. DMID's contractor will then be responsible for the technical arrangement of the committees/boards and their meetings. They will provide the signed meeting minutes and recommendations.
  - An organizational meeting must occur prior to study enrollment.
  - The format and programming of the reports must be completed prior to the organizational meeting and be approved by DMID.
  - You will need to provide timely reports for the SMC's or DSMB's review according to the charter. These reports must be reviewed and approved by DMID prior to posting for the SMC/DSMB.
  - Narrative summaries are requested for subjects with Grade 3 and above adverse events, SAEs and AEs of special interest.
  - You will submit the SMC minutes to the IND in a timely fashion after the final minutes are available.

- The safety oversight plan will be discussed in advance of study start. Keep in mind that this is a requirement for all DMID funded clinical trials. The purpose is to provide independent safety review FOR DMID as well as the IND Sponsor.
- During SMC/DSMB meetings, non-SMC attendees may be present but should not participate in the discussions unless they are designated as a presenter on the agenda, called upon by the IND Sponsor, DMID, the SMC or one of the presenters.
- For a dose-escalation study, we expect objective pausing rules be identified which would be followed before proceeding onto the next cohort. Some protocols identify a Safety Review Committee of the PI from the site, Medical Monitor from the Sponsor and DMID Medical Monitor for a review of the data between cohorts. Our preference is for objective criteria which would not require a formal meeting. Should a meeting be held, other members of the Sponsor and DMID teams should be included. There should be pausing rules for the full protocol as well which cover participants in all cohorts combined.

Protocol Deviations

- Sites must adhere to the protocol (i.e., protocol document version) which has been approved by the FDA, the DMID and the respective IRB(s).
- Eligibility waivers (i.e., exemptions from the protocol inclusion/exclusion criteria) are NOT allowed in DMID-funded clinical studies.

- All protocol deviations must be reported as a section within the SMC/DSMB safety data reports.

Quality Management Plan

- All clinical trials supported by the DMID will be required to have a Site or Protocol Specific Quality Management Plan.
- Routine internal quality audit findings and other significant findings must be reported to the DMID.
- The Quality Management Plan must be periodically reviewed by the clinical monitors to verify it is current and reports have been forwarded for the Sponsor and DMID review.

Single IRB Review

- NIH expects that all sites participating in multi-site studies, which involve non-exempt human subjects research funded by the NIH, will use a single Institutional Review Board (sIRB) to conduct the ethical review required for the protection of human subjects. A Single IRB is the IRB of record, selected on a study-by-study basis, which provides the ethical review for all sites participating in a multi-site study.
- This policy applies to the domestic sites of NIH-funded multi-site studies where each site will conduct the same protocol involving non-exempt human subjects research. Implementation of the NIH sIRB policy is expected to reduce unnecessary administrative burdens and systemic inefficiencies while maintaining appropriate human subjects protections.
- Applicants are expected to include a plan for the use of a sIRB in the contract proposals they submit to the NIH.