Pharmacy Guidelines and Instructions for DAIDS Clinical Trials Networks

Division of AIDS
Pharmaceutical Affairs Branch

National Institute of Allergy and Infectious Diseases

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SECTION 1: Glossary

For additional definitions, see DAIDS glossary.

- **ALCOA-C** – Attributable, Legible, Contemporaneous, Original, Accurate, Complete.
- **Authorized Prescriber** – A clinician authorized to prescribe in the site's jurisdiction who is listed on the current FDA Form 1572 (IND studies) or authorized prescribers list (non-IND studies) for a given protocol at the participating site.
- **Associate Pharmacist (AP)** – A licensed/registered pharmacist who performs the day-to-day pharmacy activities and study product management including but not limited to the procurement, storage, preparation, dispensing and final disposition of study products for the DAIDS-funded and/or sponsored clinical trial(s), when the Pharmacist of Record is absent.
- **Clinical Research Records** – Original documents, data, and records (e.g., hospital records, clinical and office charts, laboratory notes, memoranda, participants' diaries or evaluation checklists, paper or electronic pharmacy dispensing records, recorded data from continuous temperature monitoring devices, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, participant files, records kept at the clinic, pharmacy, and laboratories involved in the clinical trial, and any correspondence records).
- **Clinical Research Site (CRS) Leader** – The on-site senior research scientist responsible for the administrative and scientific components of the CRS. The CRS leader is responsible for overall site activities, including the day-to-day operations, performance, and compliance at the site level.
- **Clinical Trials Unit (CTU) Principal Investigator (PI) –** The Principal Investigator is listed as the Grantee on the Notice of Award and is responsible for all CTU activities and CTU performance. This includes responsibility for affiliated clinical research sites (CRS), including communications, site performance and financial management. The PI also provides CTU scientific and administrative representation to the Network(s).
- **Division of AIDS (DAIDS) Sponsored** – DAIDS is responsible for the management, (including submission of the Investigational New Drug Application (IND) to the U.S. Food and Drug Administration (FDA) and the initiation of the study) and oversight for the clinical trial or study.
- **Division of AIDS (DAIDS) Supported –** See DAIDS Glossary
- **Global Pharmacy Services Visit (GPS)** – GPS visits are performed by the group delegated by DAIDS to conduct baseline assessments of pharmacy operations as detailed in a site's most current PAB approved Pharmacy Establishment Plan. Additional special pharmacy assessments requested by PAB may also be included as part of the visit.
- **High-Efficiency Particulate Air (HEPA) filter** – A type of high-efficiency air filter that removes at least 99.97% of airborne particles 0.3 micrometers (μm) or larger in diameter.
- **Interim Site Monitoring Visit (ISMV) -** Interim Site Monitoring Visits are performed by the group delegated by DAIDS to conduct periodic on-site monitoring visits to DAIDS Clinical Research Sites to evaluate the quality and validity of study data, compliance with Good Clinical Practices, and protection of research participants.

- **Investigator of Record (IoR)** – The person responsible for the conduct of the clinical trial at a clinical research site. The person who is the signatory for the Form FDA 1572 (IND studies), or IoR Agreement (Non-IND studies). Written delegation of authority for specific study responsibilities may be given to qualified individuals at the clinical research site.
- **National Institutes of Allergy and Infectious Diseases Clinical Research Management System (NIAID CRMS)** – A comprehensive computer system that supports the management of clinical research funded by (or otherwise supported by) the Division of AIDS (DAIDS), Division of Allergy, Immunology and Transplantation (DAIT), Division of Microbiology and Infectious Diseases (DMID), and the Vaccine Research Center (VRC).
- **NIAID DAIDS Clinical Site Monitoring (DAIDS CSM)** – A module within NIAID CRMS that serves as the database of record for all monitoring data across DAIDS monitored studies.
- **PAB Protocol Pharmacist** – The PAB Pharmacist who provides expertise on all pharmaceutical aspects of protocol development and conduct and serves as a key member of the protocol team.
- **PAB Site Pharmacist** - The PAB Pharmacist who provides pharmacy oversight support, in collaboration with the PAB Site Specialist, for a specific CRS pharmacy.
- **PAB Specialist** - The PAB Specialist who provides pharmacy oversight support, in collaboration with the PAB Site Pharmacist, for a specific CRS pharmacy.
- **Pharmacist of Record (PoR)** – A licensed/registered pharmacist who performs the day-to-day pharmacy activities and study product management including, but not limited to, the receipt, storage, preparation, dispensing and final disposition of study products for the DAIDS-supported and/or sponsored clinical trial(s).
- **Pharmacy** – Any facility, building, or room used by pharmacists to perform one or more of the following functions: storage, preparation, dispensing, management of study products (examples: hospital pharmacy or institutional pharmacy, dispensary, drug storage unit, drug store).
- **Pharmacy Ancillary Supplies** – Any materials or tools that may be used in a pharmacy to perform and support the day-to-day study product preparation and dispensing activities and functions of the pharmacist, such as needles and syringes, oral syringes, prescription vials and lids, gowns, masks, IV solutions, or diluents.
- **Pharmacy Equipmen**t – Apparatus that is used to ensure the physical and scientific integrity of the study product during shipment, storage, handling, and preparation. Examples of pharmacy equipment are biological safety cabinets, refrigerators, -20°C freezers, -70°C freezers, air conditioners, air heaters, humidifiers, dehumidifiers, thermometers, vortex machines, temperature alarm systems, limited access/security systems (security alarms, key locks, biometric identification access), locking file and storage cabinets, shelving, counting trays for tablets and capsules, graduated cylinders, spatulas, study product containers, fax machines, scanners, computers, or printers.
- **Principal Investigator (PI)** – The qualified person designated by the applicant institution to direct the funded research program. PIs oversee the scientific and technical aspects of an award and the day-to-day management of the research.

- **Pre-Visit Letter (PVL**) - Letter sent to the site informing them of the upcoming site monitoring visit.
- **Study Product** - Any drug, biologic, vaccine, radiopharmaceutical, item or device that is either provided through the study or identified in the protocol as a study product. This may include, but is not limited to, the following:
    - A new drug or biological drug that is used in a clinical investigation
    - A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including a product with a marketing authorization when used or assembled (formulated or packaged) in a way different from the approved form, for an unapproved indication, to gain further information about an approved use, or for its approved labeled indication.

  The terms “investigational product”, “investigational medicinal product”, "investigational drug", "investigational new drug", “investigational agent”, and “study product” are deemed to be synonymous for purposes of this definition.
- **Sub investigator** – Any individual member of the clinical trial team designated and supervised by the investigator at a trial site to perform critical trial-related procedures and/or to make important trial-related decisions (e.g., associates, residents, research fellows). See also Investigator of Record.
- **Temperature-Controlled Environment** - The environment within a temperature-controlled building/vehicle.

United States Pharmacopeia/National Formulary (USP/NF) Definitions:

- **Room Temperature** – The temperature prevailing in a working area.
- **Controlled Room Temperature** – The temperature maintained thermostatically that encompasses the usual and customary working environment of 20°–25°C (68°–77° F). The following conditions also apply. Mean kinetic temperature not to exceed 25°C. Excursions between 15° and 30°C (59° and 86° F) that are experienced in pharmacies, hospitals, and warehouses, and during shipping are allowed. Provided the mean kinetic temperature does not exceed 25°C, transient spikes up to 40°C are permitted as long as they do not exceed 24 hours. Spikes above 40°C may be permitted only if the manufacturer so instructs. Articles may be labeled for storage at “controlled room temperature” or at “20°–25°C”, or other wording based on the same mean kinetic temperature.
- **Warm** – Any temperature between 30˚C and 40˚C (86˚F and 104˚F).
- **Excessive Heat** – Any temperature above 40˚C (104˚F).
- **Cool** – Any temperature between 8˚C and 15˚C (46˚F and 59˚F).
- **Cold** – Any temperature not exceeding 8˚C (46˚F).
- **Refrigerator** – A cold place in which the temperature is maintained thermostatically between 2˚C and 8˚C (36˚F and 46˚F).
- **Freezer -** A place in which the temperature is controlled between −25° and −10°C (−13° and 14° F). It is noted that, in some instances, articles may have a recommended storage condition below −20°C (−4° F). In such cases, the temperature of the storage location should be controlled to ±10 degrees.

Note: The USP definitions are provided as a reference. Temperature and environmental storage for study product(s) is protocol-specific.

SECTION 2: Pharmaceutical Affairs Branch Overview

The Pharmaceutical Affairs Branch (PAB) is a component of the Office of Clinical Site Oversight (OCSO), within the Division of AIDS (DAIDS) of the National Institute of Allergy and Infectious Diseases (NIAID), of the United States National Institutes of Health (NIH). The PAB is responsible for performing the following key functions:

- Provide expertise on all pharmaceutical aspects of protocol development and conduct as protocol team members.
- Coordinate and provide oversight of the Clinical Research Products Management Center (CRPMC) to ensure that study product supply, packaging, blinding and distribution activities for all the DAIDS-sponsored and/or supported clinical trials are performed in accordance with DAIDS requirements.
- Establish processes, oversee and monitor adherence to quality assurance standards and standard operating procedures for all pharmacy and product-related issues at the clinical research sites participating in the DAIDS-sponsored and/or supported trials.

I. Background

The DAIDS-sponsored and/or supported clinical trials networks have been established to develop and support the infrastructure and biomedical research needed to:

- Halt the spread of HIV through the development of an effective vaccine and biomedical prevention strategies that are safe and desirable.
- Develop novel approaches for the treatment and cure of HIV infection.
- Treat and/or prevent HIV co-infections and co-morbidities of greatest significance.
- Partner with scientific and community stakeholders to efficiently implement effective interventions.

As a sponsor of clinical investigations, the DAIDS must comply with the U.S. Food and Drug Administration (FDA) regulations, the International Conference on Harmonization (ICH)/ Good Clinical Practice (GCP), as well as regulations outlined by other international authorities, such as the European Medicines Council (EMA). The DAIDS has the responsibility of ensuring that all investigators establish and maintain adequate records of study product receipt, use, and disposition to comply with FDA regulations and the standards of research involving the use of study products in DAIDS-sponsored and/or supported clinical trials.

