Infectious Diseases Clinical Research Consortium

17 Specimen Management

17.1 Purpose

The purpose of this section is to describe the process for managing specimens and associated data collected per IDCRC protocols, and data resulting from laboratory testing of these specimens.

17.2 Scope

This section covers the process for specimen and data flow from the clinical sites to the endpoint laboratories. The IDCRC conducts trials at multiple clinical sites across the US and internationally. During the performance of all IDCRC studies, participant data and specimens are collected at multiple timepoints and stored for evaluation using endpoint assays dictated by the protocols, and/or secondary research studies. The IDCRC Laboratory Operations Unit (LOU) oversees the specimen management program for IDCRC protocols and implements the sharing and distribution of specimens and study-related laboratory data across the IDCRC and outside partners.

The LOU works in concert with the statistics and data management organization (SDMO) on each IDCRC protocol to maintain knowledge of specimen collection and location. Typically, specimens flow from the clinical sites to the DMID-supported clinical material services (DMID-CMS), and then to the endpoint laboratories. The LOU provides guidance for the movement of collected specimens from clinical sites to the DMID-CMS through regular, pre-determined shipment intervals. This approach not only protects the integrity of protocol specimens, but also enables better tracking of protocol inventories and rapid movement of subsets of specimens to specialized endpoint laboratories. The LOU also provides guidance for those protocols that have received a waiver from DMID to ship specimens directly from the clinical sites to the endpoint laboratories. The specimen management plan in these cases is detailed in the protocol-specific MOP and approved by the protocol management team.

Comprehensive specimen management also encompasses monitoring specimen discrepancies by comparing the specimen data entered in the laboratory information management system (LIMS) to specimen data in the clinical database. This ensures the resolution of all specimen discrepancies prior to distribution of specimens to the endpoint laboratories. GlobalTrace and Laboratory Data Management System (LDMS) are the two IDCRC LIMS that this document will cover.

17.3 Process

The LOU maintains a rigorous system for specimen collection, transport, storage, and management with the goal of ensuring specimen integrity. The process involves ensuring clinic and laboratory staff have received training in best practices for cold-chain management during specimen collection, specimen handling, processing, and shipping; electronic tracking to document specimen chain-of-custody from point-of-collection to point-of-testing; and working with the DMID-CMS to minimize risk of damage or loss of collected specimens. The DMID-CMS that DMID currently contracts with is ThermoFisher Scientific.

General Overview

Specimens are collected at VTEUs or affiliated clinical sites and delivered to the associated specimen processing laboratories. Specimens are processed and aliquoted according to the protocol-specific MOP, labeled in alignment with the requirements of the SDMO, and regularly shipped to the DMID-CMS for storage.

After arrival of the shipment at the DMID-CMS, it is inspected to ensure all specimens are present and accounted for in electronic shipment manifests. Specimens are then stored at the appropriate temperature (e.g., sera and plasma are stored in -80°C freezers, PBMC are stored in liquid nitrogen vapor phase freezers). The DMID-CMS concurrently accessions the specimens into their local LIMS. Specimens stored for per protocol assays to be conducted at specified endpoint laboratories are held at the DMID-CMS (or at the clinical site in cases of a waiver) and shipped in prespecified batches per the protocol-specific Central Assay Plan (CAP). Specimens that are not depleted for per protocol assays, and those collected for secondary research, remain in the DMID-CMS. These specimens may eventually be used for per protocol exploratory assays, secondary research studies (see IDCRC MOP section: Secondary Research Use of Specimens and/or Data) or culled to reduce the DMID-CMS costs. For instances when the clinical site ships specimens directly to an endpoint laboratory, after all per protocol specimens have been shipped and evaluated, residual specimens and those collected for secondary research are shipped to the DMID-CMS for use in exploratory assays, secondary research studies or culled.

The LOU will design and generate a CAP for each IDCRC protocol. The CAP summarizes the plans for testing specimens to assess immunological and other laboratory outcomes in support of per protocol objectives. It outlines the interim reports that will be distributed for each endpoint assay, including the dataset from prescribed specimen batches that will contribute to each report. Once the initial data report for a given endpoint assay has been prepared, each subsequent data report will display cumulative data from specimens for all timepoints assayed to date. The CAP provides the endpoint laboratory contacts and batching scheme for all specimens to be shipped to each endpoint laboratory for testing using specialized assays. The CAP will be provided to the assigned SDMO, endpoint laboratories, and the protocol team for review and approval. The LOU will alert the SDMO, endpoint laboratories and protocol team when changes are made to the CAP.

