Infectious Diseases Clinical Research Consortium

19 Endpoint Lab Oversight

19.1 Purpose

This section provides an overview of key aspects of endpoint laboratory oversight by the IDCRC Laboratory Operations Unit (LOU), and the expectations and responsibilities of the endpoint laboratories selected to participate in IDCRC clinical protocols.

19.2 Scope

High quality and reproducible assay data are critical to successful product development and evaluation and thus, the selection of laboratories to conduct highly standardized and robust assays in support of protocol objectives/endpoints is key to successful clinical trial execution. The LOU was established to manage and oversee clinical and research laboratory services in line with regulatory guidelines and adherence to good clinical laboratory practice (GCLP). Its responsibilities include harmonization of laboratory activities and evaluation and oversight of all assay laboratories participating in IDCRC protocols. This MOP section outlines the responsibilities and processes pertaining to the selection, verification, and certification of endpoint laboratories and the conduct of endpoint assays in support of protocol objectives/endpoints.

19.3 Process

19.3.1 General Overview

The LOU identifies, selects, and verifies laboratories with the capability and capacity to conduct assays to support each IDCRC protocol objective/endpoint. In alignment with guidelines from NIH-NIAID Division of Microbiology and Infectious Diseases (DMID), industry and US Food and Drug Administration (FDA) (Ref 2-4), the LOU uses defined key parameters for assessment of endpoint laboratories and the developmental status of the endpoint assays needed to support protocol objectives. The criteria are primarily used in the context of testing specimens collected under clinical protocols but can also be applied to non-clinical (lab-based) and secondary research studies. While concept Principal Investigators (PI), protocol chair(s) or others may suggest laboratories for endpoint assay conduct, the LOU makes the final decision to approve each endpoint laboratory and assay supporting IDCRC protocols with concurrence from the IDCRC Executive Management Team (EMT) and DMID.

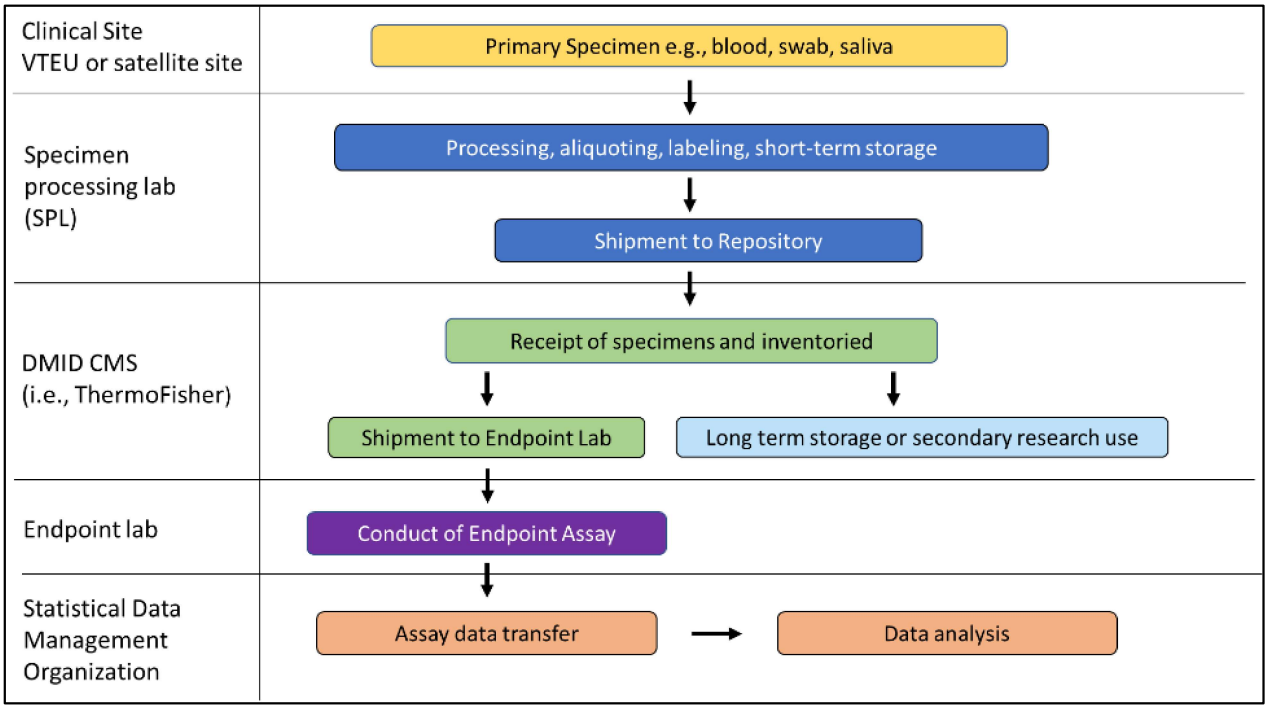
The LOU will request, review, and approve specific assay documentation (e.g., SOP, development report) to confirm each assay is sufficiently developed to support the protocol objective/endpoint. The LOU will consult with the selected endpoint laboratories on details of specimen collection, handling, and quantity to ensure that the specimens meet endpoint assay requirements. If required, the LOU will assist the endpoint laboratory with sourcing specimens for assay development (e.g., negative and/or positive control specimens). Prior to per protocol specimen testing by the endpoint laboratory, the LOU will request and review a study-specific