At a DAIDS-sponsored and/or supported clinical research site, the Clinical Research Site (CRS) Leader is responsible for oversight of all site activities, including day-to-day operations, performance, and compliance at the site level. The DAIDS requires the CRS Leader to delegate the responsibility for study product management at the clinical research site to a licensed/registered pharmacist. This pharmacist is the Pharmacist of Record (PoR).

The PoR is responsible for coordinating all research pharmacy operations and performing the day-to-day pharmacy activities related to the management of study products.

An additional licensed/registered pharmacist working at the site must be designated as the Associate Pharmacist (AP) in order to assume the responsibilities of the PoR, in his/her absence. The AP is trained by the PoR to perform pharmacy activities required of a DAIDS-sponsored and/or supported clinical trial. For the purposes of this manual, all references to the PoR also apply to the AP.

The information in these guidelines will assist pharmacists to meet the required standards of the DAIDS for the conduct of the DAIDS-sponsored and/or supported clinical trials. Pharmacists are expected to follow these guidelines, in addition to their local and country regulations governing the practice of pharmacy, for the conduct of the DAIDS-sponsored and/or supported clinical trials. For any questions or clarifications, contact the DAIDS PAB at (country specific exit code)-01-301-496-8213 or email DAIDSPAB@niaid.nih.gov.

II. Communication

The PoR must ensure that reliable methods of communication are in place to assure timely and accurate transmission of information to staff affiliated with a DAIDS clinical trial. The PoR must establish a clear plan for routine communications with the PAB and clinic staff. In addition, the PoR is strongly encouraged to participate in clinical research staff meetings, teleconferences, online meetings, and attend DAIDS-sponsored meetings. The PoR is expected to participate in any protocol team calls, pharmacists' calls, protocol start-up calls, and any other protocol-specific or site-specific calls. For any protocol-specific questions, issues, or concerns, the PoR must contact the DAIDS PAB protocol pharmacist. For any general pharmacy questions, issues, or concerns, the PoR must contact the DAIDS PAB pharmacist or specialist assigned to oversee the site. The PoR must contact PAB immediately for any urgent matters. All correspondences related to any DAIDS clinical trial must be documented and maintained appropriately in the pharmacy files.

III. Contact Information

A. Division of AIDS Pharmaceutical Affairs Branch

PAB Email Address	DAIDSPAB@niaid.nih.gov
PAB Pharmacy Establishment Plan Submissions	DAIDSPABPEP@niaid.nih.gov
PAB U.S. Postal Mail Address/phone	Pharmaceutical Affairs Branch Division of AIDS, NIAID 5601 Fishers Lane Room 9D32 Bethesda, MD 20892 Courier Zip Code: Rockville, MD 20852 USA Main Line Telephone Number: (01)-301-496-8213 PAB Fax Number: (01)- 240-627-3112

B. Clinical Research Products Management Center

The CRPMC has been established to support the DAIDS clinical trials networks. As a contract of the DAIDS, the CRPMC's primary role is the storage and distribution of study products.

CRPMC Email	USRO1CRPMCUsers@thermo.com
CRPMC U.S. Postal Mail Address and Courier Service Address	Clinical Research Products Management Center 1055 First Street, Suite 125 Rockville, Maryland 20850 U.S.A.
CRPMC Main Line Telephone Number	(01)-301-294-0741
CRPMC Fax Number	(01)-301-294-2905

i. Hours of Operation

The CRPMC's hours of operation are Monday-Friday 8:30 a.m. – 5:00 p.m. Eastern Time (ET), and the shipping hours are Monday-Friday 9:00 a.m. – 4:00 p.m. ET. The CRPMC is closed on weekends and all U.S. Federal holidays; therefore, shipments are not scheduled to leave or be picked up at the CRPMC on these days.

For U.S. Federal holiday schedules, visit the United States Government Office of Personnel Management website.

ii. Shipments

The CRPMC staff usually processes study product order requests as they are received.

For U.S. sites, the CRPMC ships orders Monday through Thursday to arrive the next business day. Wet ice and dry ice shipments are delivered in one business day.

For Non-U.S. sites, due to the time zone differences, it may take up to two business days for the PoR to receive an acknowledgement of receipt of the study product order request from the CPRMC staff. The CRPMC coordinates shipments with a courier service and the PoR to ensure that the study product orders arrive in the shortest period of time possible, on a day when pharmacy staff are present.

iii. COSMOS

The CRPMC Online Site Management and Ordering System (COSMOS) is a web-based application system that supports the CRPMC. COSMOS provides features such as ordering study product, tracking the status of orders, receipt confirmation of study product, managing study product returns/destructions, acknowledging Re-Pass and

Recovery Product notifications. For further details, refer to the COSMOS User Manual or contact the CRPMC. Sites may access the COSMOS manual online.

C. NIAID HIV/AIDS Clinical Trials Networks

The Office of HIV/AIDS Network Coordination (HANC) works with the HIV/AIDS clinical trials networks of the U.S. National Institutes of Health (NIH) with the intent of creating a more integrated, collaborative and flexible research structure. These clinical trials networks are follows:

- AIDS Clinical Trials Group (ACTG)
- HIV Prevention Trials Network (HPTN)
- HIV Vaccine Trials Network (HVTN)
- International Maternal Pediatric Adolescent AIDS Clinical Trials (IMPAACT)

These clinical trials networks have established websites where information pertaining to their respective trials can be found. This includes, but is not limited to, protocol documents, policies, and resource manuals.

SECTION 3: Responsibilities of the Pharmacist of Record

The Pharmacist of Record (PoR) must commit the necessary and appropriate amount of time to meet the pharmaceutical needs and requirements of the DAIDS-sponsored and/or supported clinical trials. At a minimum, the PoR must:

- Be available during clinic hours when study products may need to be dispensed to study participants.
- Be knowledgeable on every DAIDS-sponsored and/or supported clinical trial being conducted at the site pharmacy and must adhere to the requirements of each protocol.
- Coordinate all research pharmacy operations and perform the day-to-day pharmacy activities related to the management of study products.
- Maintain appropriate safeguards to ensure security, integrity and confidentiality of participant information and protect against unauthorized use or disclosure.

I. Professional

The professional responsibilities of the PoR include the following:

A. Training

i. Licensure/Registration

The PoR must be licensed and/or registered to practice pharmacy in the jurisdiction in which the PoR is working.

ii. Good Clinical Practice

The PoR must receive and maintain training in and follow Good Clinical Practice.

iii. Human Subjects Protection

The PoR must receive and maintain training in and follow Human Subjects Protection.

iv. Protocol-Specific Training

The PoR must participate in any protocol-specific training provided by the protocol team. If applicable, the PoR must review any of the associated documents such as the Manual of Procedures (MOPS) and Study Specific Procedures (SSPs).

v. Continuing Professional Development

The PoR is encouraged to have ongoing participation in continuing professional development activities, including the DAIDS Network meetings, the DAIDS regional trainings, professional conferences, and seminars. This will facilitate continued professional growth and awareness and may satisfy requirements to maintain licensure/registration.

vi. Supervision and Training of Pharmacy Staff

The PoR is responsible for the direct supervision of all pharmacy staff assisting with the DAIDS-sponsored and/or supported clinical trials. The AP must be trained by the PoR to perform pharmacy activities required of a DAIDS-sponsored and/or supported clinical trial. The pharmacy staff must be qualified by pharmacy licensure, education, training, and experience to perform their respective tasks. The PoR is also responsible for conducting all protocol-related and Standard Operating Procedure training for any involved pharmacy staff. Pharmacy staff training must be documented, and the training must occur before the pharmacy staff is involved in protocol related pharmacy activities. Training records must include the protocol version or the associated protocol-specific or site-specific document version number.

vii. Protection of Pharmacy Staff

The PoR must be knowledgeable of institutional and protocol-specific practices and procedures, and provide appropriate training to staff, to prevent exposure to potentially hazardous products (e.g., immunogenic, carcinogenic, chemical, mutagenic).

viii. Knowledge of Local and Country Regulations

The PoR must be knowledgeable of and follow all applicable laws and regulations governing the practice of pharmacy and study product management.

B. Study Product Information

The PoR must be able to access all versions of Package Inserts (PIs) and Investigator's Brochures (IBs), pertaining to study products being used in the DAIDS clinical trials during the conduct of the study. The PoR must maintain copies of the most recent version and previous versions of the PI and IB in the pharmacy files. The CRS Leader, or CRS Leader designee, is responsible for providing the PoR with a copy of the PI and IB. Additionally, PIs are available on the DAIDS RSC website. The information in the IB is confidential and should not be reproduced or distributed to individuals outside of the research team.

C. Monitoring Visits and Reports

The PoR must be available for all pharmacy monitoring visits. Once a monitoring visit is planned, an automatically generated email will be sent to site staff. This email will contain a link to both the Pre-Visit Letter (PVL) and the Announced Work Order. It is critical that the PoR view the PVL prior to acknowledging successful receipt. In doing so, the PoR is confirming their presence for pharmacy monitoring visits. At the end of each monitoring visit, a debriefing is held between the monitor and the site staff. The PoR is expected to attend the debriefing. Depending on the findings and nature of the visit, the monitor may have a separate debrief with the PoR.

There are four different types of Monitoring Visits as follows:

i. Site Initiation Visit

The Site Initiation Visit (SIV) is a monitoring visit to assess readiness of a site for participating in DAIDS clinical trials. Once a SIV is planned, an automatically generated email will be sent to the site staff. The Site Initiation Investigational Pharmacy Assessment (SIIPA) will be completed during the visit.

ii. Interim Site Monitoring Visit

The Interim Site Monitoring Visit (ISMV) is a routine site monitoring visit conducted during the life cycle of a clinical trial. The Investigational Pharmacy Inventory and Storage Assessment (IPISA) and Protocol-Specific Investigational Drug Audit (PSIDA) will be completed during the visit, depending on the monitoring requirements.

iii. Pharmacy Operations Visit

Each pharmacy will receive a Pharmacy Operations Visit (POV) once per year that will occur in conjunction with a regular ISMV. This assessment will be performed with the goal to provide a streamlined review of the day-to-day pharmacy operations and pharmacy equipment, with visibility to the site leader to enhance site-level pharmacy oversight. The Annual Pharmacy Operations Assessment (APOA) will be completed during the visit.

iv. Global Pharmacy Services Visit

PAB may also request pharmacy-centered baseline assessments separate from the ISMV through the DAIDS Clinical Site Monitoring (CSM) system. These pharmacy-specific assessments are Global Pharmacy Services (GPS) Visits and are conducted to provide an actual visual assessment of a pharmacy (for example: the layout of the pharmacy and storage areas, the space, the workflow, and the areas in which study product is stored and prepared, including but not limited to refrigerators and freezers). Upon receipt of the request from PAB, the GPS monitor communicates with the PoR to determine a visit date and then plans the visit.

