

PHARMACY GUIDELINES & INSTRUCTIONS FOR DAIT- SPONSORED CLINICAL TRIALS & NETWORKS

**Division of Allergy, Immunology, and
Transplantation**

Clinical Research Operations Program

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Author: Sanaz Daneshfar Hamrah, Pharm.D., BCPS



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Infectious Diseases

PHARMACY GUIDELINES & INSTRUCTIONS

FOR

DAIT-SPONSORED CLINICAL TRIALS & NETWORKS

TABLE OF CONTENTS

Page

	ABBREVIATIONS (MANUALS AND FORMS)	5
1	PHARMACY GUIDELINES OVERVIEW.....	6
1.1	<i>Background</i>	6
1.2	<i>Scope and Objectives</i>	6
1.2.1	Overview of DAIT Pharmacist Responsibilities, Clinical Research Operations Program.....	6
1.2.2	Overview of DAIT Regulatory Officer Responsibilities.....	7
1.2.3	Overview of DAIT Project Manager Responsibilities	7
1.3	<i>Contact Information and Websites</i>	8
1.3.1	Division of Allergy, Immunology, and Transplantation: Project Manager	8
1.3.2	Division of Allergy, Immunology, and Transplantation: Clinical Research Operations, Pharmaceutical Specialist (DAIT CROP, PS)	8
1.3.3	Clinical Products Center	8
1.3.4	NIAID DAIT Clinical Research Networks/Consortia	9
2	RESPONSIBILITIES OF THE PRINCIPAL INVESTIGATOR AND DELEGATEES	10
2.1	<i>Professional Responsibilities</i>	10
2.1.1	Licensure/Registration.....	10
2.1.2	Knowledge of Local and Country Regulations.....	10
2.1.3	Good Clinical Practice	10
2.1.4	Human Subjects Protection	10
2.1.5	Continuing Professional Development.....	11
2.1.6	Knowledge of Protocols.....	11
2.1.7	Investigational Product Management.....	11
2.1.8	Confidentiality	11
2.1.9	Informed Consent Verification.....	11
2.1.10	Record Keeping.....	11
2.1.11	Product Information	11
2.1.12	Blinded Studies	12
2.1.13	Adherence Counseling.....	12
2.1.14	Supervision and Training of Pharmacy Staff	12
2.1.15	Protection of Pharmacy Staff.....	12
2.1.16	Quality Management.....	12
2.1.17	Infection Control.....	12
2.1.18	Monitoring Visits and Reports	13
2.2	<i>Research Pharmacy Facility Supervision</i>	13
2.2.1	Required Space.....	13
2.2.1.1	Electrical Supply	14
2.2.1.2	Back-Up Power Supply or Generator	14
2.2.1.3	Water Supply.....	14
2.2.1.4	Ancillary Supplies	14
2.2.2	Required Security	14
2.2.3	Storage of Investigational Products	14
2.2.3.1	Controlled Room Temperature	14
2.2.3.2	Refrigerator and Freezer	15
2.2.3.3	Back-Up Plan for Investigational Product Storage	15
2.2.3.4	Extreme Humidity and Light.....	16
2.2.4	Temperature Monitoring and Alarm System	16
2.2.4.1	Continuous Temperature Monitoring and Recording System	16
2.2.4.2	Manual Temperature Review and Recording	17
2.2.4.3	Alarm System for Temperature Deviations/Excursions	17
2.2.5	Laminar Air Flow Hood and Isolator	18
2.2.5.1	Vertical Air Flow Hood.....	18

2.2.5.2	Horizontal Air Flow Hood	18
2.2.5.3	Isolator	18
2.2.6	Maintenance of Equipment	18
2.3	Administrative Responsibilities	18
2.3.1	DAIT Pharmacy Establishment Plan	18
2.3.2	Notification of Change Forms.....	19
2.3.2.1	Permanent/Temporary Notification of Change in Pharmacist of Record	19
2.3.2.2	Permanent/Temporary Notification of Change in Back-Up Pharmacist	19
2.3.2.3	Notification of Change in Pharmacist Contact Information and/or Pharmacy Address(es).....	19
2.3.3	Standard Operating Procedures	20
2.3.4	Communication	20
2.3.5	Reports.....	21
2.3.5.1	Reports to the Principal Investigator and Institutional Review Board (IRB)	21
2.3.5.2	Reports to DAIT Staff Members.....	21
2.3.6	Records and Documents.....	23
2.3.6.1	Error Corrections.....	23
2.3.6.2	Current Records and Documents	24
2.3.6.3	Document Retention.....	25
2.3.6.4	Document Archiving.....	25
2.3.6.5	Document Destruction	26
2.4	Investigational Product Management Responsibilities	27
2.4.1	Ordering	27
2.4.2	Receipt	27
2.4.3	Storage	28
2.4.4	Temperature Excursions.....	29
2.4.5	Participant Identifiers, Treatment Assignments, and Randomization	29
2.4.6	Unblinding Procedures	30
2.4.6.1	Routine Unblinding.....	30
2.4.6.2	Accidental Unblinding	30
2.4.6.3	Emergency Unblinding	30
2.4.7	Dispensing/Preparation and Authorized Prescribers	31
2.4.7.1	Investigational Product Order Form	31
2.4.7.2	Informed Consent	33
2.4.7.3	Expiration Date Review	33
2.4.7.4	Dose Calculation and Preparation Process	33
2.4.7.5	Dosing Errors.....	33
2.4.7.6	Labeling.....	34
2.4.7.7	Refills/Repeats	35
2.4.8	Accountability.....	35
2.4.9	Inventory Process	35
2.4.10	Chain of Custody.....	36
2.4.11	Obtaining Investigational Product from a Source other than the CPC	36
2.4.12	Shipping Investigational Product to a Participant	36
2.4.13	Investigational Product Disposition	36
2.4.13.1	Investigational Product Return.....	37
2.4.13.2	Investigational Product Destruction	37
2.4.13.3	Transfer of Investigational Product	39
2.4.13.3.1	Different Protocol: IP Transfer Within the Same Clinical Research Site	40
2.4.13.3.2	Different Protocol: IP Transfer to a Different Clinical Research Site.....	40
2.4.13.3.3	Same Protocol: IP Transfer to a Different Clinical Research Site.....	40
3	PHARMACY VISITS.....	42
3.1	<i>DAIT Authorized Monitor</i>	<i>42</i>
3.2	<i>Pharmacy Tours</i>	<i>42</i>
4	GLOSSARY OF TERMS	43
5	REFERENCES.....	48

APPENDICES (FORMS & INSTRUCTIONS FOR COMPLETION)

DAIT/NIAID Investigator of Record—FDA Form 1572

DAIT Pharmacy Establishment Plan (Form A)

Change in Pharmacist of Record (Form B)

Change in the Back-Up Pharmacist (Form C)

Change in Pharmacist Contact Information and/or Pharmacy Address (Form D)

Investigational Product Request (Form E)

Shipment Receipt Acknowledge (Form F)

Accountability Record (Form G)

Investigational Product Transfer (Form H)

Investigational Product Return (Form I)

Investigational Product Destruction (Form J)

Freezer/Refrigerator Temperature Record (Form K)

Temperature Excursion (Form L)

ABBREVIATIONS (MANUAL AND FORMS)

ALCOA	Attributable, Legible, Contemporaneous, Original, Accurate
BSA	Body Surface Area
CFR	Code of Federal Regulations
CM	Clarification Memo
CPC	Clinical Products Center
CRIS	Clinical Research Information System
CRO	Contract Research Organization
CROP	Clinical Research Operations Program
CRS	Clinical Research Site
CTA	Clinical Trial Agreement
CV	Curriculum Vitae
DAIT	Division of Allergy, Immunology, and Transplantation
DHHS	Department of Health and Human Services
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HEPA	High-Efficiency Particulate Air
HSP	Human Subjects Protection
IB	Investigator's Brochure
ICH	International Council on Harmonization
IoR	Investigator of Record
IP	Investigational Products
IRB	Institutional Review Board
MO	Medical Officer
MOP	Manual of Procedures
NF	National Formulary
NIAID	National Institute of Allergy and Infectious Diseases
NIH	National Institutes of Health
PI	Principal Investigator
PID	Participant Identification
PM	Program Manager
PoR	Pharmacist of Record
PPI	Product Package Insert
PS	Pharmaceutical Specialist
QA	Quality Assurance
QC	Quality Control
QM	Quality Management
RMC	Regulatory Management Center
RO	Regulatory Officer
SECD	Sponsor Essential Clinical Document
SID	Study Identification
SIV	Study Initiation Visit
SOP	Standard Operating Procedure
USP	United States Pharmacopeia

1 PHARMACY GUIDELINES OVERVIEW

1.1 Background

The National Institutes of Health (NIH) is the nation's medical research agency, includes 27 Institutes and Centers, and is a component of the U.S. Department of Health and Human Services (DHHS). NIH is the primary federal agency that conducts and supports basic, clinical, and translational medical research, and investigates the causes, treatments, and cures for both common and rare diseases. The National Institute of Allergy and Infectious Diseases (NIAID) is one of the institutes within NIH. The Division of Allergy, Immunology, and Transplantation (DAIT) is a division within NIAID. As a funding and operations sponsor of clinical trials, DAIT is responsible for ensuring compliance with U.S. Food and Drug Administration (FDA) regulations within the Code of Federal Regulations (CFR), the International Council for Harmonization (ICH) guidelines, Good Clinical Practice (GCP) guidelines, and local and country regulations governing the proper receipt, use, and disposition of investigational products (IPs) being evaluated in DAIT-funded/sponsored clinical trials. This responsibility includes assuring that all clinical site investigators establish and maintain sufficient records of IP disposition to comply with the above referenced regulations.