The SDMO maintains a visit completion report, which contains projected dates for each participant visit. This report is available to the LOU and DMID. This calendar allows the LOU to approximate the date that all specimens for each dataset should be collected and shipped to the DMID-CMS, and thus available for shipment to an endpoint laboratory. The LOU will inform endpoint laboratories of approximate dates of specimen availability.

At specific times during the lifecycle of a protocol, the LOU will request that the SDMO programmatically generate a picklist of specimens to be shipped from the DMID-CMS (or directly from the clinical site in cases of a waiver) to an endpoint laboratory. Examples of the times picklists may be requested are as follows:

- When certain milestones have been reached for a predefined subset or all subjects as dictated by the CAP
- Once all specimens have been collected and shipped to the DMID-CMS
- After the study is complete and the transfer of residual specimens from subjects who consented for secondary research use has been approved according to the process outlined in the IDCRC Secondary Research Use of Specimens and/or Data

The SDMO will draft a specimen request form that notes the protocol number, the endpoint laboratory—including laboratory contact and mailing address—the assay to be performed, participant specifics (e.g.,

specific groups, subset of a group, random selection based on age), type of specimen (e.g., serum, PBMC), number of vials per timepoint, and other relevant information. The SDMO will then circulate the picklist for review and approval by the LOU and request signatures from the protocol specific DMID representative and respective endpoint laboratory.

Once the specimen request form is signed by all parties, the SDMO will generate the approved picklist and provide it to the DMID-CMS (or clinical site in cases of a waiver). The DMID-CMS (or clinical site in case of a waiver) will identify, pull, and pack specimens, and notify the endpoint laboratory contact by email of the planned shipment with a courtesy copy to IDCRC.Shipments@fredhutch.org. With approval of the shipment by the endpoint laboratory contact, the DMID-CMS (or clinical site in case of a waiver) will ship the specimens and provide the e-manifest and courier tracking number by email. The manifest will provide protocol number, specimen type, specimen ID and specimen location in the shipping box. If a receiving lab needs additional information, this should be requested of the SDMO prior to specimen request form signoff (e.g., multiple vials from the same participant timepoint need to be pooled for an assay; which vials belong to multiple timepoints from the same participant to be run in the same assay). The endpoint laboratory will receive the specimens and report any discrepancies between the shipment and the manifest. A testing picklist may also be requested by the endpoint laboratory or the LOU to identify specimens at the endpoint laboratory that require additional evaluation (e.g., reagents become available for newly circulating variants or endpoint labs modify their assay process). The testing picklist approval process will follow the steps detailed above, but the approved testing picklist of specimens is provided directly by the SDMO to the endpoint laboratory.

The SDMO will work with each endpoint laboratory to create a Data Transfer Plan (DTP) ahead of data upload to ensure data format is agreed upon and reflects the needs of the study statisticians. The SDMO will draft data report shells for each endpoint assay and send to the respective endpoint laboratory, LOU, DMID representative, and protocol chair(s) for review, edits, and approval. The endpoint laboratory will conduct the prescribed assays on the specimens, and data will be uploaded to the SDMO in accordance with the DTP. The uploaded data are analyzed as described in the protocol and/or SAP and will be included in the data report and provided to the endpoint laboratory, LOU, DMID representative, and protocol chair(s) for review, edits, and approval before sharing with the protocol team and others, as necessary (e.g., industry partners, FDA).

IDCRC protocols are supported by one of two SDMOs: Emmes and the Statistical and Data Science Unit (SDSU). Each use distinct LIMS—GlobalTrace and LDMS, respectively. The processes for using each are described in more detail in the following sections.

GlobalTrace (summarized below, see study MOP/Global Trace User's Guide for detailed instructions)

When Emmes is the assigned SDMO for an IDCRC protocol, specimen processing and shipment data will be entered and stored in GlobalTrace. Emmes may provide sites with write-on labels for use on primary specimen containers. Each data collection form notes the specimen type and intended use (e.g., sera for antibody assays, sera for secondary research), the subject ID, visit number, date of blood draw, secondary use consent designation, and other data fields as required by the protocol and specimen processing SOPs. The clinic staff collect the specimens from study participants, label the primary specimen containers and deliver them to the site-affiliated specimen processing lab, along with the corresponding data collection forms. The completed data collection forms are source documents and should be stored in the specimen processing lab.

Specimens are processed into derivatives (e.g., sera, plasma, PBMC) and aliquoted. Emmes will also provide rolls of paired sets of identical barcodes: one barcode will be applied to the aliquot vial, and the matching barcode will be placed on the GlobalTrace form. Each aliquot must be labeled with its own

unique barcode label.