A site pharmacy visit report is issued in the DAIDS CSM system fifteen calendar days after the monitoring visit. The PoR will receive an email to inform them the report has been released. The PoR will review and acknowledge receipt of all pharmacy visit reports (SIIPA, IPISA, PSIDA, POV and GPS) in the DAIDS CSM system within 15 business days of receipt of email notification of report distribution. The PoR will review and provide resolution for the findings within 15 business days of receipt of the email notification from the NIAID CRMS.

II. Oversight of Pharmacy Facilities

The pharmacy must be secure, clean, and of adequate size for the PoR to perform the day-to-day pharmacy activities for DAIDS-sponsored and/or supported clinical trials. In addition, the pharmacy must be appropriately equipped to allow the PoR to provide appropriate storage and quarantine of study products, ensuring protection from vermin, extreme humidity, heat/cold, and light.

All equipment must be exclusively for pharmacy use. There may be study product specific needs that require additional equipment which will be referenced in the protocol or other protocol-specific documents (e.g., MOPS or SSP). All pharmacy equipment must be maintained in accordance with manufacturers' recommended guidelines and access must be limited to pharmacy staff only. The pharmacy facilities must be in compliance with all local laws and regulations.

The responsibilities of the PoR, regarding the pharmacy facilities, include the following:

A. Pharmacy Space

The pharmacy must be of adequate size, organized, and have adequate countertop space and ample lighting. Sufficient pharmacy space and equipment for storing, preparing, and dispensing study products are necessary so that:

- Pharmacists and other pharmacy staff can work comfortably and efficiently.
- The potential for errors is reduced .
- Study products can be adequately separated from other products.
- There is a designated area for quarantined study product.
- Equipment and supplies can be accommodated.
- Pharmacy records can be stored in an organized fashion and be easily retrievable.
- Hand washing and cleaning facilities are available for cleaning purposes.
- Work surfaces are adequate for the preparation of study products, study product accountability, and record management.

B. Environment

i. Water Supply

The pharmacy must have sustainable access to clean, running water for adequate sanitation.

ii. Electrical Supply

The pharmacy must have electrical supply that is available 24 hours a day, 7 days a week, and 365 days a year, through regular or alternate sources.

iii. Extreme Humidity and Light

Every study product storage area must be maintained so that study products are not exposed to extreme ranges of low or high humidity and direct or excessive light. In some climatic regions, the relative humidity may need to be controlled to prevent the growth and spread of unhealthy biological pollutants (i.e., mold), via an additional air-cooling system, humidifier or dehumidifier. If the research protocol specifies a humidity range for a specific study product, humidity must be monitored. If a humidity excursion occurs, the excursion must be reported to the CRPMC, copying the PAB Protocol Pharmacist.

C. Security

Access to the pharmacy must be limited to authorized pharmacy staff. This includes all areas of study product storage and pharmacy files. These areas must have sufficient security systems in place, such as but not limited to locks, alarms, window bars, and/or security personnel. The pharmacy must maintain a visitor's log to document visits by non-pharmacy personnel (e.g. maintenance personnel, monitors, auditors, etc.). When pharmacy personnel are not present in the pharmacy, the pharmacy must be locked. If security has been compromised, the CRS Leader and the PAB must be notified. This breach of security, along with additional correspondences, must be documented and retained in the pharmacy files.

D. Storage and Temperature Monitoring

i. Controlled Room Temperature Storage of Study Products

The pharmacy must be maintained at the appropriate room temperature setting to preserve the integrity, stability, and effectiveness of study products for each protocol. To maintain the pharmacy at controlled room temperature, the use of air cooling and heating equipment may be necessary. In addition, the pharmacy must be of adequate size and have sufficient space and shelving for the room temperature storage of study products.

ii. Refrigerator and Freezer Storage of Study Products

The pharmacy refrigerator(s) and freezer(s) must be maintained at the appropriate temperature range to preserve the integrity, stability, and effectiveness of study products for each protocol. The PAB recommends the use of pharmaceutical grade refrigerators and freezers. These units often have:

- Microprocessor-based temperature control with a digital temperature sensor (thermocouple, resistance temperature detector [RTD], or thermistor)
- Fan-forced air circulation with powerful fans or multiple cool air vents promoting uniform temperature and fast temperature recovery from an out-of-range temperature.

To prevent false readings caused by sudden changes in temperature that can occur

when opening a refrigerator or freezer door, a buffered temperature probe may be the most accurate way to measure temperatures. A probe is "buffered" by immersing it in a vial filled with liquid (e.g., glycol, ethanol, glycerin), loose media (e.g., sand, glass beads), or a solid block of material (e.g., Teflon®, aluminum).

The pharmacy refrigerator(s) and freezer(s) must be:

- Of adequate size and sufficient capacity for the storage and segregation of study products
- Kept in a clean and sanitary condition
- Maintained in good working order
- Capable of maintaining temperatures within the specified storage temperature range setting.

iii. Other Storage Conditions

There may be study products that require specialized storage conditions (e.g., liquid nitrogen/liquid nitrogen vapor phase, -150°C to -210°C). Any specialized equipment or materials required to maintain appropriate storage temperature conditions are described in the protocol or other protocol-specific documents (e.g., MOPS or SSP) and should be available prior to receipt of study product.

E. Temperature Quality Management System

Monitoring of study product storage equipment and temperatures is a daily responsibility to ensure the integrity of study product supply. Daily is defined as any day that the pharmacy is staffed. The PoR has the ultimate responsibility for appropriate temperature storage and monitoring of study product for the safe use of study product.

The PoR is responsible for ensuring:

- The pharmacy has the required equipment to monitor the storage conditions.
- The daily temperature monitoring log for all storage conditions is maintained.
- The temperature data from the continuous temperature monitoring device is reviewed on a regular basis.
- The historical temperature data is maintained and can be retrieved upon request.
- The temperature data is reviewed for any temperature deviations or excursions.
- Variations or trends are identified that may indicate a need for equipment adjustment or service or other uncontrollable factors.
- If a pharmacy technician or pharmacy intern is delegated the activity of performing the daily manual temperature recording and documentation of the review of the continuous temperature data, this activity is detailed in an SOP which demonstrates full documented PoR oversight.

Implementing routine temperature monitoring activities can help identify temperature excursions quickly and ensure immediate action is taken to correct them, preventing loss of study product and the potential for dispensation of inappropriately stored study product.

All pharmacy study product storage areas, refrigerators, and freezers must have **TWO INDEPENDENT** temperature monitoring devices.

Temperature Quality Management System consists of five components:

i. Daily Manual Temperature Monitoring and Daily Temperature Log

The device used for the daily manual temperature monitoring must have the capability of capturing the current temperature, and minimum and maximum temperature memory. A daily temperature monitoring log is required to manually record:

- Current Temperature
- Minimum and maximum temperatures
- Date
- Time
- Name/Initials of person who checked and recorded the temperature
- Any actions taken if a temperature excursion occurred
- If a reading is missed, leave a blank entry in the log and add a comment as to why the reading is missing

Temperature data must be analyzed during the recording to determine if the temperature is in the appropriate range. Sites may choose a device that can be read quickly such as a digital minimum-maximum thermometer with memory or another continuous temperature monitoring device. The daily manual temperatures should not come from the same device that is recording the continuous temperatures. If two independent continuous temperature monitoring and recording devices are used, the PoR should designate the device from which daily temperatures will be manually recorded. All thermometers should be accurate to ±0.5° C (±1° F). All instructions, such as maintenance, setting and resetting, calibration, provided by the manufacturer for using the device must be followed. The daily manual system is also used to verify that the alarm system is functioning properly.

ii. Continuous Temperature Monitoring and Recording

Site pharmacies must have equipment that can record the temperature 24 hours a day, 7 days a week, and 365 days a year. Continuous temperature monitoring and recording provides detailed temperature information for the designated study product storage area in which the system is installed. The frequency, duration and range of any deviation/excursion is recorded and can be used by the CRPMC or the manufacturer to determine if the study product can be safely administered or must be replaced. Should the continuous temperature monitoring device fail the daily manual temperature monitoring device and completed daily temperature monitoring log provides a backup.

An electronic temperature data logger is a device that records temperatures at programmed time intervals, and should be set, ideally, with a maximum interval of 15 minutes with more frequent recording desirable. Electronic data must be stored on a system that is backed up on a regular, recurrent basis. Data storage capacity must either meet the need of providing temperature data reports for years of study product storage conditions, or if there is limited data storage capacity of the electronic temperature data logger, then interval data reports should be created and stored either electronically or printed and saved.

PAB does not recommend the following Temperature Monitoring Devices

- Alcohol or mercury thermometers, even if placed in a fluid-filled, biosafe, liquid vial
- Bimetal stem
- Chart recorders
- Infrared devices
- Devices that do not have a current and valid Certificate of Calibration Testing

iii. Review and Analysis of Continuous Temperature Monitoring Data

Temperature data must be analyzed and reviewed regularly, but at least monthly to:

- Determine if any out of range temperatures were recorded.
- Identify any variations due to controllable causes.
- Observe for any trends that may indicate the equipment requires adjustment or service.
- Ensure that the temperatures are being recorded.
- QC the daily manual temperature log.

Documentation of the continuous temperature monitoring data review must include the date range and temperature range, and initial and date completed. Examples may include:

- Printing the data from the electronic log and initial/date the log…
- Electronically sign the log.
- Create a continuous temperature monitoring review log to capture the dates of the temperature that were reviewed, initial and date.