assay plan to ensure a comprehensive plan is in place to manage and test specimens. The LOU will facilitate communications between the Statistical and Data Management Organization (SDMO) and each endpoint laboratory to establish a data transfer plan (DTP) for each assay and modifications of existing DTPs as needed. Testing of per protocol specimens will not commence until all applicable agreements are in place (e.g., materials transfer agreement [MTA]) and the LOU (and DMID if applicable) has received and approved all requested assay documentation.

Once the protocol is active, the LOU will monitor specimen shipments to endpoint laboratories and communicate testing priorities to ensure assays are conducted and data uploaded to meet study timelines. The LOU will review interim and final data reports and work with endpoint laboratories to investigate issues identified upon assay data review and assist with resolution as needed.

In addition to selection and support of endpoint laboratories and assays, the LOU provides fiscal oversight of the endpoint laboratories including budget estimates for concepts, and budgets submitted for mid-year funding and research performance progress report (RPPR) cycles. In partnership with the SDSU, the LOU contributes to concordance analyses to compare different assays, or the performance of the same assay conducted at different laboratories.

The LOU also oversees specimen management for all IDCRC clinical and lab-based protocols. This oversight ensures high-quality specimens are provided to the endpoint laboratories to test in their specialized assays. The figure below depicts the typical clinical trial specimen flow managed by the LOU.



19.3.2 Endpoint Laboratory Selection and Onboarding

New concepts may be proposed by IDCRC/VTEU investigators, external investigators, industry partners or DMID. The criteria used by the LOU for endpoint laboratory selection will depend on the type of study performed (e.g., Investigational New Drug [IND] versus observational), the type of endpoint assay (e.g., diagnostic, immunogenicity, pharmacokinetic/pharmacodynamic), the quality and completeness of required assay documentation (see next section), and the protocol specified objective/endpoint (e.g., primary, secondary, exploratory) as the requirements for assays will be different depending on the scope of the trial. During the concept or pre-development stages, the LOU will evaluate the capabilities and capacity of endpoint laboratories proposed by the concept PI or will identify potential IDCRC/VTEU internal or external laboratories with assay capabilities that align with the per protocol objectives/endpoints. Based on this evaluation, the LOU will select, verify, and certify each endpoint laboratory. The process involves a rigorous assessment of current laboratory capabilities and previous studies conducted at the respective endpoint laboratory, adherence to established protocols, and compliance with GCLP and applicable regulatory guidelines[2-4] to ensure consistent and transparent evaluation. IDCRC internal and/or external subject matter experts (SME) may be consulted for specific assay questions. Throughout the selection process, the LOU will maintain detailed documentation of the selection and certification processes, including assessments, findings, and outcome.

Once the endpoint laboratory has been selected, the LOU will onboard the laboratory using its internal SOPs. Onboarding of the endpoint laboratory will include a request for more detailed information on laboratory environment, assay development, specimen management, quality management system in place, and internal and/or external quality assurance (EQA) testing for their assays. In some instances, assays may require further development before they are implemented in the protocol. If needed, the LOU may assist in sourcing specimens from within the IDCRC network or externally and facilitate the transfer if specific specimen types, controls, or matrices are required to complete assay development to the applicable stage.