The NIH home page is <http://www.nih.gov>

The NIAID home page is <http://www.niaid.nih.gov>

The DAIT home page is <http://www.niaid.nih.gov/about/dait>

1.2 Scope and Objectives

The purpose of this pharmacy handbook is to provide DAIT, DAIT contractors, and all participating clinical sites with requirements related to the appropriate handling of IPs and supplies utilized in DAIT/NIAID-sponsored clinical trials. These requirements are in compliance with applicable federal (CFR and ICH E6) and state regulations, international standards, good clinical practices, and institutional policies and procedures. This document provides general standards and requirements pertaining to IP handling; additional instructions may be found in the study-specific protocol, manual of procedures (MOP), and institution-specific standard operating procedures (SOPs). These requirements apply to all clinical trials funded/sponsored by DAIT and are not limited to sites/centers within the United States.

The guidelines in this handbook will assist: (i) clinical site principal investigators and pharmacists to meet the DAIT-required standards for the conduct of the DAIT-funded/sponsored clinical trials; and (ii) DAIT staff who oversee the clinical operations for DAIT-funded/sponsored clinical trials. In addition to the local and country regulations governing the practice of pharmacy, pharmacists are expected to follow these guidelines for the conduct of the DAIT-funded/sponsored clinical trials. For any questions or clarifications, contact the DAIT Pharmacist at +1-240-627-3512.

1.2.1 Overview of DAIT Pharmacist Responsibilities, Clinical Research Operations Program

The pharmaceutical specialist (PS) is the DAIT pharmacist within NIAID/NIH. The PS is unblinded to studies and works closely with the DAIT Medical Officers (MO), Project Managers (PM), and Regulatory Officers (RO) by providing consultations on all pharmaceutical aspects of protocol development and processes such as issues with pharmacy operations, supplies, labeling, packaging, blinding, administration, and

distribution of IPs for all DAIT- funded/sponsored clinical trials. In addition, the PS assists with process development, adherence to quality assurance standards, SOPs, and deviation and violation reviews for all pharmacy and product-related issues at the clinical research sites participating in DAIT trials. The PS is the point of contact for all drug purchases at government pricing.

1.2.2 Overview of DAIT Regulatory Officer Responsibilities

A DAIT RO is assigned to each DAIT-funded/sponsored clinical trial and is responsible for ensuring that a trial meets all applicable federal and local regulations. The RO is also responsible for ensuring that all product information is accurately reflected in the regulatory application(s) for the clinical trial that has/have been submitted to relevant Health Authorities. The RO works closely with the MO, PS, and PM in all matters related to the clinical trial and clinical trial supply, including: (i) ensuring that the proposed IP and its placebo to be used in the clinical trial meet all regulatory requirements for use in the proposed country; (ii) review and approval of all relevant product labels to be used in the clinical trial; (iii) review and resolution of any deviations and violations involving the IP/placebo during the course of the trial. The RO must be informed of: (i) all quality assurance questions/issues related to the IP/placebo; (ii) any errors that occur in drug administration to subjects; and (iii) any instance that potentially affects the quality, identity, strength, or purity of the IP/placebo (including but not limited to temperature excursions, expiry dating, and questions related to repackaging). For study drug deviation/violation issues related to an IP that has been provided to DAIT/NIAID under a Clinical Trial Agreement (CTA), the RO is the point of contact for communications with that study drug manufacturer. The PM, PS, and RO are all responsible for ensuring that documentation related to the IP is accurately reflected in trial documentation, and the RO is responsible for all required Health Authority notifications throughout the course of the clinical trial.

1.2.3 Overview of DAIT Project Manager Responsibilities

For each DAIT-funded/sponsored trial, the project manager (PM) acts as the study lead and DAIT point of contact who is responsible for all study activities such as site evaluation and establishment, IP quantity determination, development of IP labels, pharmacy manual, study forms, and all communication and coordination with the study sites. Additionally, PMs engage and inform the Clinical Products Center (CPC) during protocol development, protocol progress, and subsequent amendments, and they submit contact information on the site PI and pharmacist with periodic updates. Moreover, PMs coordinate and may conduct site initiation visits and provide study training to all participating sites. PMs initiate the first IP order request after the site is activated. Investigational product shipments, transfers, expirations, returns, destructions, deviations, and temperature excursions also are monitored by PMs. PMs handle all study activities or deviations in consultation with the Regulatory Officer (RO) and DAIT Pharmacist (PS). Please refer to each section for more details.

1.3 Contact Information and Websites

1.3.1 Division of Allergy, Immunology, and Transplantation: Project Manager

Name: Designated Project Manager

Telephone: Will be provided in the specific protocol

Email: Will be provided in the specific protocol

Mailing Address: Will be provided in the specific protocol

1.3.2 Division of Allergy, Immunology, and Transplantation: Clinical Research Operations, Pharmaceutical Specialist (DAIT CROP, PS)

Name: Sanaz Daneshfar Hamrah, Pharm.D., BCPS

Telephone: +1-240-627-3512

Email: hamrahsd@niaid.nih.gov

Mailing Address:

Clinical Research Operations Program

Division of Allergy, Immunology, and Transplantation

National Institute of Allergy and Infectious Diseases

5601 Fishers Lane #7D30

Bethesda, MD 20892 USA *[for U.S. mail]*

Rockville, MD 20852 USA *[for courier deliveries]*

1.3.3 Clinical Products Center

The Clinical Products Center (CPC) was established to support DAIT clinical research networks/consortia. As a DAIT contractor, the CPC's primary role is inventory management, storage, distribution, and destruction of IPs and medical supplies.

The hours of operation are: 8 a.m. – 5 p.m., U.S. Eastern Time, Monday-Friday, and the shipping hours are: 8 a.m. – 3 p.m., U.S. Eastern Time, Monday-Friday. The CPC is closed on weekends and all U.S. federal holidays (except for emergency shipments and emergency unblinding, which can be performed 24 hours per day, 7 days per week, 365 days per year).

For the schedule of U.S. federal holidays, visit the website:

http://www.opm.gov/Operating_Status_Schedules/fedhol/index.asp

- The CPC staff usually processes IP order requests as they are received.
- For U.S. sites, the CPC ships orders to arrive the next day. Wet ice and dry ice shipments are delivered in one day; on Fridays, IP shipments that need to be iced are shipped the following Monday.
- For non-U.S. sites, due to the time zone differences, it may take up to two business days for the Pharmacist of Record (PoR) to receive an acknowledgement of receipt of the IP order request from the CPC staff. The CPC coordinates shipments with a courier service and the PoR to ensure that the IP orders arrive in the shortest period of time possible, on a day when pharmacy staff is present.

1.3.4 NIAID DAIT Clinical Research Networks/Consortia

Currently, DAIT-sponsored clinical trials are conducted under grants awarded to individual investigators or under the following fifteen DAIT-funded clinical trials networks/consortia:

- Asthma & Allergic Diseases Cooperative Research Centers (AADCRC)
<http://www.niaid.nih.gov/research/cooperative-research-centers>
- Atopic Dermatitis Research Network (ADRN) <http://www.nationaljewish.org/research-science/clinical-and-translational-research/atopic-dermatitis-research-network>
- Autoimmunity Centers of Excellence (ACE)
<http://www.autoimmunitycenters.org>
- Clinical Islet Transplantation Consortium (CIT) <http://www.citistudy.org>
- Clinical Trials in Organ Transplantation (CTOT) <https://www.ctotstudies.org>
- Clinical Trials in Organ Transplantation in Children (CTOT-C)
<https://www.ctotc.org>
- Consortium For Food Allergy Research (CoFAR)
<https://web.emmes.com/study/cofar>
- Cooperative Clinical Trials in Pediatric Transplantation (CCTPT) (no website)
- Genomics of Transplantation Cooperative Research Project (GTCRP)
<http://www.rhoworld.com/rho/services/projects/gtcp>
- Human Immunology Project Consortium (HIPC)
<http://www.immuneprofile.org/hipc>
- Immune Tolerance Network (ITN) <http://www.immunetolerance.org>
- Inner City Asthma Consortium (ICAC)
<http://www.medicine.wisc.edu/asthma/icacmain>
- Primary Immunodeficiency Treatment Consortium (PIDTC)
<http://www.rarediseasesnetwork.org/PIDTC/index.htm>
- Consortium of Eosinophilic Gastrointestinal Disease Researchers (CEGIR)
<http://www.rarediseasesnetwork.org/cms/CEGIR>

2 RESPONSIBILITIES OF THE PRINCIPAL INVESTIGATOR AND DELEGATEES

At each DAIT-funded/sponsored clinical research site, the site principal investigator (PI) is responsible for overall site activities, including day-to-day operations, performance, and compliance at the site level. This person is identified on the Form FDA 1572 or DAIT NIAID Investigator of Record (IoR) Form and is the on-site senior research scientist responsible for the administrative and scientific components of the clinical research site. DAIT requires that the PI delegate the responsibility for IP management to a licensed/registered pharmacist at the clinical research site. This pharmacist is identified as the Pharmacist of Record (PoR). The PoR or his/her designee(s) are responsible for coordinating all issues related to the management of IPs and for performing the day-to-day pharmacy activities of a DAIT-funded/sponsored clinical trial.