Retention and Availability of Temperature Data Reports – Upon request, the PoR must be able to provide a copy of the temperature data for the storage condition of all study products at any time in the past that the study product has been in the pharmacy. If the study has been ongoing for many years, a report for many years of temperature storage conditions may be required. The files of the recorded temperature data enable the DAIDS-authorized monitor to confirm that temperatures have been within the appropriate temperature range at all times.

iv. Temperature Deviations/Excursions Notification or Alarm System

Every pharmacy refrigerator, freezer and room temperature storage area must have a temperature deviations/excursions notification or alarm system to notify authorized personnel, 24 hours a day, 7 days a week, 365 days a year, of any temperature deviation/excursion from the acceptable temperature range, so that the PoR may take immediate action to prevent loss of study product. The PoR has the ultimate responsibility for the safe use of study product in the event of any temperature deviations or excursions.

v. Temperature Deviations/Excursions Reporting and Quarantine

The continuous temperature monitoring device is designated as the primary device to determine whether a temperature excursion has occurred. If during review of the manual temperatures, an excursion is noted, the data from the primary device prevails. If the primary device does not indicate an excursion, no temperature excursion needs to be reported to the CRPMC. The PoR should make every effort to investigate why there may be a discrepancy (e.g. check for recalibration and maintenance of device, power source, placement of probe, etc.).

When study products experience a temperature deviation or excursion, (outside the range permitted by the protocol), the study product should be immediately quarantined at the appropriate storage temperature, and the occurrence reported directly to the CRPMC, copying the PAB Protocol Pharmacist, using the DAIDS PAB Temperature Excursion Reporting Form (TERF). The PoR should await final disposition instructions from the CRPMC. The CRPMC will adjudicate the reported temperature excursion and communicate study product suitability to the CRS pharmacy.

For study product deemed not suitable for use that has been received by the participant, the PAB Protocol or PAB Site Pharmacist will instruct the PoR or AP to report this to the site investigator as soon as possible. For blinded studies this report must not unblind the investigators or other study personnel to the participant's treatment assignment.

Controlled Room Temperature excursion – If the study protocol states store between 20˚C and 25˚C with excursions permitted within 15˚C and 30˚C (59˚F and 86˚F), the temperature excursion must be reported to the CRPMC using the TERF. The study product may remain in active inventory and dispensed to study participants.

F. Back-up Plan for Study Product Storage

The PoR must have a back-up plan, which may include the use of duplicate pharmacy equipment, in place to ensure that appropriate storage conditions for study products are maintained in the event of equipment or power failure. All equipment must be easily identified as to location and any other specific identifiers (e.g., make, model, serial number). This plan must meet all storage, security, access, equipment, and monitoring guidelines stated in this manual.

G. Compounded Sterile Products Preparation

The use of a biological safety cabinet (BSC), compounding aseptic isolator, clean room, or laminar air flow hood are standard practice for injectable study product preparation. This equipment provides an ISO Class 5 environment (or better) and is the standard for compounded sterile preparations. Routine cleaning and disinfecting are required for maintaining a safe environment. For the DAIDS-sponsored and/or supported clinical trials, PAB requires utilization of a BSC Class II Type A2 or better when preparing investigational sterile products.

The PoR must be knowledgeable of practices and procedures that prevent contamination and cross-contamination of study products and must prevent the dispensing of any study product that may have been contaminated. For trials involving sterile products, the PoR is responsible for the aseptic preparation and compliance with any local regulations pertaining to the preparation of sterile products. The PoR should have comprehensive knowledge, understanding, and proficiency with aseptic techniques and use and maintenance of applicable equipment. Training and evaluation of aseptic technique should be reassessed and documented at least annually for staff performing preparation of sterile product.

Examples of equipment or facilities used for compounded sterile preparation include:

i. Laminar Air Flow Hood

- **Horizontal Air Flow Hood**

  A horizontal airflow hood provides an aseptic environment for the aseptic preparation of injectable study products. This hood provides a flow of filtered air originating at the back of the cabinet and exiting toward the person preparing study product under the hood. The horizontal air flow increases the likelihood of study product exposure to both the preparer and other personnel in the room.

- **Vertical Air Flow Hood**

  A vertical airflow hood (e.g., work bench, cabinet, IV hood) provides an aseptic environment for the aseptic preparation of injectable study products. This hood provides a flow of filtered air originating at the top of the cabinet and exiting via holes in the base. Vertical flow cabinets can provide greater operator protection.

ii. Biological Safety Cabinet

A ventilated cabinet for compounded sterile preparations, personnel, product, and environmental protection having an open front with inward airflow for personnel protection, downward HEPA air-filtered laminar airflow for product protection, and HEPA-filter exhausted air for environmental protection. See Section iv. “Classification of BSCs/Isolators” for additional information.

iii. Compounding Isolators

- **Compounding Aseptic Isolator**

A compounding aseptic isolator is designed to maintain an aseptic compounding environment within the isolator throughout the compounding and material transfer processes. Air exchange into the isolator from the surrounding environment should not occur unless the air has first passed

through a HEPA filter. A compounding aseptic isolator is used for non-hazardous study product and has a positive air pressure.

- **Compounding Aseptic Containment Isolator**

A compounding aseptic containment isolator is designed to provide worker protection from exposure to undesirable levels of airborne drug throughout the compounding and material transfer processes. Air exchange with the surrounding environment should not occur unless the air has first passed through a HEPA filter capable of containing airborne concentrations of the physical size and characteristics of the study product being compounded. Where hazardous drugs are prepared, the exhaust air from the isolator should be appropriately removed by properly designed building ventilation. A compounding aseptic containment isolator has negative air pressure.

See Section iv. "Classification of BSCs/Isolators" for additional information.

iv. Classification of BSCs/Isolators

Type	Airflow	Product Protection	Personnel Protection	Environmental Protection
Class I	In at front, rear and top through HEPA filter	No	Yes	Yes
Class II Type A1 *	70% recirculated through HEPA filter; 30% exhaust through HEPA filter	Yes	Yes	Yes
Class II Type A2	Same as Class II, Type A, but plena is under negative pressure to room and exhaust air is ducted	Yes	Yes	Yes
Class II Type B1	30% recirculated through HEPA filter; 70% exhaust via through HEPA filter and hard ducted	Yes	Yes	Yes
Class II Type B2	No recirculation through HEPA filter and hard ducted	Yes	Yes	Yes
Class III (Isolator)	Supply air inlets and exhaust through 2 HEPA filters and exhausted to outside via hard connection	Yes	Yes	Yes

*Considered Obsolete

v. Clean Room

A room in which the concentration of airborne particles is controlled to meet a specified airborne particulate cleanliness class. Microorganisms in the

environment are monitored so that a microbial level for air, surface, and personnel gear are not exceeded for a specified cleanliness class.

H. Maintenance of Equipment

There must be a program for inspecting, testing, and maintaining pharmacy equipment and documenting the results. All pharmacy equipment must be maintained and evaluated for appropriate performance, in accordance with the manufacturer's instructions. All equipment should be certified or calibrated annually, or as per manufacturer's recommendations and in compliance with any local regulations. Maintenance and calibration records for all pharmacy equipment should be retained in the pharmacy and/or immediately available upon request.

I. Back-up Power Supply or Generator

All equipment supporting pharmacy operations must be supported by a back-up power source (e.g., back-up battery power source or generator).

The back-up power supply should be tested quarterly, or more frequently as specified by manufacturer specifications or per individual institution policy and should receive maintenance at least annually. Documentation of testing and maintenance should also be recorded and maintained. Ideally, back-up generators should have sufficient capability to run continuously for the duration of the longest possible blackout (e.g., 72 hours or longer). In addition, plans should be made to ensure that there is access to an adequate supply of fuel.

III. Administrative

The administrative responsibilities of the PoR include the following:

A. Pharmacy Establishment Plan Documents

i. Pharmacy Establishment Plan

The PoR must complete a DAIDS PAB Pharmacy Establishment Plan (PEP) for each pharmacy associated with a Clinical Research Site (CRS). The PEP documents that the pharmacy has the required personnel, facilities, and equipment necessary for studies involving controlled room temperature. The PEP must be submitted directly to PAB at DAIDSPABPEP@niaid.nih.gov for review and approval if one of the following conditions exists:

- It is the beginning of a new funding cycle for the Clinical Trials Networks.
- A new pharmacy is being established.
- The pharmacy is moving to a new location.
- There is a significant change in procedures outlined in the previously approved DAIDS PAB PEP.
- Upon PAB request

Once the PEP is received, processed, and approved by the PAB, the PAB approval email must be printed and filed with the approved DAIDS PAB PEP. When a new pharmacy has been established, upon approval of the PEP, the PoR

will receive an email from the NIAID CRMS support with login details and information on how to access DAIDS CSM.

ii. Pharmacy Establishment Plan Addendum

In certain circumstances a full revision of the PEP may not be required to communicate changes. In these circumstances, the PoR or AP may be requested to submit a PEP Addendum to communicate changes to PAB; however, upon review by the PAB, submission of a revised DAIDS PAB PEP may be required for approval.

Once the PEP Addendum is received, processed, and acknowledged by the PAB, the PAB acknowledgement email must be printed and filed with the site's most current, approved DAIDS PAB PEP, along with a copy of the submitted PEP Addendum document.

Types of changes which may be submitted to PAB using a PEP Addendum may include:

- PoR direct report (Individual at the site that the PoR reports to)
- Information communication at the site (hardcopy documents vs. electronic)
- Administrative IT equipment (computers, printers, fax/phones)
- Minor infrastructure –within same location (heating/cooling/humidity controls, sinks)
- Pharmacy document storage
- Prescription receipt and/or communication
- Inventory procedures
- Security changes (new locks, security system, cameras, etc.)
- Temperature monitoring equipment
- Temperature monitoring procedures
- Equipment changes

iii. PEP Modules

The PoR must complete the modules below, if applicable to the CRS pharmacy. The PEP modules must be submitted directly to PAB at DAIDSPABPEP@niaid.nih.gov for review and approval if one of the following conditions exists:

- Refrigerated Storage Module – This module must be submitted for review and approval to DAIDS PAB before the CRS is able to participate in any protocol requiring study product(s) storage under refrigerated storage conditions (2°C – 8°C).
- -20° C Freezer Storage Module – This module must be submitted for review and approval to DAIDS PAB before the CRS is able to participate in any protocol requiring study product(s) storage under -20° C freezer storage conditions.
- -70° C Freezer Storage Module – This module must be submitted for review and approval to DAIDS PAB before the CRS is able to

participate in any protocol requiring study product(s) storage under -70° C freezer storage conditions.