After scanning each specimen barcode, the users must link the specimen by entering the data recorded on the GlobalTrace data collection form. Other applicable details may also be defined.

The site-affiliated specimen processing lab will ship specimens to the DMID-CMS at a frequency dictated by the protocol-specific MOP. The labs will create a shipment in GlobalTrace, then add specimens to it. A shipping manifest will be generated in GlobalTrace as specimens are scanned and prepared. After a shipment is sent electronically in GlobalTrace, an email with an html manifest is sent to the specimen processing lab, the DMID-CMS, and Emmes. Upon receipt of the physical shipment, the DMID-CMS uses the QC Scan feature in GlobalTrace to confirm the contents of the box. Any discrepancies are communicated back to the site by rejecting the electronic shipment back to the site for reconciliation, after which they resend the electronic shipment back to the recipient. Upon acceptance of the shipment, the specimens will be accessioned into the DMID-CMS inventory.

Following the picklist approval process detailed above, specimen batches are shipped to endpoint labs. Within GlobalTrace, the endpoint laboratory confirms receipt of the shipment electronically and follows the same steps as the DMID-CMS to inventory samples. Resultant assay data are uploaded to Advantage eClinical using specimen barcode numbers. The endpoint assay data are integrated with existing study data by the attributes defined in GlobalTrace.

Laboratory Data Management System

When the SDSU is the assigned SDMO for an IDCRC protocol, specimen processing and shipping data will be entered and stored in the LDMS. Frontier Science and Technology Research Foundation (FSTRF) will compile LDMS data before sending it to the Statistical Center for HIV/AIDS Research and Prevention (SCHARP). An overview of the specimen management process is depicted in Figure 1, below. SCHARP will provide sites with primary specimen label templates that will be used to generate the labels for primary specimen containers. Clinic staff collect specimens from study participants, label the primary specimen containers and deliver them to the site-affiliated specimen processing lab, along with the corresponding LDMS specimen tracking sheet. This completed specimen tracking sheet is a source document and should be stored in the specimen processing lab.

Specimen processing lab staff enter participant ID, primary specimen, and aliquot information from the specimen tracking sheet into LDMS. Aliquot labels are generated using the data entered into LDMS, and specimens are then processed into derivatives and aliquoted (e.g., sera, plasma, PBMC). FSTRF provides all LDMS data to the SDSU via a data feed that refreshes once every 24 hours.

All processed specimens are shipped at the frequency dictated in the protocol-specific MOP to the DMID-CMS (or maintained at the clinical site in cases of a waiver). The specimen shipment is accompanied by an electronic LDMS manifest which is sent via email to the DMID-CMS. The DMID-CMS will accession the specimens into their InTrak system with a barcode reader, capturing the LDMS-generated unique global specimen ID for each aliquot. The DMID-CMS will reconcile the specimens received with the electronic manifest provided by the site processing lab. The DMID-CMS will provide SCHARP with a .csv file containing the entire IDCRC inventory at least weekly. For certain protocols, or as determined by DMID, this inventory file will be requested more frequently. SCHARP will reconcile the inventory data with the LDMS data they receive from FSTRF.

If there is a shipping discrepancy, the DMID-CMS will email the sender and copy IDCRC.Shipments@fredhutch.org (SCHARP and LOU alias). If the source of the discrepancy is not identified and resolved between the sending lab and the DMID-CMS, the LOU and/or the SCHARP will assist in determining and resolving the discrepancy.