The PoR should commit the necessary and appropriate amount of time to meet the pharmaceutical needs and requirements of the specific DAIT-funded/sponsored clinical trial. The PoR must be available when IPs are requested to be dispensed to study participants. Satellite IP storage areas that meet DAIT requirements (storage and maintaining the blind) and are overseen by the PoR are permitted at the site clinic when the research pharmacy is closed. Based on Form FDA 1572 or the “DAIT NIAID Investigator of Record” form (*See FDA 1572 Form*), the PI is ultimately responsible for all aspects of the study within his/her clinical site. An additional licensed/registered pharmacist working at the site is required as the Back-up Pharmacist to assume the responsibilities of the PoR in his/her absence. The Back-up Pharmacist is trained by the PoR to perform pharmacy activities required of a DAIT-funded/sponsored clinical trial. For the purposes of this manual, all references to the PoR also apply to the Back-up Pharmacist.

2.1 Professional Responsibilities

2.1.1 Licensure/Registration

The PoR must be licensed and/or registered to practice pharmacy in the jurisdiction in which s/he is practicing. For international sites, DAIT Project Managers (PMs) will review the standard of practice for sites outside of the U.S. to ensure appropriate infrastructure is in compliance with local laws and regulations (i.e., pharmacy technicians are licensed to practice as a dispensing pharmacist in some countries such as Canada).

2.1.2 Knowledge of Local and Country Regulations

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

2.1.3 Good Clinical Practice

The PoR must receive training in and follow Good Clinical Practice (GCP) guidelines.

2.1.4 Human Subjects Protection

The PoR must receive training in and follow Human Subjects Protection (HSP) guidelines.
<http://phrp.nihtraining.com>

2.1.5 Continuing Professional Development

The PoR is encouraged to have ongoing participation in continuing professional development activities, including IP-related topics. This will facilitate continued professional growth and awareness in addition to satisfying requirements to maintain licensure/registration.

2.1.6 Knowledge of Protocols

The PoR should be knowledgeable of every DAIT-funded/sponsored clinical trial being conducted at his/her site pharmacy and the IPs involved. In addition, the PoR must adhere to the requirements of each clinical trial protocol and/or MOP.

2.1.7 Investigational Product Management

The PoR should coordinate all research pharmacy operations and perform the day-to-day pharmacy activities related to the management of IPs. (*See Section 2.4 Investigational Product Management Responsibilities*).

2.1.8 Confidentiality

The PoR must maintain appropriate safeguards to ensure security, integrity, and confidentiality of participant information and protect against unauthorized use or disclosure. The PoR must remove participant identifiers when asked to provide copies of pharmacy documents, to ensure that confidentiality is maintained.

2.1.9 Informed Consent Verification

The PoR should have a system in place to ensure that the study participant has given informed consent to participate in the research study prior to dispensing the study intervention. (*See Section 2.4.7.2 Informed Consent*).

2.1.10 Record Keeping

The PoR must maintain all pharmacy records using the “ALCOA” Method (*See Glossary*). (*See Section 2.3.6.2 Current Records and Documents*).

2.1.11 Product Information

The most current Investigator’s Brochure (IB) or Product Package Insert (PPI) is distributed with the final version of a protocol to the study coordinator or regulatory coordinator at the clinical research site, who is responsible for distribution to the PoR. The PoR must maintain all essential information pertaining to IPs in DAIT- funded/sponsored clinical trials. In addition, these records must be kept in the pharmacy files, and copies must be provided to the DAIT Regulatory Management Center (RMC).

- Maintaining Copies of Investigator’s Brochures (IB)

The content of an IB may change during the course of the trial. The PoR should keep on file the most current version as well as all previous IB versions during the course of the trial. The information in the IB is confidential and should not

be reproduced or distributed to individuals outside of the research team. The IB is to be used only by the pharmacists, the investigators, and other health professionals on the research team.

- Product Package Inserts (PPI)

The PoR should keep on file the most up-to-date PPI of every IP being used in a DAIT-funded/sponsored protocol.

2.1.12 Blinded Studies

The PoR must maintain the scientific integrity of the clinical trials and take all precautionary measures to prevent “unintended” unblinding of any participant treatment assignments. This includes limiting access to treatment assignment records and IPs in blinded trials.

2.1.13 Adherence Counseling

The PoR may be responsible for counseling a study participant on the proper use and/or administration of IPs for a DAIT-funded/sponsored clinical trial.

2.1.14 Supervision and Training of Pharmacy Staff

The PoR is responsible for the direct supervision of all pharmacy staff assisting with DAIT-funded/sponsored clinical trials. The Back-up Pharmacist should be trained by the PoR to perform pharmacy activities required in the DAIT Pharmacy Guidelines. The pharmacy staff must be qualified by pharmacy education, pharmacy training, and experience to perform their respective tasks. The PoR is also responsible for conducting all protocol related and SOP training for any involved pharmacy staff. All training should be documented and maintained in the up-to-date Pharmacy Binder for study personnel.

2.1.15 Protection of Pharmacy Staff

The PoR should be knowledgeable of practices and procedures and provide appropriate training to staff to prevent exposure to potentially hazardous agents (i.e., immunogenic, carcinogenic, chemical, and mutagenic agents). All trainings need to be documented.

2.1.16 Quality Management

The PoR should be involved in the development and implementation of a Quality Control (QC) and Quality Assurance (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 each study participant is dispensed the correct study treatment and dose of the proper drug, biologic, vaccine, or radiopharmaceutical, as defined by the protocol.

2.1.17 Infection Control

The PoR must be knowledgeable of practices and procedures that prevent contamination and cross-contamination of IPs, and must prevent the dispensing of any IP that may have been contaminated. For trials involving sterile products, the PoR is responsible for maintaining sterility of aseptic drug products (i.e., for aseptic preparation of doses and

maintenance of sterile products). The PoR should have comprehensive knowledge, understanding, and proficiency with aseptic techniques and use of applicable equipment (i.e., laminar air flow hood).

2.1.18 Monitoring Visits and Reports

The PoR should be available for all pharmacy monitoring visits. In addition, it is recommended that the PI be available during any monitoring visits. At the conclusion of the monitoring visit, a debriefing is held between the monitor and the site staff. The PoR should attend the debriefing. After the pharmacy monitoring visit, the monitoring group generates a site pharmacy visit report, which can be part of the complete visit report, and sends it to the site. The PoR should review the site pharmacy visit report(s) and address and correct any pharmacy-related issues identified. (*See Section 3 Pharmacy Visits*).

2.2 Research Pharmacy Facility Supervision

The research pharmacy must be secure, clean, and of adequate size for the PoR to perform the day-to-day pharmacy activities for DAIT-funded/sponsored clinical trials. In addition, the pharmacy must be appropriately and adequately equipped to allow the PoR to provide proper storage of IPs (i.e., ensuring controlled access, protection from vermin, extreme humidity, heat/cold/light, as well as space separation for active vs. placebo IP). All equipment must be exclusively for pharmacy use. The research pharmacy facilities must be in compliance with all local laws and regulations.

The IPs, as well as any drugs, devices, or study intervention supplies specifically provided for a DAIT-sponsored trial will be stored per manufacturer's label requirements, dispensed, accounted for, and documented.

In circumstances in which a site cannot comply with the general standards in this document, the site must immediately inform the PI and the medical monitor (program officer). An approval must be obtained from the DAIT PM who must in turn notify the DAIT RO and DAIT CROP PS for their internal approval.