- Biosafety Cabinet/Isolator Module – This module must be submitted for review and approval to DAIDS PAB before the CRS is able to participate in any protocol requiring study product(s) preparation within a Biosafety Cabinet/Isolator.
- Transportation/Chain of Custody Module – This module must be submitted for review and approval to DAIDS PAB if any pharmacist-labeled, participant-specific study products are transported and/or stored in a location other than the pharmacy. To assist with generating a site-specific Chain of Custody document, a template is available.
- Additional Pharmacy Room Temperature Storage Area Module – This module must be submitted for review and approval to DAIDS PAB if the pharmacy needs additional room temperature storage for DAIDS study products.

iv. Pharmacist of Record Information and Associate Pharmacist Information

The PoR and/or AP must submit the applicable form if there are different pharmacists for different networks at the site.

- Pharmacist of Record Information form – This form must be submitted for review and approval to DAIDS PAB if there are different Pharmacists of Record or the same PoR for different networks. CRS pharmacies may only have one PoR per network. The PoR may not serve as the AP for another CRS at a different physical location.
- Associate Pharmacist Information form – This form must be submitted for review and approval to DAIDS PAB if there are different APs for different networks. For each network, there must be at least one AP, but no more than a maximum of three APs.

For any questions or concerns regarding the need for submission of a new DAIDS PAB PEP, the PoR must contact DAIDSPABPEP@niaid.nih.gov.

B. Notification of Change Forms

If there are any changes in pharmacy personnel and/or other pharmacy-related information after the PAB approval of the site's DAIDS PAB PEP, the appropriate Notification of Change form must be completed and submitted immediately to DAIDSPABPEP@niaid.nih.gov. These forms are to be used in place of a revised PEP; however, upon review by the PAB, submission of a revised DAIDS PAB PEP may be required for approval.

Once the form is received, processed, and acknowledged by the PAB, the PAB acknowledgement email must be printed and filed with the site's most current, approved DAIDS PAB PEP, along with a copy of the submitted notification form.

The Notification of Change forms are as follows:

- Permanent Notification of Change in PoR – This form must be completed when there is a new permanent PoR at the clinical research site.
- Notification of New, Additional or Change in AP – This form must be completed when there is a new AP, an additional AP, or a departing AP at the clinical research site.
- Notification of Change in Pharmacist Contact Information and/or Pharmacy Address(es) – This form must be completed when there is a new pharmacy phone number, fax number, Pharmacist email address, mailing address, shipping address, and/or address of the physical location.
- PoR Temporary Leave of Duty Notification Form – This form must be completed when PoR will be on temporary leave of duty greater than 21 days in duration and to notify PAB which AP has been designated as the primary contact for monitoring issues during the leave for each network. If the Primary Monitoring Contact is not already an AP, a Notification of Change in AP form must be completed for that individual and submitted to DAIDSPABPEP@niaid.nih.gov.

Note: For sites under National Institute of Child Health and Human Development (NICHD), the site pharmacy approvals and processing of notification forms will be performed by the NICHD contractor that provides site pharmacy oversight.

C. Standard Operating Procedures

The PoR should have detailed, written instructions governing pharmacy operations and study product management, for conducting the DAIDS- sponsored and/or supported clinical trials and to assure compliance with all applicable laws and regulations. At a minimum, the pharmacy should have written SOPs that govern the receipt, storage, inventory process, accountability, record keeping, preparation, labeling, handling, dispensing, chain of custody, final disposition of study products, and quality management for study products.

For any activity that is delegated there must be a detailed SOP in which the PoR (or in absence of PoR the AP) demonstrates full documented oversight of the delegated duty. Any activity delegated must be within the authorized scope and practice of that individual's education, experience, license, and/or certification. All SOPs should align with DAIDS requirements as well as institutional, local, and in-country requirements and practices.

Examples of some applicable SOPs may include, but are not limited to, the following:

- Accountability of Study Product
- Chain of Custody of Study Product
- Cleaning and Disinfecting of Pharmacy Equipment and Pharmacy Facilities
- Cold Chain Management of Study Product
- Communication between Pharmacy and the Clinic
- Delegation and Oversight of Pharmacy Activities Performed by Non-Pharmacist Pharmacy Staff
- Destruction of Study Product

- Dispensing of Study Product
- Emergency Plan for Equipment Failure or Prolonged Power Failure
- Emergency Unblinding Procedures
- Inventory and Expiration Date Review of Study Product
- Labeling of Study Product (e.g. participant-specific, retest date extension)
- Maintenance of Pharmacy Equipment and Pharmacy Facilities
- Management of Damaged, Expired, or Recalled Study Product
- Management of Study Product Essential Information and Related Documents
- Ordering and Receipt of Study Product
- Pharmacy Quality Management Plan
- Plan for Back-up Storage of Study Product
- Prescriptions for Study Product
- Quarantine of Study Product
- Return of Study Product
- Shipment of Pharmacist Prepared Study Product to Participants
- Storage and Security of Study Product
- Temperature Monitoring and Documentation
- Training of Pharmacy Personnel (e.g., aseptic preparation, protocol training, SOP training)

For certain protocols, the PoR may be required to generate protocol-specific SOPs, as indicated in the protocol or study-specific procedures.

D. Reports

Incidents may be reportable to PAB and/or the IoR, depending on the type of incident. A more detailed report for PAB may be necessary.

i. Reports to the Pharmaceutical Affairs Branch

Pharmacy-related incidents that occur at a CRS pharmacy must be reported directly to PAB as soon as the PoR becomes aware of an incident or matter that could affect the outcome of a study. Incidents should be reported using the DAIDS PAB Incident Report Form (IRF), within one business day of identification.

ii. Reports to the Investigator of Record

In the case of any situation that could affect the safety of a study participant or the outcome of a study, a report must be submitted to the IoR at the clinical research site.

This report would differ from the report submitted to the PAB in that it must not unblind the investigators or other study personnel to the participant study treatment assignment. If the PoR is unsure that the report is written in a way that will not unblind the IoR, the PoR must contact the DAIDS PAB protocol pharmacist.

iii. Examples of Reportable Incidents

Examples of reportable incidents to PAB and the IoR that may occur at a CRS pharmacy include, but are not limited to, the following:

- Participant was dispensed an incorrect study product.

- Participant was dispensed an expired study product.
- Participant was dispensed an improperly stored study product.
- Participant was dispensed an incorrect dose.
- Participant was dispensed an incorrect formulation.
- Participant was assigned an incorrect study identification (SID) or participant identification (PtID) number, or incorrect study kit number.
- Accidental unblinding activity, such as treatment assignment, by the site pharmacy staff using discretion so that the report does not unblind the investigators or other study personnel.
- Participants exchanged or shared study product.
- Improper storage of study product.
- Accountability discrepancy that was not able to be reconciled.
- Study product was dispensed or administered to incorrect participant or an individual not participating in the protocol.

E. Records and Documents

The PoR must maintain pharmacy records utilizing good documentation practices in accordance with ALCOA-C, and the policies on Requirements for Source Documentation in DAIDS-Funded and/or Sponsored Clinical Trials and Storage and Retention of Clinical Research Records. All pharmacy records must be kept in a secure area with limited access, such as a locked file cabinet. The pharmacy records should only be accessible for official audits or inspections or to authorized pharmacy staff, the DAIDS authorized monitors or auditors, or the DAIDS PAB.

i. Error Corrections

- Anytime an error is made, the appropriate error correction procedure must be followed in order to avoid inadequate source documentation. Any change or correction to a pharmacy record or document should be dated, initialed, and, if necessary, include a written explanation. In addition, the original entry should not be obscured. This applies to both written and electronic changes/corrections.
- Only use dark (blue or black) ink.
- Never use pencil to write entries.
- Never use correction fluid (e.g., “white-out”).
- Never obliterate entries that require correction.
- Never destroy or re-write original documents, even if they require error correction.
- Do not alter past-dated notes, chart notes/progress notes (e.g., by writing alongside or adding to prior entries).

For handwritten corrections or adding additional information:

- Draw one line through an error. Ensure the previous entry has not been obscured.
- Document the correct information, initial, and date beside the information. If additional information is needed to justify the change, it will be noted. If space is limited, an * (asterisk) can be used and the note can be placed in a different location on the document.
- Ensure all corrections are clear and legible.
- Do not write over an entry to correct or change it.

For electronic/typed corrections:

- Electronic versions of documents can only be modified by authorized personnel.
- Access to electronic versions must be controlled by password or other secure means.
- A history (audit trail) must be maintained of changes and deletions to electronic versions.
- Strike through the entire line where error was made, if possible.
- Type in initials, date, and reason for change.
- On next available line, type all information including the corrected information.

ii. Current Records and Documents

At a minimum, the following pharmacy records, and other documents that govern the practice of pharmacy at the site, must be maintained in the pharmacy:

- Copy of the current Pharmacy Guidelines and Instructions for DAIDS Clinical Trials Networks that is readily accessible. Most current, approved, signed DAIDS PAB PEP attached to the notification of the PAB approval email
- Copies of or access to completed Notification of Change forms, which were submitted to the PAB, attached to the PAB acknowledgement emails
- Most recent version of the protocol and Letters of Amendment (LoA) for which the site has IRB approval, and any additional versions of the protocol if there are participants being followed on that version
- All significant protocol-specific communications and Clarification Memos (CM)
- All study product accountability records. Logs should reflect inventory conducted at least once monthly at regularly spaced intervals.

- All study product records, such as invoices, packing slips, import permits, tax waiver documents, transfers receipts, return or destruction forms, recall notices, shelf life extensions and associated receipts
- Temperature-monitoring records – Daily temperature logs should be retained as hardcopy. Continuous temperature records are preferably stored electronically, but if a hard copy is necessary it should be filed in an organized manner to allow easy retrieval.
- Randomization information, such as Pharmacist's Prescription List (SID list), treatment assignment information, or email randomization
- Records needed to document chain of custody for study products
- Current Form FDA 1572 or DAIDS IoR Agreement
- Current Authorized Prescribers' Signature List
- Copy of the most current site Delegation of Duties log
- Current Pharmacists' Signature List of printed names, signatures and initials of the PoR and other authorized pharmacy staff
- Pharmacy specific Delegation of Duties log if applicable
- Original prescriptions – Follow local regulations as to the requirements for a prescription to be considered an original prescription.
- Most recent version of the Protocol Study-Specific Procedures (SSP) or Manual of Operational Procedures (MOPS), if applicable
- Current protocol-specific Site Implementation Plan (SIP), if applicable
- For each study product, the current Product Package Insert or the most recent version of the Investigator's Brochure (IB); the previous versions of the IBs must be retained.
- Drug Supply Statement (Refer to Ordering Section for more information.)
- Pharmacy Quality Management Plan (this may be a component of the site Clinical Quality Management Plan)
- Written communications with clinical research site staff and others (e.g., the DAIDS staff, SDMC staff)
- Reports to PAB and/or IoR
- Training documentation
- Site pharmacy SOPs
- Closeout Letters
- Pharmacy licensure or registration documentation, as applicable

For all electronic data, a back-up file must be maintained to prevent the accidental loss of data in the event of a power outage or other unexpected event.

iii. Document Retention

Record retention applies to clinical research records that are generated, stored and retained, as required by U.S. regulations, laws, and policies while conducting DAIDS- sponsored and/or supported clinical trials. Record management requirements for DAIDS-sponsored and/or supported clinical trials may be subject to additional Federal, State, local, and/or institutional regulations/policies.