For endpoint assays that are contracted by third party entities, the LOU's oversight responsibilities will be defined during the pre-development and/or development stage of the protocol in collaboration with the protocol chair, DMID and third-party representative(s) and will include review of all required assay documentation (e.g., SOPs, development report, study plan, study report). Prior to onboarding external or laboratories funded by third-party entities, the LOU will work with the LG to assess which agreements are required and assist as needed to facilitate their execution (e.g., MTA, confidential disclosure agreement [CDA]).

The LOU designs and maintains a central assay plan (CAP) for each protocol that describes the specimen batching and testing plan for each endpoint assay. The CAP will source its information from the protocol and MOP, and is shared with the endpoint laboratories, SDMO and other protocol team members for review and revisions. The final version is stored on the protocol specific SharePoint site. Any revisions to the CAP (e.g., alignment with a protocol amendment,

changes to an assay plan) will be communicated by the LOU to the endpoint laboratories and protocol team.
The LOU is responsible for creating budget estimates for the laboratory portion of the ECP and works closely with the endpoint laboratories on the final budgets that align with the approved testing plan described in the CAP. Hereby a first line of communication between LOU and endpoint laboratory will be established which will be manifested throughout the study. In addition, the LOU will solicit and review budgets for the mid-year and RPPR cycles and contribute to drafting funding memos in collaboration with the Clinical Operations Unit (COU).

The LOU also plays a role in certifying endpoint laboratories and reviewing assay documentation (e.g., SOPs, development reports, study plans) for lab-based protocols. Emphasis is placed on the laboratory's proficiency in conducting specialized assays and adherence to specific protocol requirements. Regulatory and GCLP guidelines and criteria as described for clinical trials are used to guide the review process[1-4].

19.3.3 Review and Approval of Assay Documentation

It is the expectation from the IDCRC LG and LOU that all selected endpoint laboratories adhere to stringent quality control and quality assurance protocols, safeguarding specimen integrity and compliance with regulatory requirements. The LOU will use different sources of guidelines and regulations to assess the status of diagnostic, bioanalytical and immunological endpoint assays.[2-4] The LOU will assess the format and content of the endpoint assay SOP and any supporting documentation provided to confirm that the assay parameters align with the specifications for the respective development stage (e.g., developed, optimized, qualified, validated). The LOU will provide feedback and may request additional information if needed. Additional information may include but is not limited to assay development plans and/or reports, assay verification reports, internal and external quality assurance and proficiency testing for the respective assay, peer-reviewed publications reporting on the assay method and/or development, and comparison to gold standard or concordance studies. It is the responsibility of the endpoint laboratories to prepare and compile high quality and complete assay documentation for timely submission to meet study timelines.

In certain cases, and to align with DMID policy, DMID review of assay development reports may be required prior to LOU approval of the reports. The LOU may consult with IDCRC internal or external subject matter experts (SME) prior to approval and if needed, communication between the SME and the endpoint laboratory will be moderated by the LOU. Once all questions have been adequately answered and final documents received, the LOU will communicate its approval by email to the endpoint laboratory PI. If the endpoint assay at any time during the clinical trial or research project requires modification (e.g., reagent substitution due to supply chain issues, addition of circulating variant reagents), the endpoint laboratory and/or PI will inform the LOU and submit revised documentation for LOU review (and DMID if applicable) and approval before any changes to per protocol testing may be implemented.

An assay study plan is also a requirement for each endpoint assay, written and signed off by the endpoint laboratory before any per protocol testing may occur. The study plan will be drafted by the laboratory and include general background information, key contacts and agreements, internal specimen management plan, quality assurance plan, a summary of the assay protocol including controls, data transfer and statistical analysis, and a timeline for testing. The LOU will review and provide feedback on the study plan and approve once all details have been adequately described; in some cases, review by other stakeholders may be applicable (e.g., DMID). The endpoint laboratory is responsible for adhering to previously agreed upon timelines for submitting, revising, and finalizing the study plan. The LOU will provide a study plan template although the endpoint laboratory may use their internal template if it captures the required content. Should modifications to the study plan be required, the endpoint laboratory will inform the LOU and submit a revised study plan for LOU review (and other stakeholders if applicable) and approval prior to implementing the new version.