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

2.2.1 Required Space

The pharmacy should be of adequate size and organized, and have adequate countertop space and ample lighting. Sufficient pharmacy space and equipment for storing, preparing, and dispensing IPs, and for preparing associated documentation is necessary so that:

- Pharmacists and other pharmacy staff can work comfortably and efficiently.
- The potential for errors is reduced.
- Each IP can be adequately segregated from other products.
- Space is adequate enough to accommodate the equipment and supplies.
- Pharmacy records can be stored in an organized fashion and be easily retrievable.

- Hand washing and cleaning facilities are available.
- Work surfaces are adequate for IP preparation and accountability and for record management.

2.2.1.1 Electrical Supply

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

2.2.1.2 Back-Up Power Supply or Generator

All equipment supporting pharmacy operations must have a back-up power source. Testing and maintenance must be conducted in accordance with IP manufacturer's recommendations and must be documented.

2.2.1.3 Water Supply

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

2.2.1.4 Ancillary Supplies

The PoR should ensure that there is sufficient stock of ancillary supplies for preparing and dispensing IPs.

2.2.2 Required Security

The pharmacy must have access limited to authorized pharmacy staff only. This includes all areas of IP storage and pharmacy files. These areas must have sufficient security systems in place, such as locks, alarms, window bars, and/or security personnel, to prevent unauthorized entry and access to IPs and pharmacy files at all times. When pharmacy personnel are not present in the pharmacy, the pharmacy must be locked.

2.2.3 Storage of Investigational Products

2.2.3.1 Controlled Room Temperature

The research pharmacy must be maintained at the appropriate room temperature setting to preserve the integrity, stability, and effectiveness of IPs for each protocol. Based on United States Pharmacopeia (USP) & National Formulary (NF) requirements, "controlled room temperature" is defined as temperature maintained between 20°C to 25°C (68°F to 77°F), and allows for excursions between 15°C and 30°C (59°F and 86°F) that may be experienced during storage, shipping, and distribution. Transient spikes up to 40°C (104°F) are permitted as long as they do not exceed 24 hours (*See Glossary, United States Pharmacopeia/National Formulary (USP/NF) Definitions*). Temperature must be recorded. In order to maintain the pharmacy at controlled room temperature, the use of air cooling and heating equipment may be necessary. In addition, the pharmacy should be of adequate size and have sufficient space and shelving for the room temperature storage of IPs. (*See Section 2.2.4 Temperature Monitoring and Alarm System*).

2.2.3.2 Refrigerator and Freezer

- **Refrigerator (Controlled Cold Temperature)**

The research pharmacy refrigerator must be maintained at the appropriate temperature range to preserve the integrity, stability, and effectiveness of IPs for each protocol. Based on USP & NF requirements, “controlled cold temperature” is defined as temperature maintained between 2°C and 8°C (36°F and 46°F), and allows for excursions between 0°C and 15°C (32°F and 59°F) that may be experienced during storage, shipping, and distribution. Transient spikes up to 25°C (77°F) may be permitted if the manufacturer so instructs and provided that such spikes do not exceed 24 hours unless supported by stability data or the manufacturer instructs otherwise (*See Glossary, United States Pharmacopeia/National Formulary (USP/NF) Definitions*). Temperature must be recorded. It is recommended to have a lock on the refrigerator, which should be of adequate size and sufficient capacity for the storage of IPs requiring refrigeration. The pharmacy refrigerator must be used exclusively for storage of IPs. It must be kept in a clean and sanitary condition, be in good working order, and be capable of maintaining the appropriate temperatures. (*See Section 2.2.4 Temperature Monitoring and Alarm System*).

- **Freezer**

The research pharmacy -20°C freezer must be maintained at the appropriate temperature range to preserve the integrity, stability, and effectiveness of IPs for each protocol. Based on USP & NF requirements, “freezer” is defined as temperature maintained between -25°C and -10°C (-13°F and 14°F). There may be other freezer requirements for specific DAIT protocols, such as -20°C and -70°C freezers. Temperature excursions may be permitted if supported by stability data or the manufacturer instructs otherwise. Temperature must be recorded. The pharmacy freezer should be of adequate size and sufficient capacity for the storage of IPs that must be kept frozen. The pharmacy freezer must be used exclusively for the storage of IPs. It must be kept in a clean and sanitary condition, in good working order, and be capable of maintaining the appropriate temperatures. (*See Section 2.2.4 Temperature Monitoring and Alarm System*).

2.2.3.3 Back-Up Plan for Investigational Product Storage

The PoR must have a back-up plan in place to ensure that appropriate storage conditions for IPs are maintained in the event of equipment or power failure. This plan must meet all storage, security, access, equipment, and monitoring guidelines stated in this manual.

2.2.3.4 Extreme Humidity and Light

Every IP storage area must be maintained so that IPs are not exposed to extreme ranges of low or high humidity and light. In some climate regions, the relative humidity may need to be controlled, monitored, and recorded daily. Based on USP & NF standards, average relative humidity is defined as 40% or lower. If necessary, an additional air cooling system, humidifier, or dehumidifier may be used to control the relative humidity. The IPs must not be exposed to excessive light or direct sunlight.

2.2.4 Temperature Monitoring and Alarm System

Any IP storage area (e.g., pharmacy room temperature storage, refrigerator, and freezer) must have a temperature monitoring and recording system (see below) in place. This process must include a continuous method of monitoring and manual system of checking (at least once a day) and documenting the temperature 24 hours a day, 7 days a week, and 365 days a year. There must be an alarm system to alert authorized pharmacy personnel, 24 hours a day, 7 days a week, 365 days a year, of temperature deviations/excursions from the acceptable temperature range, so immediate action may be taken to prevent loss of IPs.

2.2.4.1 Continuous Temperature Monitoring and Recording System

Any IP storage area (e.g., pharmacy room temperature storage, refrigerator, and freezer) must have a system in place to continuously monitor and record the temperature.

Continuous temperature monitoring and recording provides real time temperature information for the designated IP storage area in which the system is installed. Additionally, the frequency, duration, and range of any deviation/excursion is recorded and can be used by the CPC and the manufacturer to determine if the IP can be safely administered or should be replaced.

Continuous temperature monitoring and recording devices are available from multiple manufacturers, with varied monitoring and recording capabilities. The device should monitor and record/document the temperatures and, if electronic, the data should be uploaded to a computer file or printed and stored as a hard copy. Some examples of different systems available in the market are as follows:

- **Chart Recorder**

This device records temperatures for 24 hours, 7 days, or 31 days. The chart paper should be replaced at the appropriate interval, depending upon the model. When replacing the paper, the previous paper record should be reviewed and filed in the pharmacy files. If this device is battery-operated, the batteries must be replaced regularly, per equipment manufacturer's recommendations.

- **Electronic Temperature Data Logger**

This device records temperatures at programmed time intervals, and should be set, ideally, at a minimum of every 15 minutes. The data captured by the temperature recording device must be downloaded and saved, and the paper record should be reviewed and filed in the pharmacy files. The files of the recorded temperature data enable the DAIT- authorized monitor to confirm that temperatures have been maintained within the appropriate temperature range.

All instructions provided by the manufacturer for using the device, such as maintenance, setting and resetting, and calibration, must be followed.

2.2.4.2 Manual Temperature Review and Recording

A handwritten recording of the temperatures should be documented in a temperature monitoring log at least once a day (real-time) and 5 days a week, regardless of the use of an electronic temperature data logger device. The PoR may use the “*DAIT Investigational Product Freezer/Refrigerator Temperature Log*” form to record all daily manual temperature records (*See Form K*).

An accurate and functional secondary temperature-measuring device should be kept in all room temperature storage areas and in every refrigerator and freezer where IPs are stored in order to provide real-time temperature readings. All thermometers should be accurate to $\pm 0.5^{\circ}\text{C}$. At a minimum, it is recommended that the minimum/maximum thermometer be used for real time temperature readings, as it also serves as a backup should the continuous temperature monitoring device fail. The thermometer should be checked daily to verify that the temperature is in range, and the temperature should be manually documented on a temperature monitoring log. The daily manual temperature verification is also used to verify that the alarm system is functioning properly, alerting the PoR if the temperature is out of the acceptable temperature range. The temperature monitoring log is to be reviewed to identify trends that may indicate that equipment requires adjustment or service.

All instructions provided by the manufacturer for using the device, such as maintenance, setting and resetting, and calibration, must be followed.

2.2.4.3 Alarm System for Temperature Deviations/Excursions

Every pharmacy refrigerator, freezer, and room temperature storage area must have an 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 IP.

All instructions provided by the manufacturer for using the device, such as maintenance, setting and resetting, and calibration, must be followed.

2.2.5 Laminar Air Flow Hood and Isolator

Based on USP 797 guidelines, using an aseptic technique, biological safety cabinet (BSC), aseptic isolator, or IV hood is standard of practice for injectable IP preparation, and is expected to be followed for DAIT-funded/sponsored clinical trials. If acquiring the above equipment is not feasible, admixing of all injectable IPs should be outsourced to a licensed IV Infusion Pharmacy.