Pharmacy source documents, primarily the pharmacy accountability records or any other record that captures receipt and dispensing data, must be kept in the pharmacy until otherwise directed by the sponsor. These documents must be available for expedient retrieval, inspection, and photocopying of information, if requested by a properly authorized DAIDS or authorized regulatory employee or representative or any auditor/inspector acting in an official capacity.

iv. Document Archiving

Pharmacy source documents, including pharmacy accountability records, must be retained or archived as directed by the sponsor. When possible, these documents should not be archived independently but should be kept together with the case report forms. The pharmacy records should be placed at either the front or the back of the case report forms, but never in the middle.

Pharmacy records must be placed in a folder or envelope, and clearly marked as "pharmacy records," when records are being archived. Order forms, receipts for study product transfers and returns, and packing slips may be discarded when the pharmacy source documents are being archived unless there is unique information on these records that is not available from other sources. Contact a DAIDS PAB pharmacist for assistance in determining when archived documents may be destroyed. All clinical research records must be stored in a manner that ensures privacy, confidentiality, security, and accessibility.

v. Document Destruction

Completed Non-IND studies that have met or exceeded the 3-year retention period (per 45 CFR 46.115): CRFs and pharmacy records will not be stored by DAIDS. These non-IND studies are listed on the DAIDS Regulatory Support Center website.

DAIDS has determined that the documents associated with these studies no longer require storage and may be destroyed in accordance with investigator's institutional policies. Documents from studies that are not included in these lists must be stored in accordance with local institutional policy.

Due to the confidential nature of the information in an Investigator's Brochure (IB), please contact the DAIDS RSC Safety Information Center for more details regarding destruction.

SECTION 4: Study Product Management Responsibilities

The following sections address the responsibilities of the PoR, regarding the various activities performed in the pharmacy. The PoR is ultimately the responsible party for all activities in the pharmacy related to study product management. If another pharmacist, pharmacy intern or pharmacist technician is delegated the responsibility of ordering or receipt of study product, there must be a detailed SOP in which the PoR demonstrates full documented oversight of the delegated duty. Any activity delegated must be within the authorized scope and practice of that individual's education, experience, license and/or certification.

I. Ordering

Upon protocol registration approval, the PoR at the clinical research site pharmacy will receive ordering instructions from the CRPMC. This may include a Drug Supply Notification as well as a Drug Supply Statement. The PoR and AP should order study product by utilizing the COSMOS system. The PoR must ensure that there is sufficient supply of study product, ancillary supplies, and any other specialized equipment needed for the conduct of a study.

II. Receipt

All study products are shipped on a clinical research site-specific, investigator-specific, protocol-specific basis by the CRPMC. The CRPMC packages study products in shipping containers designed to maintain the appropriate storage conditions during shipment. Each shipment of study products, from the CRPMC includes a packing list. Temperature monitoring device(s) may be included with the shipment, along with instructions for reading and final disposition of the device(s). For non-U.S. clinical research sites, shipments may also contain a copy of an invoice and other documents required for drug importation.

Upon receipt in the pharmacy, the PoR must verify that the quantity, lot number, and expiration date of study products received matches that indicated on the packing list, study products were received in good condition, and storage conditions have been maintained. The PoR must complete the shipment receipt confirmation in COSMOS. The study products can be placed in active inventory upon completion of the receipt confirmation without any discrepancies and/or in transit excursions. If there are any discrepancies and/or excursions in transit, it must be documented on the receipt confirmation. The PoR must contact the CRPMC immediately and quarantine the study products in a separate area under the appropriate storage conditions. The quarantined study products must not be dispensed until confirmation from the CRPMC that they are suitable for use. The PoR must attach the CRPMC's email communication to the related packing list.

III. Accountability

The PoR must have an established method in place to account for all study products. Accountability records at a minimum must be protocol and LOT specific. The DAIDS Study Product Accountability Record, an equivalent electronic accountability record containing the same information, or other protocol-specific PAB-provided document, must be used to document the receipt, management, and final disposition of all study products received from the CRPMC or other source.

The following entries on the Study Product Accountability Record should have a corresponding document:

Study Product Accountability Record Entry	Corresponding Document(s)
Shipments received from the CRPMC or other source	Invoice, Packing Slip
Study Products Dispensed	Prescriptions
Study Product Destruction	N/A. Documentation found in COSMOS
Study Product Transfers	DAIDS Study Product Transfer Form
Study Product Returns	N/A. Documentation found in COSMOS

Each time a study product is received from the CRPMC or other source, dispensed to a participant, and/or returned to the CRPMC or other source or destroyed, it must be documented on the DAIDS Study Product Accountability Record. The inventory balance documented on the Study Product Accountability Record should match the actual study product inventory on hand at all times. Every entry on the Study Product Accountability Record must be made in dark indelible ink. Never use pencil to write an entry.

An explanation of correction, or other relevant comment, may be written on the back of the Study Product Accountability Record, by first writing "see back" in the comment space for that line, then writing "Line No. X" and the explanation on the back, where "X" is the relevant line number of the form.

All entries on the Study Product Accountability Record must match the dispensing activity. The original prescription for the corresponding entry in the Study Product Accountability Record must be maintained in the pharmacy. Each reference made to the Study Product Accountability Record, in this manual, applies to the DAIDS Study Product Accountability Record, an equivalent electronic accountability record containing the same information, or other protocol-specific PAB-provided document.

IV. Storage

The PoR must ensure that the appropriate storage conditions are maintained for all study products at all times. This must include, but is not limited to:

- Suitable security
- Clear separation from primary care medication and other non-study medications, if applicable
- Appropriate temperature controls and temperature monitoring measures to prevent exposure to extreme temperature, light, and humidity
- Being free of infestation by rodents, birds, insects, and other vermin
- Adequate ventilation and sanitation
- Separation of expired or otherwise compromised study products from active inventory

Study products must be stored in accordance with the current protocol. Requirements for storage may also take into account regulatory requirements or current United States

Pharmacopeia/National Formulary standards so that the integrity, stability, effectiveness, and security of the study products are maintained.

Study products must be separated by clinical research site, by protocol, by drug name, strength, and lot number. For blinded studies, the active study product must not be stored alongside the placebo product; there must be a clear separation between active and placebo study products. Study products that are designated for return to the CRPMC or for destruction must be removed from active inventory and placed in quarantine while awaiting final disposition.

Only pharmacist-labeled, participant-specific study product may be transported to or stored within the clinic (See Chain of Custody Section). If the clinic will store study product for any period of time before administering to the participant, then temperature monitoring of the study product storage unit/shelf must be ensured according to the protocol.

V. Participant Identifiers, Treatment Assignments, and Randomization

The process by which a participant is assigned a participant identifier may vary according to the network, site, or protocol. Depending on the network, a participant may be assigned a participant identification number (PID/PtID), specific to an institution, but may also receive a separate study identification number (SID) unique to the treatment assignment or protocol-specific randomization code (if applicable) for each protocol in which the participant is enrolled.

For most DAIDS blinded protocols, the PoR is unblinded to a participant's randomized treatment assignment. In order to dispense a study product, the PoR must be provided with the study treatment assignment information. Each network may have a different mechanism for providing the study treatment assignment information.

Treatment assignment information provided to the PoR is confidential and must remain in the pharmacy and be accessible only to the PoR and other authorized pharmacy staff. The PoR must maintain the scientific integrity of studies and take all precautionary measures to prevent unblinding of any participant treatment assignments. This includes limiting access to treatment assignment records and study products in blinded studies to pharmacy staff only.

VI. Dispensing/Preparation and Authorized Prescribers

The PoR must be knowledgeable of the protocol and local laws and regulations, in order to ensure a prescription is acceptable. Study products can be dispensed only after the PoR has received the signed prescription from the IoR, or a licensed clinician directly responsible to the IoR, as stated on the Form FDA 1572. Further details may be provided in the protocol for when new prescriptions are required (e.g., dosing changes, step entry, etc.).

By signing the Form FDA 1572, the IoR has certified that the study product will be administered only to participants under the IoR’s personal supervision or under the supervision of sub-investigators responsible to the IoR.

If the Form FDA 1572 is not required for protocol registration, then an IoR Agreement Form replaces the Form FDA 1572. Prescribers must be clinicians authorized to prescribe in the site’s jurisdiction.

A. Prescriptions

- The PoR must receive a prescription signed by an authorized prescriber prior to dispensing study product.
- Prescriptions must be either handwritten with dark (blue or black) ink, typed, or computer-generated.
- Signatures on the prescriptions are to be handwritten or electronically signed.
- Signature stamps are not permitted.
- Signing blank prescription forms is not permitted.
- It is not permitted for an individual who is not an authorized prescriber to sign a prescription with an authorized prescriber's name and then add her/his own name to it in an effort to make it legal. For example, study staff may not sign a doctor's name to a prescription and then add her/his name to it if s/he is not an authorized prescriber.
- Post-dated prescriptions are not permitted. For example, it is not acceptable for a prescription written in January to have a February date.
- Study staff may prepare electronically or hand-written prescriptions in advance for an authorized prescriber to review and sign; however, no study product should be dispensed until after the PoR receives the signed prescription.
- The authorized prescriber is responsible for ensuring that the prescription is written in accordance with all essential aspects and requirements of the protocol and local laws and regulations.
- The code corresponding to the treatment assignment must be provided to the PoR on the signed prescription, unless otherwise specified in a protocol-specific document. The PoR uses this code to identify the participant's treatment assignment prior to dispensing study product. This code must be provided to the PoR each time a new prescription is written. Prescriptions should include the following:
    - Date of issue
    - Participant name and/or identifier (PID)
    - Network name and protocol number
    - Treatment assignment (e.g., SID, or kit number)
    - Study Product name, dose, strength, formulation, route, volume (if applicable)
    - For blinded studies there may be a protocol-specific randomization code, and the study product name must be written in a blinded fashion.
    - Study Product quantity or volume to be dispensed (e.g., number of tablets in a bottle or mL of the prepared study product in syringe or in IV bag)
    - Study Product directions for use
    - Authorized Prescriber's signature and date of signature

    - Prescriptions may also include the following:
        - Body Surface Area (BSA) calculation or height and weight of participant, including units (i.e., kg, lbs, cm, inches)

- Any special instructions (i.e., dose reduction, dose escalation)

B. Informed Consent Verification

A method must be in place so that the PoR is notified in writing that the participant has signed the informed consent to participate in the research study and that this notification is documented. This information must be provided to the pharmacist prior to dispensing any study product, for example by providing a copy of the signature page of the informed consent form or by having a notation on the prescription.