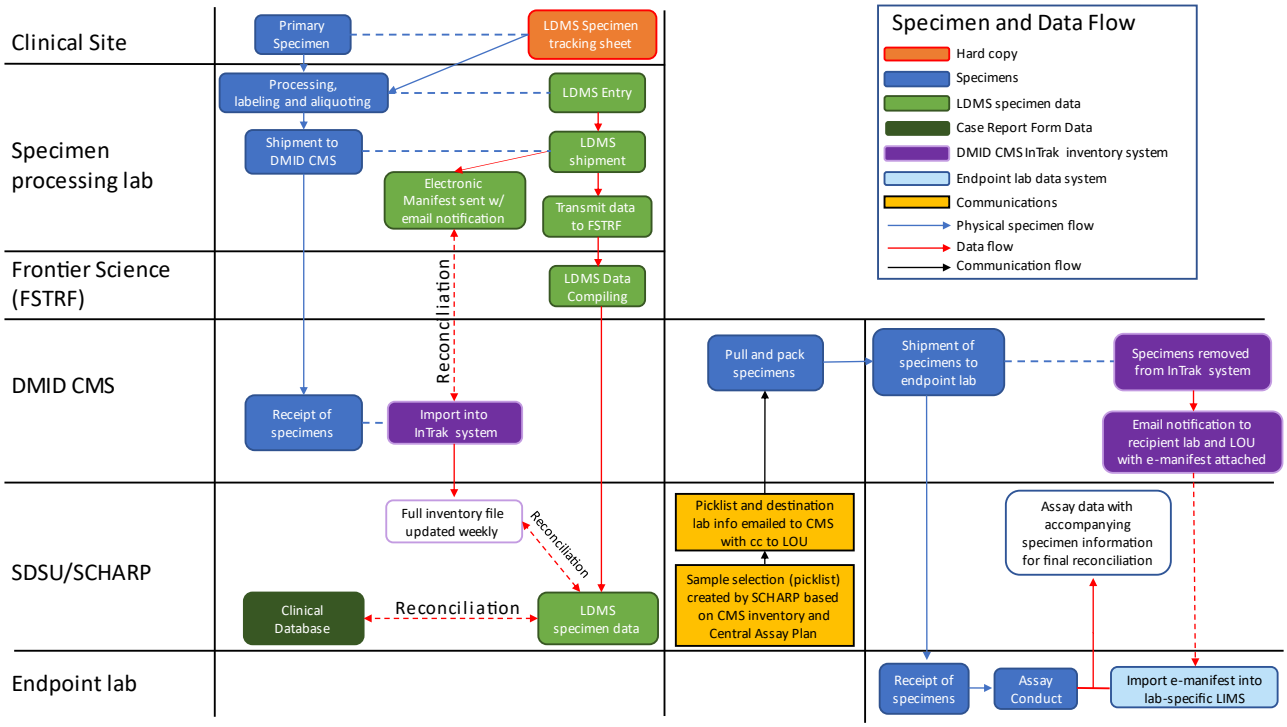
The LDMS data housed at SCHARP will be reconciled with the case report form database. Specimen data discrepancy reports are emailed to sites and labs weekly. Discrepancies may be addressed in various ways

depending on whether the source of the discrepancy is obvious or needs to be investigated with the clinical site and/or processing laboratory.

Once a picklist has been approved by the LOU, DMID representative, and endpoint laboratory, SCHARP will provide the approved picklist to the DMID-CMS (or to the clinical site in cases of a waiver). The DMID-CMS (or clinical site in cases of a waiver) will prepare the shipment and send once the endpoint laboratory has confirmed by email its ability to receive the shipment. The DMID-CMS (or clinical site in cases of a waiver) will include a hardcopy of the manifest in the shipment and email the endpoint laboratory an electronic manifest and courier tracking number. Once specimens are received at the endpoint laboratory, the laboratory will compare the electronic manifest to the specimens received. If there is a discrepancy, they will notify the DMID-CMS (or clinical site in cases of a waiver) and copy IDCRC.Shipments@fredhutch.org. If the source of the discrepancy is not identified and resolved between the endpoint laboratory and the DMID-CMS (or clinical site in cases of a waiver), the LOU/SDSU team will assist.

The endpoint laboratory will upload assay data to SCHARP and include the global specification ID for each vial. SCHARP will use this specimen information received with the assay data to reconcile any discrepancies.

Figure 1. Overview of Specimen and Data Flow (via DMID CMS) for Protocols Assigned to SDSU/SCHARP



IDCRC Policy for Specimen Custody, Management and Access

NIH grant recipient institutions own the title to biological specimens resulting from any activity pursuant to a grant-supported project awarded to that institution, unless otherwise specified in the grant or in study-specific contractual agreements. Therefore, while the IDCRC institutions normally own the title to specimens collected at their institution, IDCRC policy governs the custody, management and access to all specimens collected as part of IDCRC clinical research studies. These specimens will be managed by the

IDCRC through its policies regarding submission, storage, and access to specimens for secondary research. Specifically, the IDCRC will manage the distribution of specimens and data through the process of application, review and approval outlined in MOP 18.2 Secondary Research Use of Specimens and/or Data.

Further, the IDCRC maintains an umbrella Material Transfer Agreement document to facilitate moving specimens among IDCRC institutions (refer to the IDCRC SharePoint at LOC Non-monetary Agreements LOC, MTAs). The MTA document indicates that the provider of the specimens retains title to the specimens they are sharing.

It is a requirement to include in manuscripts or other communications using any IDCRC specimens: *Supported by the Infectious Diseases Clinical Research Consortium through the National Institute of Allergy and Infectious Diseases, part of the National Institutes of Health, under award number **UM1AI148684** (and by VTEU grant award number and/or other appropriate funding source). The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.*