2.2.5.1 Vertical Air Flow Hood

A class II or III vertical air flow hood or BSC should minimize exposure to injectable IPs during preparation. A class II, type B, or class III BSC is recommended because the air is vented to the outside. Those with air recirculation are the least protective.

2.2.5.2 Horizontal Air Flow Hood

A horizontal airflow hood (e.g., work bench, cabinet, and IV hood) provides an aseptic environment for the aseptic preparation of injectable IPs. This hood provides a flow of filtered air originating at the back of the cabinet and exiting toward the person preparing IP under the hood. The horizontal air flow increases the likelihood of IP exposure to both the preparer and other personnel in the room.

2.2.5.3 Isolator

An aseptic containment isolator is a device that is sealed or is supplied with air through a microbial retentive filtration system, a high-efficiency particulate air (HEPA) filter, and may be reproducibly decontaminated. An isolator may be used in place of a BSC.

(See Glossary. Every laminar air flow hood, BSC, and isolator must be maintained and evaluated for proper performance, in accordance with the manufacturer's instructions.)

2.2.6 Maintenance of Equipment

There should be a program for inspecting, testing, and maintaining pharmacy equipment and documenting such activities. When possible, maintenance of pharmacy equipment should be coordinated with other equipment maintenance at the facility. All equipment should be certified or calibrated routinely, per equipment manufacturer's recommendations.

2.3 Administrative Responsibilities

2.3.1 DAIT Pharmacy Establishment Plan

The PoR should complete a “*DAIT Pharmacy Establishment Plan*” form (*See Form A*) or equivalent if information is obtained through a feasibility questionnaire or other modality. The PoR should submit the form to the PM and copy the PS for review and approval if one of the following conditions exists:

- It is the beginning of a new funding cycle for the clinical network or consortium.
- A new site is being established.
- The pharmacy is moving to a new location (will be treated as new site pharmacy).
- There is a significant change in procedures outlined in the previously approved DAIT Pharmacy Establishment Plan.
- Upon DAIT PM request.

For any questions or concerns regarding the need for submission of a new DAIT Pharmacy Establishment Plan, contact the DAIT PM or PS.

2.3.2 Notification of Change Forms

If there are any changes in pharmacy information after the approval of the site's "DAIT Pharmacy Establishment Plan" form (See Form A), the appropriate "Notification of Change" form (See Form B and/or C) should be completed and submitted immediately to the PM and a copy sent to the PS. Upon review by the PM, submission of a revised DAIT Pharmacy Establishment Plan may be required for approval.

Once the form is received, processed, and acknowledged by the PM, the *acknowledgement* email should be printed and filed with the site's most current, approved "DAIT Pharmacy Establishment Plan," along with a copy of the submitted notification form.

2.3.2.1 Permanent/Temporary Notification of Change in Pharmacist of Record

This document should be completed when there is a new permanent/temporary PoR at the clinical research site, or when a Back-up Pharmacist is temporarily stepping in as the PoR (See Form B).

2.3.2.2 Permanent/Temporary Notification of Change in Back-Up Pharmacist

This document should be completed when there is a new Back-up Pharmacist, an additional Back-up Pharmacist, or a departing Back-up Pharmacist at the clinical research site (See Form C).

2.3.2.3 Notification of Change in Pharmacist Contact Information and/or Pharmacy Address(es)

This document should 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 of the new pharmacy (See Form D).

2.3.3 Standard Operating Procedures

The PoR should have detailed, written instructions governing pharmacy operations for conducting the DAIT-funded/sponsored 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, distribution, labeling, handling, dispensing, blinding, unblinding, and final disposition of IPs. For some protocols, the PoR may be required to generate protocol-specific SOPs, as indicated in the protocol- or study-specific procedures. The Pharmacy SOPs should be available to DAIT NIAID monitors for the purpose of site evaluation and on-site review. The following is the list of Pharmacy SOPs that are collected for the site participation evaluation:

1. Validation and Calibration of Storage Equipment (freezers, refrigerators, temperature monitoring devices) when New and Yearly Thereafter.
2. Maintaining the Cold Chain (including continuous monitoring and recording, alarms when out of range, security).
3. Transport of Study Product to a Satellite or Study Site.
4. Temperature Excursions (include communication with the Sponsor).
5. Preparation and Dispensing of Study Product (include a double check for study product treatment group, preparation and dose when the study pharmacist does, and does not, prepare the product).
6. Back-up Plan for Equipment Malfunction or Failure Including Power Failure/ Outage.
7. Pharmacy QA Processes (QC of all pharmacy documents and study product inventory).
8. Quarantine of Study Product Due to Expiration, Recall, or Temperature Excursion.
9. Investigational Product Return to Sponsor and On-Site IP Destruction.
10. Treatment Assignment Records and Unblinding Treatment Assignment in Emergencies.

2.3.4 Communication

The PoR should ensure that reliable methods of communication are in place to assure timely and accurate transmission of information to the clinical staff and DAIT PM. The PoR should also participate in protocol initiation calls, protocol team calls, and any other protocol-specific or site-specific calls as indicated and needed. In addition, at the study initiation visit (SIV), the DAIT PM ensures the presence of a proper communication pathway between pharmacy and clinical staff.

For any protocol-specific questions, issues, or concerns, the PoR should contact the PM. All correspondence related to any DAIT-funded/sponsored clinical trial must be documented and maintained appropriately in pharmacy files, with copies sent to the DAIT Regulatory Management Center.

2.3.5 Reports

2.3.5.1 Reports to the Principal Investigator (PI) and Institutional Review Board (IRB)

In the case of any situation that could affect the safety of a study participant or the outcome of a study (i.e., accountability issues), a report with a corrective action plan must be submitted to the PI and IRB at the clinical research site per local requirements, and DAIT/NIAID must be notified. This report must not unblind the investigators or other study personnel to the study treatment assignment. If the PoR is unsure that the report is written in a way that will not unblind the PI, s/he must contact the DAIT PM or DAIT PS for assistance.

The following are examples of incidents that are reportable to the PI and the “DAIT Project Team.” For reporting to the IRB, sites must follow instructions per their specific IRB:

- Participant was dispensed an incorrect IP
- Participant was dispensed an expired IP
- Participant was dispensed an improperly stored IP
- Participant was dispensed an incorrect dose of the IP
- Participant was assigned an incorrect study identification (SID) or participant identification (PID) number or an incorrect study kit number
- Unblinding activity by the site PoR
- Participants exchanged or shared IP
- Improper storage of IP
- IP was dispensed or administered to an individual not participating in the protocol
- IP was dispensed or administered to an individual who was not properly consented for the specific protocol

2.3.5.2 Reports to DAIT Staff Members

The PoR must prepare a written report with a corrective action plan to inform the PI and PM as soon as s/he becomes aware of an incident or matter that could affect the outcome of a study, such as errors or issues pertaining to IP preparation, accountability, administration, or IP dispensing. The report must be submitted via email, fax, mail, or courier to the DAIT PM.

The following are examples of incidents that are reportable to the PM (with a copy to the PS and RO):

- Participant was dispensed an incorrect IP
- Participant was dispensed an expired IP
- Participant was dispensed an improperly stored IP
- Participant was dispensed an incorrect dose of the IP
- Participant was assigned an incorrect SID or PID number or an incorrect study kit number
- Unblinding activity by the site PoR
- Participants exchanged or shared IP
- Improper storage of IP
- Accountability discrepancy that was not able to be reconciled
- IP was dispensed or administered to an individual not participating in the protocol
- IP was dispensed or administered to an individual who was not properly consented for the specific protocol

The PoR's incident report to the PM must include the following:

- Clinical research site name and site number
- Network or consortium name and protocol number (i.e., ITN Protocol ITN100 or ACE Protocol ALE00)
- PID and SID numbers or kit identification numbers
- Detailed description of the incident, including date
- Reason(s) for the incident
- Information regarding any site SOPs that were not followed
- Resolution and/or follow-up of the incident
- Description of the steps that have been taken to prevent similar problems in the future
- Statement of whether the incident resulted in a reportable adverse experience report

- Clinic staff who were notified of the incident and date of notification
- Any associated documentation related to the incident

2.3.6 Records and Documents

The PoR should maintain pharmacy records in accordance with the Policy on *Requirements for Source Documentation in DAIT Sponsored/funded Clinical Trials*, and using the “ALCOA” Method *(See Glossary)*. This policy also serves to ensure data quality by creating audit trails and enabling verification that data are present, complete, and accurate.

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 to authorized pharmacy staff, the DAIT authorized staff and monitors, and the health authority (e.g., Food and Drug Administration auditors).