C. Expiration Date Review

It is the responsibility of the PoR to review the expiration date information of the study product provided to ensure that study product dispensed will not reach expiration prior to participant use or administration.

D. Shelf Life Extension

Study products on an ongoing stability program may undergo shelf life extension or repass dating evaluations at designated time points. These products may not have any date (e.g., date of manufacture or expiration date), or they may have a date of manufacture, but may not have an expiration date, printed on the label. At each of the stability program time points, documentation of the current extension or repass dating will be provided to the PoR through the COSMOS system. The CRPMC will issue recovery notices when the repass date will no longer be extended.

E. Preparation

For study products requiring reconstitution, mixing, dilution and/or drawing up into a syringe, refer to the protocol and any additional protocol documents, if available, for protocol-specific instructions on preparation. Protocol documents may include the protocol, study-specific procedures, manual of operations, or a Pharmacists Study Product Management Procedures manual. In addition, requirements for preparation must also consider regulatory requirements or current quality standards (e.g., USP/NF standards) so that the integrity, stability, and effectiveness of the study products are maintained.

F. Labeling

The PoR must properly label all study products to ensure safe administration by the clinicians or use by study participants. Participant confidentiality must be considered when preparing prescription labels. It is the PoR's responsibility to know the requirements for his/her jurisdiction so that the labels comply with all applicable labeling requirements.

Prescription labels for study products should be distinguishable from other labels by an appropriate legend, "Study Product" or "For Investigational Use Only".

Study products must have participant-specific labels before they leave the pharmacy.

Labels should include the following:

- Name, address, and telephone number of the dispensing pharmacy
- Participant name or identifier
- Dispensing date
- Authorized Prescriber's name

- Network name and protocol number
- Study product prescribed: name, dose, strength, formulation, route, volume
- Number of dosing units dispensed (For example, number of tablets, mL of the prepared study product in syringe or in IV bag)
- Directions for use
- Beyond use date and time or date of expiration
- Any additional requirements as specified in the protocol

Note: For blinded studies, labels must be prepared in a manner that maintains the blinding of the study.

G. Adherence Counseling

The PoR may be responsible for counseling a study participant on the proper use and/or administration of study products for a clinical trial.

H. Refills/Repeats

Protocols or study-specific procedures may require a new prescription or provide specific dispensing information. In such cases, the information in the protocol must be followed.

If it is in accordance with the protocol, institutional, local and/or country regulations, the PoR may dispense refills/repeats of study products if written on the prescription.

VII. Unblinding Procedures

Unblinding is the action by which the treatment of a participant enrolled in a blinded study is revealed.

A. Routine Unblinding

The PoR is not responsible for the routine unblinding process. The PoR must read any DAIDS, network and/or protocol-specific procedures, if available, regarding routine or emergency unblinding to prevent inappropriate unblinding. The process and procedures may vary among networks and/or protocols.

B. Accidental Unblinding

If a dispensing error or other untoward event occurs that may have caused the unintentional unblinding of the participant's treatment assignment, the PoR must report the incident utilizing the DAIDS PAB IRF to the DAIDS PAB protocol pharmacist immediately. The PoR should also report the unblinding incident to the IoR in a blinded fashion.

C. Emergency Unblinding

The DAIDS Emergency Unblinding Policy specifies that the site PoR may serve as a source of emergency unblinding. If used as a source for unblinding, the site PoR must receive a written request or may accept a verbal request, however, the written request must be received within 24 hours. In addition, the PoR must adhere to the following:

- Provide the unblinding information to only the site IoR in a timely fashion.
- Document the provision of unblinding information in the pharmacy records.

- Notify the DAIDS PAB protocol pharmacist. If the blinded treatment assignment code is broken, every effort should be made to minimize the number of persons at the site who are informed of the treatment assignment. The PoR must report the unblinding request to the DAIDS PAB protocol pharmacist immediately. The report should include the following specifics:
    - Name of the site IoR initiating request for emergency unblinding
    - All PID or PtID numbers, and if applicable, SID numbers or kit identification numbers
    - Network name and protocol number
    - Name, title and position of all individuals who were unblinded
    - Date of the unblinding
    - Reason for unblinding the individual
    - Method of transmitting the unblinding information, for example, telephone, email, facsimile, etc.
    - Statement about whether or not the participant and the participant's primary physician were informed of the participant study treatment
- Refer to the network specific and/or protocol-specific procedures for emergency unblinding

VIII. Quality Management Plan (Quality Control and Quality Assurance)

Quality Management (QM) is part of a system of oversight required for the conduct of NIAID (DAIDS) sponsored and/or supported clinical research. A QM system includes defined quality requirements comprised of site procedures, forms and templates, quality control (QC), quality assurance (QA), corrective and preventative action (CAPA) processes and continuous quality improvement activities that support process standardization, data accuracy, completeness and data integrity.

The PoR is responsible for the development and implementation of a QC and QA plan for his/her respective pharmacy to ensure that safety and standards of good pharmacy practice are upheld. Additionally, the pharmacy QC/QA plan helps to ensure that the right study participant is dispensed the correct study treatment and dose of the proper drug, biologic, vaccine or radiopharmaceutical, as defined by the protocol, at the right time.

A. Quality Management

Quality management is a collective term that includes quality control and quality assurance. These principles can be applied to review and verify that aspects of study product management are correct and complete.

- A systematic process for quality management and problem-solving activities should be implemented to internally review and evaluate the quality and appropriateness of the research pharmacy operations and protocol compliance
- Aspects reviewed may include study product storage, control, accountability, dispensing, and final disposition.
- When problems are identified, the actions that are taken to resolve the problems should be appropriately documented and reported.
-

i. Quality Control

Quality control encompasses real-time independent observations, verification, and documentation to ensure correctness and completeness.

- The PoR must ensure that the day-to-day activities of study product management are conducted correctly and accurately.
- Quality control should be exercised at all aspects of study product management including, but not limited to, accountability, preparation, dispensation, and final disposition of study product.

ii. Quality Assurance

Quality assurance describes a more periodic and systematic retrospective examination of clinical trial documents to verify correctness and completeness.

- The PoR should conduct an audit monthly, but no less frequently than quarterly, to ensure compliance with regulations, policies and standards.
- In addition to periodically monitoring for quality assurance in the research pharmacy, the PoR should also audit and review for quality assurance activities in the clinic, if applicable (e.g. storage of pharmacist labeled participant-specific study product in the clinic, chain of custody procedures, cold chain management procedures, etc.).
- Notify PAB of any missing study products, incorrect dosing, incorrect storage, or any other issues that could impact the study or safety of study participants. See "Reports" Section for additional information.

B. Examples

Examples of Clinical Quality Management Plan Pharmacy Component Elements Include:

- Study Product Management Record Keeping
- Study Product Management Processes
    - Study Product Preparation Procedures
    - Study Product Dispensation Procedures
    - Study Product Chain of Custody Procedures
    - Study Product Storage and Temperature Monitoring Processes
- Staff Training/Qualifications
    - Institution-Specific
    - Protocol-Specific
    - DAIDS-Specific
- Tools, Documents, and Forms
    - Internal Sources (e.g., study product preparation worksheet, site specific chain of custody form, etc.)
    - External Sources (e.g., DAIDS PAB TERF or the DAIDS PAB IRF)
- Summary Reports
    - Trend Analysis
    - Corrective and Preventive Action (CAPA) Plans

- Continuous Quality Improvement Activities

Note: The PoR should communicate any findings, summary reports, or continuous improvement activities resulting from QA/QC procedures to the IoR/CRS Leader while maintaining participant blinded treatment assignment.

IX. Chain of Custody

Throughout the conduct of the study, couriers or staff personnel, other than the PoR or other authorized site personnel, may come into possession of participant-specific study product. To ensure the integrity of the pharmacist-labeled, participant-specific study product, an unbroken trail of accountability, also referred to as chain of custody, must be documented as authorized study personnel take and relinquish its possession.

Documents used to track the chain of custody must be maintained in the same manner as all other source documents. A template for creating a site-specific Chain of Custody document is available.

X. Transport/Cold Chain Management

When study product must be transported from the site pharmacy to a different physical location (e.g. another pharmacy or clinic) the following considerations must be made:

A. Controlled Room Temperature

For study products requiring controlled room temperature storage (see Glossary for definition), the following should be considered:

- If the transit time is less than 15 minutes, a temperature monitoring device is not required.
- If transport occurs in a continuous temperature-controlled environment (e.g., within a building or connected building), a temperature monitoring device is not required.
- If transport occurs in a non-temperature-controlled environment and the transit time is greater than 15 minutes, a temperature monitoring device and transport container are required. At a minimum, the monitoring device must be a thermometer with a min/max reading and the temperature recorded at the beginning and end of the transport. The study product may be transported in a transport container (e.g., hard-sided or Styrofoam™ container).

B. Refrigerated/Frozen

For study products requiring refrigerated or frozen storage, the following should be considered:

- If study product is to be transported, a temperature monitoring device and transport container are required. The device used for the monitoring and recording of temperatures must have the capability of capturing the current temperature, and minimum and maximum temperatures reached at the beginning, during, and end of transport (e.g. min/max thermometer with memory, data logger).
- The transport container/insulated transport container must be a container suitable for transporting refrigerated or frozen study product with appropriate materials. Examples of suitable containers and/or packaging materials for use within the container include, but are not limited to, the following:

- Portable vaccine refrigerator/freezer
- Qualified containers and packouts
- Hard-sided insulated containers or Styrofoam™
- Coolant materials such as phase change materials (PCMs) that can be conditioned to appropriate temperature (e.g., gel packs or coolant packs)
- Insulating materials such as bubble wrap and corrugated cardboard—enough to form two layers per container

Note: The PoR must adhere to any protocol-specific requirements for transport or cold chain management, including temperature monitoring and recording. If temperature monitoring during transit is required, it must be appropriately documented.