19.3.4 Continuous Monitoring of Endpoint Laboratories and Assays and Data Review

The LOU will monitor the endpoint assay testing throughout the study, ensuring that testing adheres to the approved study plan, CAP and DTP including timelines for assay conduct and data upload. The LOU works in collaboration with the SDMO to provide estimated dates when specimen batches may be expected to be received at the endpoint laboratory for per protocol testing, and in collaboration with the endpoint laboratories for estimated dates for assay data upload. In addition, the LOU will monitor the data uploads to the SDMO as described in the DTP and in alignment with the CAP. Delays in assay conduct or data upload are communicated by the endpoint laboratories to the LOU along with revised estimated timelines. The LOU will review interim and final data reports generated by the SDMO and if inconsistencies or issues are identified, the LOU may assist the endpoint laboratory in troubleshooting the issue or request repeat testing. Any EQA reports that will be generated from the endpoint laboratory throughout the study will be shared with the LOU for review. Should the EQA report show any performance issues or receive a “fail” result for a round of testing, the endpoint laboratory will share their troubleshooting efforts and corrective action plan(s) with the LOU.

In some instances, together with other IDCRC and/or DMID representatives, the LOU may participate in onsite or virtual laboratory audits. During such audits, the team will assess the capabilities of the respective laboratory and review laboratory procedures and documentation with an emphasis on endpoint assay documentation. As needed, issues or problems identified during these audits will be discussed with the EMT (and DMID if applicable) for further discussion and development of corrective and preventive action plans.

19.3.5 Study Close Out and Specimen Destruction

At the end of the study, the endpoint laboratories will submit an analytical study report to the LOU for review after all per protocol testing is completed and data uploaded to the SDMO, and

within a timeframe agreed upon during endpoint laboratory onboarding. The report will describe procedures and parameters used in the conduct of the endpoint assay and a summary of the testing including specimen and data management. It is the responsibility of the endpoint laboratories to communicate any delay in providing the report to the LOU. All protocol specimens remaining at the endpoint laboratory including residual specimens (leftover from testing) or unopened specimens (e.g., backup aliquots shipped but not tested) are to be handled as dictated by the protocol; in most cases, labs will destroy both types of specimens per laboratory internal SOP. If the endpoint laboratory does not have a procedure available, the LOU will support the lab to establish one. After all testing is completed, and if testing of residual or unopened specimens is desired for purposes not dictated in the protocol, approval for testing is required via the IDCRC Secondary Research Use of Specimens and/or Data (refer to MOP section 18).

19.3.6 Communications and Oversight Responsibilities

The LOU serves as the pivot point for laboratory assay information and liaison between the different stakeholders and the endpoint laboratory team. Clear, precise, and timely communication is essential for the successful conduct of the study and will be established early, typically in the protocol pre-development stage. The LOU will regularly communicate with the endpoint laboratory to request the lab's ability to receive and store per protocol specimens and testing status updates as well as to share upcoming milestones and timelines. The LOU lab protocol coordinators will be responsible for sharing updates related to assay development and conduct with the protocol teams. The LOU will ensure team members are available during all stages of the protocol as point of contacts for endpoint laboratory staff and will facilitate scheduling of ad hoc or standing meetings as needed. It is the endpoint laboratory's responsibility to respond to protocol-specific requests for information and/or updates in a timely manner and adhere to pre-defined milestones as discussed with the LOU and in line with the overall protocol timelines.

Should endpoint laboratory operational issues arise during the clinical trial which cannot be resolved after discussion between the LOU and the endpoint laboratory, the IDCRC Leadership Group and sponsor (DMID) may be consulted to assist in a resolution.

19.3.7 Capacity Building

One goal of the IDCRC is to expand endpoint assay capabilities and capacity within the IDCRC and VTEU network. The LOU will use its expertise and experience to support the in-network laboratories for assay development and improvement of existing assay frameworks so they may be considered for selection as an endpoint laboratory for an IDCRC protocol(s). While the strong preference is for IDCRC and VTEU-affiliated laboratories to participate as endpoint laboratories for IDCRC protocols, should capacity and/or capability not readily be available, the LOU will expand the search for qualified endpoint laboratories outside of the network and assess interest and availability within academic or industry laboratories. In addition, the LOU

leads efforts to harmonize assay protocols across sites and networks and supports assay and technology transfers across laboratories as part of the overall IDCRC capacity building endeavors.

References

1. IDCRC Lab Studies Process_20221213
2. NIAID DMID ORA guidance document: Assay Development/Qualification/Validation Requirements for Nonclinical and Clinical Immunological Assays, V2.0, April 3, 2017
3. Bioanalytical Method Validation, Guidance for Industry, US FDA, May 2018
4. ORA, DMID, NIAID Guidelines – Clinical and Non-Clinical Good Assay Practice (GAP), draft version