2.3.6.1 Error Corrections

Anytime an error is made, the following proper 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 and 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 black or blue ink
- Never use a 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 or are stained
- Do not alter past-dated notes, chart notes/progress notes (e.g., by writing alongside or adding to prior entries)

For handwritten corrections:

- Draw a single line through the incorrect information
- Initial, date, and state reason for change
- Insert the correct information

For electronic/typed corrections:

The electronic system should not allow for any changes to occur and if it does:

- Strike through the entire line where the error was made, if possible
- Type in initials, date, and reason for change
- On the next available line, type all information including the corrected information

2.3.6.2 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:

- Readily accessible copy of the current Investigational Product & Pharmacy Guidelines for DAIT Clinical Research Networks/Consortia
- Most current, approved, signed DAIT Pharmacy Establishment Plan attached to the notification of the PM's approval email
- Copies of completed and submitted Notification of Change forms, attached to the PM's acknowledgement email(s)
- Most recent version of the protocol for which the site has IRB approval, and any additional versions of the protocol if there are participants being followed on those versions
- All Protocol Bulletins and Clarification Memos (CMs)
- All IP accountability records
- All IP records, such as orders, invoices, packing slips, import permits, tax waiver documents, transfer receipts, and return or destruction forms and associated receipts
- Temperature monitoring records
- Randomization information, such as Pharmacist's Prescription List, SID/PID list, treatment assignment information, or e-mail randomization
- Records needed to document chain of custody for IPs
- Current Prescribers' Signature List
- Current Pharmacists' Signature List of printed names, signatures, and initials of the PoR and other authorized pharmacy staff

- Original IP order or request form
- Most recent version of MOP, if applicable
- For each investigational product, the current PPI or the most recent version of the IB; the previous versions of the IB should be retained, if needed.
- Written communications with clinical research site staff and others (e.g., DAIT staff, CPC, PPD monitors)
- Training documentation
- Site pharmacy SOPs
- Other equivalent documentation approved by the sponsor

All electronic data must be 21 CFR Part 11 compliant, and 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.

2.3.6.3 Document Retention

Record retention and management applies to clinical research records (*See Glossary*) that are generated, stored, and retained, as required by U.S. regulations, laws, and policies while conducting DAIT-funded/sponsored clinical trials. These records may be subject to additional federal, state, local, and/or institutional regulations/policies. DAIT/NIAID, as a study sponsor, maintains a Trial Master File (termed Sponsor Essential Clinical Documents or SECD) for each DAIT-sponsored study. These files, which are maintained at the DAIT RMC, contain documents obtained from the Clinical Site File (which is maintained at the clinical research site).

2.3.6.4 Document Archiving

The forms listed below and documents should be kept in the pharmacy until the study/trial has reached the DAIT CRIS (*See Glossary*) status of “CONCLUDED,” “RECRUITMENT COMPLETED,” or “CLOSED TO FOLLOW UP.” Upon study or site closure, a copy of all pharmacy forms and documents will be reconciled with the trial-specific DAIT SECD held at the RMC. However, these documents should be available for expedient retrieval, inspection, and photocopying of information, if requested by a properly authorized DAIT or health authority employee or representative.

After the study has reached the DAIT CRIS status of “CONCLUDED,” “RECRUITMENT COMPLETED,” or “CLOSED TO FOLLOW UP,” pharmacy source documents, including pharmacy accountability records, should be retained or archived. When records are being archived, all pharmacy records should be placed in a folder or envelope and clearly marked as “pharmacy records.”

Pharmacy source documents should be filed in the clinical site pharmacy binder. However, these documents should be available for expedient retrieval, inspection, and photocopying of information, if requested by a properly authorized DAIT or health authority employee or representative.

These documents include and are not limited to:

- A. Pharmacy Establishment Plan (Form A)
- B. Change in PoR (Form B)
- C. Change in Back-up Pharmacist (Form C)
- D. Change in Contact Information (Form D)
- E. Investigational Product Request (Form E)
- F. Investigational Product Receipt (Form F)
- G. Investigational Product Accountability Record
(Form G)
- H. Investigational Product Transfer (Form H)
- I. Investigational Product Return (Form I)
- J. Investigational Product Return for Destruction
(Form J)
- K. Investigational Product Temperature Log (Form K)
- L. Investigational Product Temperature Excursion
(Form L)
- M. Deviations Reports (Pharmacy-generated reports)

All clinical research records must be stored in a manner that ensures privacy, confidentiality, security, and accessibility.

2.3.6.5 Document Destruction

Pharmacy source documents should be kept until the study appears on a DAIT list of protocols whose records may be destroyed. Due to the confidential nature of the information in an IB, it must be destroyed. This destruction may be by use of a mechanical shredder, an incinerator, cutting or tearing into small parts, or other methods of destruction (i.e., deleting the electronic copies of the IB).

2.4 Investigational Product Management Responsibilities

The following sections address the responsibilities of the PoR regarding the various activities performed in the pharmacy.

2.4.1 Ordering

- After receipt of all required documents from a site, completion of site registration by the DAIT RMC, and completion of all necessary site activation activities, a site activation letter is generated by the “DAIT Project Team” (*See Glossary*) and sent to the site by the PM.
- DAIT “*Investigational Product Request*” form (*See Form E*) should be completed by the PM for the initial order of IP for a site, reviewed and approved by the DAIT RO, and sent to the CPC.
- Any subsequent ordering of a drug and/or supply will be initiated by the PoR (after the initial order placement by the PM and RO) and sent to the CPC (Eminent) for processing. The CPC sends Form E to the DAIT PS (for blinded studies) or DAIT PM (for unblinded studies) for approval before shipment to the site. The CPC must provide the PM and RO the lot number(s) of the IP to be sent to the site if different from the original batch records. When applicable, the RO must ensure that the documentation for the specific IP lot to be shipped has been submitted to the appropriate health authorities.
- The PoR must ensure that sufficient supplies of IPs are always available at the site pharmacy to meet participant needs during the conduct of a study. The PoR also can contact the DAIT CRO (*See Glossary*) for any issues or questions.

2.4.2 Receipt

All IPs are shipped on a clinical research site-specific, investigator-specific, and protocol-specific basis by the CPC. The CPC packages IPs in shipping containers that meet the IP manufacturers’ validated shipping processes and are designed to maintain the proper storage conditions during shipment. Each shipment of IPs from the CPC includes a packing list and product receipt form. Temperature monitoring device(s) such as TempTale may be included with the shipment, along with instructions for reading and returning the device(s) or its log report (if needed).

For a non-U.S. clinical research site, a shipment may also contain a copy of an invoice and other documents required for drug importation.

Within two hours of receipt in the pharmacy, the PoR must verify: the identity of the IP by reviewing the labels on the IP vs. the IP name on the protocol; the quantity of IPs received matches the quantity indicated on the packing list; the IPs were received in good condition (check containers and packaging for signs of leakage, etc.); and that storage conditions have been maintained. The PoR should use the “*Investigational Product Receipt*” form (*See Form F*) for this verification and fax the completed form back to the CPC.

The IPs can be placed in released (active) inventory if they do not appear damaged and if there are no discrepancies in any information checked above including temperature deviations/excursions.

Under no circumstances should any IP affected by a temperature excursion be administered to clinical study subjects before such excursion is reported and evaluated by the “DAIT Project Team.”

If any of the preceding conditions occur:

- The PoR should contact the CPC and PM immediately for further instructions and document the notification on the packing list.
- The IPs must be quarantined in a separate area under the proper storage conditions.
- The PoR must not dispense the affected IPs until the PM notifies the PoR in writing or by email or fax that the IP may be safely used.
- The PoR should maintain a hardcopy document of the notification allowing use from the PM, attached to the related packing list, and submit a copy to the DAIT RMC for filing in the site-specific SECD file.

2.4.3 Storage

The PoR must ensure that the proper storage conditions are maintained for all IPs. This should include, but is not limited to:

- Suitable security (i.e., controlled and limited access)
- 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 quarantined and expired IPs from active stock
- Identifying material received from each shipment (i.e., date and initial each item in a specific shipment received)

IPs should be stored in accordance with the IP manufacturer’s instructions as provided in the current clinical protocol, IP product labeling, and/or IP manufacturer’s Investigator’s Brochure. Requirements for storage may also take into account regulatory requirements or current *United States Pharmacopoeia/National Formulary* standards so that the integrity, stability, effectiveness, and security of the IPs are maintained as long as use of such requirements do not contradict the IP manufacturer’s information.

IPs should be separated by protocol number, drug name, and lot number. For blinded studies, the active IP must be stored clearly and adequately separated from the placebo agent. IPs that are designated for return to the CPC or for destruction must be removed from active stock and placed in quarantine while awaiting final disposition.