XI. Obtaining Study Product from a Source other than the CRPMC

If a study product is obtained from a source other than the CRPMC, the PoR must refer to the protocol document or study-specific documents regarding the manner in which study products will be obtained.

XII. Returning Study Product Back to the Same Participant by the PoR

If study product in a participant's possession is to be used in a succeeding treatment period, the PoR may return the same study product back to the same participant. For example, if a study product is dispensed in a quantity sufficient for a 30-day period and the participant returns for a follow-up visit 28 days later, there is a two-day supply of study product that may be returned to the same participant.

Before returning any study product, the PoR must exercise his/her professional judgment, and consider the following:

- Expiration date of the study product
- Physical integrity of the study product
- Storage conditions of the study product while in the participant's possession
- If the participant will continue on the same study treatment
- Study design, study visit schedule, instructions of the protocol, and study procedures
- Participant's study product adherence pattern
- Quantity of study product needed by the participant until the next pharmacy visit
- Potential exposure of the study product to infectious or hazardous conditions

Returned study product must not be combined with the new supply of study product. The participant must be instructed to use the returned study product first, before opening and using unopened containers. Returns from one participant must not be dispensed to a different participant.

XIII. Shipping Study Product to a Participant

For rare, unanticipated instances or emergency cases, study product may be mailed/couriered directly from the site to a study participant. This method should only be used on a short-term, protocol-specific basis and only if permissible by the local institution and/or IRB/EC.

The study product must be packaged and labeled appropriately and monitored with an appropriate temperature monitoring device for the storage condition requirements (if applicable). A mechanism to confirm that the study participant received the study product must be ensured. This could be accomplished via documented delivery confirmation receipt (electronic or certified mail or express courier with a return receipt).

If this method is to be implemented, each site pharmacist must develop appropriate procedures for mailing or in-person courier of study product to identified participants and must also include appropriately documented chain of custody. Cold chain management considerations may be applicable and are dependent on the required storage conditions for the study product. All procedures and related documentation should be maintained in the pharmacy files.

Prior to implementation, site pharmacists must coordinate with site clinic staff to determine the appropriateness of this method for applicable protocols and participants. There may be additional protocol-specific requirements to be incorporated into these procedures, and site pharmacists should direct study product-related queries to the respective DAIDS PAB Protocol Pharmacist.

XIV. Final Disposition of Study Product

The PoR is responsible for ensuring that study products that can no longer be used are reconciled and either appropriately transferred, returned to the CRPMC or other source, or destroyed in accordance with applicable procedures.

A. Study Product Return

The PoR at a U.S. clinical research site must return any study product received from the CRPMC, back to the CRPMC, unless otherwise specified by a protocol-specific document. The PoR and AP should initiate return of study product by utilizing the COSMOS system. The study product to be returned must be removed from active stock and placed in quarantine in a separate area from active stock. Recalled study product must be quarantined immediately and be returned, as indicated by the recall notice from the CRPMC.

To comply with federal regulations, the DAIDS protocol study products, provided by the CRPMC, are to be returned to the CRPMC for one of the following reasons:

- Study product has expired
- Study product has been recalled
- Study product has been returned by the participant
- Protocol has been administratively closed
- All participants have completed the study treatment
- A site has been deregistered from a protocol
- Study product had a temperature excursion and can no longer be safely used
- Study product is damaged
- PoR has received notification from the CRPMC that study product is no longer being used in the protocol
- Pharmacy has closed

- Requested by the DAIDS PAB protocol pharmacist
- Quarantined study products should be returned to the CRPMC on a quarterly basis or more frequently as appropriate.

B. Study Product Destruction

The Study Product Destruction process applies to non-U.S. clinical research sites utilizing study products received from the CRPMC and/or products designated as study products in a DAIDS protocol. The study products to be destroyed must be quarantined in a separate area from the active stock.

The process for study product destruction may be initiated by the PoR, the CRPMC or the PAB. The PoR should initiate destruction of study product by utilizing the COSMOS system. The CRPMC will facilitate the destruction process, with the utilization of a DAIDS Authorized Witness (DAW). Non-U.S. clinical research sites are permitted to use local, institution-approved vendors to perform the destruction of study product activities in accordance with local, in-country, and regulatory regulations.

Initiation by the PoR:

The study product destruction process may be initiated by the PoR for the following reasons:

- Study product has expired
- Study product is damaged
- Participant return
- Receipt of "Preparation for Destruction Notice" from the CRPMC
- Request from the PAB

The PoR should refer to the Protocol or the Drug Supply Statement (DSS) for instructions on the final disposition of study product, prior to destruction initiation.

Initiation by the CRPMC:

The study product destruction process may be initiated by the CRPMC by sending a "Preparation for Destruction Notice" document to the PoR. This document will include one of the following reasons for destruction:

- Study product has expired
- Protocol has been administratively closed
- All participants have completed the study treatment
- A site has been deregistered from a protocol
- Study product had a temperature excursion and can no longer be safely used
- Study product is damaged
- PoR has received notification from the CRPMC that study product is no longer being used in the protocol
- Pharmacy has closed
- Requested by the DAIDS PAB protocol pharmacist

Initiation by the PAB:

The study product destruction process may be initiated by the PAB for any reason deemed necessary.

C. Transfer of Study Product

Study products provided through the CRPMC must not be transferred without prior authorization from the CRPMC/PAB.

A request for the transfer of study product from one protocol to another protocol must be from a completed or discontinued protocol for which study products are no longer needed, or from an active protocol where sufficient supply exists to support another protocol. Not all study products can be transferred.

i. Protocol to Protocol Study Product Transfers Within A Single Clinical Research Site

The following are the requirements before protocol to protocol study product transfers can occur:

- Study product will be used in an active protocol within the same clinical research site.
- Study product for both protocols are supplied through the CRPMC.
- Study product was never dispensed or stored outside of the pharmacy.
- Study product is still within expiration date.
- Study product has been stored properly.
- Receipt of authorization from the manufacturer, if applicable
- Completion and submission of the Transfer Request Form by the PoR and approved by the CRPMC/PAB

ii. Participant Transfer from One Clinical Research Site to Another

When the PoR is informed that a participant is transferring to another clinical research site, consider the following:

- If the PoR is not blinded to the study product, the participant's study treatment assignment information, not the actual study product, must be transferred from the PoR at the original clinical research site to the PoR at the new clinical research site.
- If the PoR is blinded to the study product, in the case of participantspecific kits, the kits themselves may need to be transferred from the PoR at the original clinical research site to the PoR at the new clinical research site.

If participant-specific kits are to be transferred from one clinical research site to another, the DAIDS PAB protocol pharmacist and the CRPMC must be notified for approval prior to the transfer.

Consult the specific HIV/AIDS Clinical Trials Network website for network-specific information on transfer of participants and transfer of study products. In

the event that no such information exists, the following steps should be followed:

- Contact the PoR at the receiving site and discuss the participant's protocol and drug history.
- Send the following information to the receiving PoR either electronically through an encrypted, secured file or by express mail/courier
    - Participant's identification numbers and study treatment code/randomization information
    - Participant-specific pharmacy log
    - Participant's current week on study
    - Amount of drug received most recently by the participant and the date it was received
    - Copy of the document that informed the PoR of the participant's study treatment assignment
    - Signed copy of participant's informed consent
    - Date and time of the participant's appointment at the receiving site (if appropriate)
- Arrange for the safe and temperature appropriate transfer of the participant's study product to the receiving clinical research site, if applicable

SECTION 5: Pharmacy Visits

I. DAIDS-Authorized Monitor

A DAIDS-authorized monitoring group conducts monitoring visits at the DAIDS-sponsored and/or supported clinical research sites. The monitoring visit is used to evaluate and assess adherence to the protocol and U.S. Code of Federal Regulations and ICH guidelines, evaluate pharmacy facilities and operations, and perform special assignments and additional assessments, when requested by the DAIDS. The site coordinator, site leader, PoR and IoR will be notified in advance of a visit via an automatically generated email from NIAID CRMS support and are expected to acknowledge the notification in the DAIDS CSM. The monitor will assess the pharmacy, pharmacy operations, and any pharmacy storage areas. The PoR must make available any information and pharmacy records requested by the monitor. At the end of each monitoring visit, a debriefing is conducted by the monitor, and the PoR is expected to attend this debriefing. The frequency of monitoring visits may vary as determined by the DAIDS.

II. Audits/Inspections

There may be an occasion for an inspection or audit by a regulatory agency. If DAIDS receives the initial notification, the site will typically be informed through the OCSO Program Officer. If the site is informed of a pharmacy specific inspection or audit by a regulatory agency, the site PoR should notify the PAB site pharmacist immediately upon awareness. A DAIDS authorized pre-inspection or audit may be conducted prior to known visits to assist the site in readiness. The site PoR must make available any information and pharmacy records requested.

III. Pharmacy Tours

The PoR must use his/her discretion when allowing visitors to tour the pharmacy. When tours are for the purpose of touring pharmacy areas used for the DAIDS studies, the visitors must be escorted at all times, and the visit should be conducted only under the direct supervision of the PoR. If network staff or the DAIDS staff, other than PAB, are touring the pharmacy, every effort must be made to prevent the unblinding of a protocol(s), by not allowing access to study products, study accountability logs, shipping forms, and confidential participant files.

IV. Sponsor Visits

On-site visits may be necessary by PAB personnel. This may involve an on-site assessment of pharmacy facilities, equipment and resources, as well as, review of pharmacy- and protocol-specific records, processes, and procedures. These visits may be conducted in conjunction with other OCSO and DAIDS program staff.

SECTION 6: References

1. CDC Vaccine Storage and Handling Toolkit, January 2020
2. COSMOS User Manual - DAIDS, Version 1.0, October 2019
3. DAIDS Clinical Research Policies and Standard Procedures Documents
4. DAIDS Regulatory Support Center
5. International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH)
6. U.S. Food and Drug Administration Code of Federal Regulations
7. U.S. Office of Personnel Management: Federal Holidays
8. U.S. Pharmacopeia/National Formulary