2.4.4 Temperature Excursions

A temperature excursion occurs any time there is a deviation from the storage conditions described in each specific protocol storage requirement, taking into account the rounding rules. For example, if the storage conditions state “Store between -20°C (+5°C) and - 70°C (-10°C),” then -14.4°C would be rounded down to -14°C, and -80.5°C would be rounded up to -81°C. This would be considered a temperature excursion. Alternatively, a temperature of -19.5°C would be rounded up to -20°C, and -80.4°C would be rounded down to -80°C. This would not be considered a temperature excursion. When a temperature excursion occurs at a clinical site, the site staff must immediately notify the site’s Study Coordinator and the “DAIT Project Team” of the temperature excursion. As applicable, care should be taken to maintain the blind when discussing the temperature excursion with the protocol’s clinical staff and DAIT PM. In that case, DAIT PS or CPC should be contacted for further assistance to keep the blind.

The site should record all the details on the “*Investigational Product Temperature Excursion*” form (See Form L), send a copy of the form to the PI and DAIT PM (DAIT PS or CPC in case of blinded studies), and file the completed form in the pharmacy binder. Missing data for any period of time will be managed as a temperature excursion. Under no circumstances should any IP affected by a temperature excursion be administered to clinical study subjects before the product is evaluated by the DAIT PM (DAIT PS or CPC in case of blinded studies). Pending such evaluation, any IP affected by a temperature excursion should be quarantined from active IP inventory under the mandatory appropriate storage conditions until the DAIT PM or PS has provided guidance. The IP affected by a temperature excursion should not be marked in any way until instructed to do so by the DAIT staff. The DAIT PM, PS, or CPC will provide written notification/instructions *via* email after contacting the affected IP’s manufacturer.

2.4.5 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.

For many DAIT blinded protocols, the PoR is unblinded to a participant's treatment assignment. In order to dispense an IP (for example, an investigational drug or placebo, a vaccine or placebo, or a patient kit) the PoR is provided with the study treatment assignment information. The study treatment assignment information corresponds to an identifying number, which could be in the form of a kit number, SID, or PID.

The number corresponding to the treatment assignment must be provided to the PoR on the signed prescription or order form, unless otherwise specified in a protocol-specific document (See Section 2.4.7.1 Prescriptions). The PoR uses this number to identify the participant's treatment assignment prior to dispensing IP. This number must be provided to the PoR each time a new prescription is written.

Treatment assignment information provided to the PoR is confidential and must remain in the pharmacy and be accessible only to the PoR.

2.4.6 Unblinding Procedures

Unblinding is the action by which the treatment of a participant enrolled in a blinded study is revealed. The PoR must read the network- and/or protocol-specific procedures, if available, regarding routine or emergency unblinding to prevent inappropriate unblinding. The process and procedures may vary among network and/or protocols. The DAIT Pharmacist can be contacted for assistance.

2.4.6.1 Routine Unblinding

The PoR is not responsible for the routine unblinding process. The process may vary among networks and/or protocols; therefore, the PoR should read the network- and/or protocol-specific procedures for routine unblinding.

2.4.6.2 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 with the corrective action plan to the "DAIT Project Team" immediately. The report should include the following specifics:

- Clinical research site name and number
- Network or consortium name and protocol number (i.e., ITN Protocol ITN100 or ACE Protocol ALE00)
- All PID and SID numbers or kit identification numbers
- Name, title, and position of all individuals who were unblinded
- Description of the event that led to the unblinding
- Dates associated with the event that led to the unblinding

(See Section 2.3.5 Reports)

2.4.6.3 Emergency Unblinding

The PoR should never reveal to study staff or participants which IP was dispensed for a participant in a blinded study. Please refer to and follow the specific protocol and/or "IP Dispensing and Administration Manual" for any unblinding request.

There may be a very rare case of extreme emergency in the absence of the PI in which revealing the treatment to a clinician will be necessary. It is expected that the PoR will use his/her professional judgment in handling any request for emergency unblinding of a participant's study treatment. Frequently, the situation can be resolved simply by stopping treatment, so that breaking the blind is unnecessary and may be resolved by following the directions given in the protocol or protocol-specific procedures.

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.

If an emergency unblinding occurs, the PoR must report the incident to the PI and the “DAIT Project Team.” The report should include the following specifics:

- Clinical research site name and number
- All PID and SID numbers or kit identification numbers
- Network/consortium name and protocol number, for example, ITN Protocol ITN100 or ACE Protocol ALE00
- Name, title, and position of all individuals who were unblinded
- Date of the unblinding
- Reason for unblinding the individual(s)
- Method of transmitting the unblinding information, for example, telephone, facsimile, etc.
- Statement about whether or not the participant and his/her primary physician were informed of the participant’s study treatment (*See Section 2.3.5 Reports*).

2.4.7 Dispensing/Preparation and Authorized Prescribers

IPs can be dispensed only after the PoR has received the signed, written order of the PI or a licensed clinician directly working with the PI, as stated on Form FDA 1572 or the DAIT Investigator of Record Agreement Form, for IND exempt studies. Prescribers must be clinicians authorized to prescribe in the site’s jurisdiction. It is also recommended that a quality control process be created in order to ensure a double-check system is in place for prescribing, dispensing, dose calculations, and randomizing of IP.

2.4.7.1 Investigational Product Order Form or Prescription

- The PoR must receive an IP order form signed by an authorized prescriber (*See Glossary*) prior to dispensing IP.
- The IP order form should be filled in with black or blue ink, typed, or computer generated.
- Signatures on the order forms 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 an IP order form with an authorized prescriber's name and then add her/his own name to it in an effort to make it legal (i.e., study staff may not sign the doctor's name to the order form). Post-dated order forms are not permitted. For example, it is not acceptable for an order form written in January to have a February date.
- By signing the Form FDA 1572, the PI has certified that the IP will be administered only to subjects under his/her personal supervision or under the supervision of co-investigators responsible to him/her.
- An authorized prescriber must sign the order form before sending it to the research pharmacy.
- Study staff may prepare electronic or handwritten order forms in advance for an authorized prescriber to review and sign; however, no IP should be dispensed until after the PoR receives the signed IP request form.
- The authorized prescriber is responsible for ensuring that the IP order form is filled-in or written in accordance with all essential aspects of the protocol and local laws and regulations.

The IP order form (Prescription) should include but is not limited to the following:

- Participant name (or initials)
- Date prescription is signed by an authorized prescriber
- Network/consortium name and protocol number, for example, ITN Protocol ITN100AI or ACE Protocol ALE00
- Participant identifier (PID number)
- Treatment assignment (e.g., SID or kit number)
- Medication/placebo name, dose, strength, formulation, and route (or, for some blinded studies, a protocol-specific randomization code)
- Quantity or instructions to indicate amount to be dispensed
- Directions for use
- Authorized prescriber's signature
- If applicable, body surface area (BSA) calculation (or, height and weight of participant)

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

2.4.7.2 Informed Consent

Investigational product should be dispensed by the PoR only to a participant who has signed the informed consent form(s) for the clinical trial. A process should be in place to ensure that the PoR has received either:

- A copy of the subject's signed informed consent form associated with the most current version of the protocol; or
- A notation on the prescription from the authorized prescriber stating that the subject has signed the Informed Consent Form associated with the most current version of the protocol

2.4.7.3 Expiration Date Review

Before dispensing IP, the PoR must verify the IP identity and the expiration date of the IP against the product label and/or expiration memos as applicable. The PoR also must ensure that the expiration date of the IP dispensed is after the date of the participant's next scheduled visit.

If extension of the expiration date by the IP manufacturer occurs, the site will receive an extension memo from the trial sponsor (DAIT/NIAID) prior to the expiration date noted on the original expiry memo. When date extension information is not provided, expired IP should be stored separately (quarantined) until returned or destroyed. Place all expiration and extension memos in one section of the pharmacy binder.

2.4.7.4 Dose Calculation and Preparation Process

In order to ensure the safety of the clinical study subject, it is extremely important that the correct IP is stored, dispensed, prepared, administered, and/or destroyed in accordance with the instructions provided for each clinical protocol. All doses should be prepared by, or preparation must be reviewed and verified by, a trained pharmacist and/or physician. Delegation of the pharmacist or physician responsibilities must be approved by the DAIT PM and documented in the "Delegation Log" by the site before dosing.

For IPs requiring reconstitution, mixing, dilution, and/or drawing up into a syringe, refer to the "clinical protocol" or "IP dispensing and administration" manual for protocol-specific instructions on preparation. Protocol documents may include the protocol, study-specific procedures, MOP, or "IP dispensing and administration" manual.

2.4.7.5 Dosing Errors

Upon the PoR becoming aware of a dosing error, the PoR must immediately contact the PI, study coordinator, and the "DAIT Project Team" *via* telephone and an email message containing dates and details describing the error. The PoR will obtain all documents needed to close the "Dosing Error" report and

will ensure that the documents are filed in the pharmacy binder. *Please refer to section 2.3.5.1 and follow instructions of how to report to the PI, IRB, and “DAIT Project Team.”*

2.4.7.6 Labeling

All IP labeling will be prepared and performed by CPC and approved by the “DAIT Project Team” before study initiation (*DAIT SOP 1003*). The PoR must also properly label all IPs to ensure their safe administration by the clinical site staff, or use by study participants. Patient confidentiality must also be considered when preparing dispensing labels. It is the PoR’s responsibility to know the labeling requirements for his/her jurisdiction so that the labels comply with ICH, GCP, and all local applicable labeling requirements.

Labels for IPs should be distinguishable from other labels by stating “Investigational Product” or “For Investigational Use Only.” A copy of the protocol-specific labels prepared at the pharmacy are required to be placed in the pharmacy binder.

IPs 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 participant identifier
- Dispensing date
- Authorized prescriber’s name (Principal Investigator or Co- investigator)
- Network/Consortium name and protocol number, for example, ITN Protocol ITN100AI, ACE Protocol ALE00
- Medication prescribed: name, dose, strength, formulation, route
- Number of dosing units dispensed
- Directions for use
- “Do Not Use After” date or date of expiration
- For Investigational Use Only

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

2.4.7.7 Refills/Repeats

The PoR may dispense refills/repeats of IPs if in accordance with institutional, local, and/or country regulations and written on the prescription. Please refer to the study MOP and/or the IP Dispensing and Administration manual for specific dispensing information.

2.4.8 Accountability

Prior to study initiation, the PoR must establish a method to account for all IPs. The “*DAIT IP Accountability Record*” form (See Form G) should be used to document the receipt, management, and final disposition of all IPs received from the CPC or other source unless a study-specific *Accountability Record* is available for use.

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

<i>Investigational Product Accountability Record Entry</i>	<i>Corresponding Document(s)</i>
Shipments received from the CPC or other source	Invoice, Packing Slip, & <i>DAIT IP Receipt (Form F)</i>
IPs Dispensed	Prescriptions & <i>DAIT IP Accountability Record (Form G)</i>
IP Destruction	<i>DAIT IP Destruction (Form J)</i>
IP Transfers	<i>DAIT IP Transfer (Form H)</i>
IP Returns	<i>DAIT IP Return (Form I)</i>

- Each time an IP is received from the CPC or other sources, dispensed to a participant, and/or returned to the CPC or other sources or destroyed, the action must be documented on the *IP Accountability Record*. The inventory balance documented on the *IP Accountability Record* should match the actual IP inventory, on hand, at all times.
- Every entry on the IP Accountability Record should be made in black or blue ink. Never use pencil to write an entry. Never use “white-out.”
- An explanation of correction, or other relevant comment, may be written on the back of the *IP 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 *IP Accountability Record* must match the dispensing activity. The original IP requested by the study physician for the corresponding entry in the *IP Accountability Record* must be maintained in the pharmacy binder.

2.4.9 Inventory Process

The PoR must conduct physical inventories of IP, at a minimum of once a month (28-31 calendar days) to verify that the quantity available matches the inventory balances on the *IP Accountability Record*. These periodic physical inventories must be documented on the *DAIT IP Accountability Record*. The PoR must look at the expiration date of the

IP when conducting a physical inventory and determine if additional IPs need to be ordered.

If a *physical* count is done every time an IP is dispensed, a monthly (28–31 calendar days) physical inventory count is still recommended on the accountability record.

If there is a discrepancy between the accountability records and the available IP, the PoR must attempt to find the cause for the discrepancy and reconcile it. If the attempt to reconcile the difference is unsuccessful, the PoR must notify the PI and PM immediately. The action to reconcile the accountability record or the adjusted balance (to match the actual inventory) must be documented in the pharmacy binder with a written report to the PI and PM (*See Section 2.3.5 Reports*).

2.4.10 Chain of Custody

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

Documents used to track the chain of custody must be maintained in the same manner as all other source documents.

2.4.11 Obtaining Investigational Product from a Source other than the CPC

At any time during the life cycle of the clinical trial, if an IP is obtained from a source (i.e., hospital pharmacy for commercially available products) other than the original source (CPC), the PoR should contact the protocol-specific PM for further instructions. Generally, the site is asked to write a report and submit to the “DAIT Project Team” or a deviation might be filed in the study files.

2.4.12 Shipping Investigational Product to a Participant

In rare instances or emergency cases, IP may be mailed or sent by courier or postal service to a study participant as per PI’s request and PM’s approval. Shipment of IP is not meant to continue on a long-term basis for a study participant who has permanently relocated. A shipment of IP may continue during the time it takes to get a study participant transferred to another clinical research site in the same network. The IP must be packaged and labeled appropriately per the CPC instructions (i.e., TempTale may be required) and a mechanism to document that the study participant received the IP is required (e.g., sending the package by certified mail or express courier with a return receipt, or by the inclusion of a self-addressed, stamped postal card to be mailed by the participant to acknowledge receipt).

2.4.13 Investigational Product Disposition

The PoR and PM are responsible for ensuring that IPs that can no longer be used are reconciled and either appropriately transferred, returned to the CPC or other source, or destroyed. The PoR must contact the PM for further instruction to: (i) destroy IP in accordance with the site’s SOP with a certificate of destruction provided to the DAIT PM; (ii) return to the CPC; or (iii) ship to another party named by DAIT/NIAID.

2.4.13.1 Investigational Product Return

The PoR at a clinical research site must return IP, received from the CPC, back to the CPC, unless otherwise specified by a protocol-specific document or the PM. A “*DAIT IP Return*” form (*See Form I*) must be completed and submitted following the form’s accompanying instructions. The IP to be returned must be removed from active stock and placed in quarantine in a separate area from the active stock. Recalled IP must be quarantined immediately and be returned, as instructed by the recall notice from the CPC.

To comply with Title 21 CFR 312.59, the IPs provided by the CPC will be returned to the CPC for any one or more of the following reasons:

- IP has expired
- Protocol has been administratively closed
- All participants have completed the study treatment
- IP had a temperature excursion and can no longer be safely used
- IP is damaged
- PoR has received notification from the CPC that IP is no longer being used in the protocol
- Pharmacy has closed
- DAIT Project Manager has made the request

Quarantined IPs should be returned to the CPC as instructed in the “DAIT IP Return Form” (See Form I).

2.4.13.2 Investigational Product Destruction

As a sponsor of clinical studies, DAIT/NIAID must comply with the U.S. FDA regulations (CFR 21 312.59) governing the proper disposition of unused IPs being evaluated in clinical trials. DAIT has the responsibility of assuring that all clinical research sites establish and maintain sufficient records of IP disposition to comply with FDA regulations and the standards of research involving the use of IPs. The *Investigational Product Destruction* form (*See Form J*) is a standard form to be used by all sites for all IPs received from the DAIT CPC or other sources. This form does not and should not take the place of any other forms used to account for IPs such as patient specific accountability forms, protocol-specific forms, patient return forms, IP preparation forms, and any other documents used by the site.

In some cases, “On-Site Destruction” of IPs received from the CPC or other sources may be requested or granted as per PM’s direction (with approval of the DAIT RO) if a “certificate of destruction” can be provided to the “DAIT Project Team”. The unused IPs to be destroyed must be quarantined in a separate area from the active stock.

General Instructions

1. Prior to destroying any DAIT-funded/sponsored unused IPs, the PoR should complete the “*Investigational Product Destruction*” form (See Form J) for all IPs designated for destruction. If a protocol-specific destruction form is provided within a specific protocol, that form takes precedence.
2. This form should be submitted via email for verification and approval to the protocol-specific PM. If there is a study close-out visit scheduled, the PoR must submit the destruction form to the PM at least two weeks prior to the scheduled visit. The original “*Investigational Product Destruction*” form should be retained in the pharmacy files. The “DAIT Project Team” will verify and return the form, in PDF format, to the PoR via email. The approved form must be used during the destruction visit.
3. The approved form must be signed by the PoR and the DAIT monitor (if a close-out visit is scheduled). The approved form with the original signatures and any copies of destruction certificates or memos must be kept in the pharmacy files and a copy sent to the PM within 21 days of destruction.
4. The PoR should retain copies of the signed, approved “*Investigational Product Destruction*” form in the pharmacy files.

The process for “On-Site IP Destruction” may be initiated by the PoR or PM and must be approved by the DAIT RO and/or DAIT PS.

Initiation by the PoR for any of the following reasons:

- IP has expired
- IP is damaged
- Participant return
- Receipt of “Preparation for Destruction Notice” from the CPC
- Request from the PM
- Study closure
- Pharmacy closure

A “DAIT IP Destruction” form (See Form J) should be completed and submitted. Follow the form’s accompanying instructions. The PoR should refer to the protocol for instructions on the final disposition of IP, prior to completing this form.

Initiation by the PM:

The IP destruction request can be initiated by the PM, and the process may be initiated by CPC sending a “Preparation for Destruction Notice” document to the PoR. This document will include one of the following reasons for destruction:

- IP has expired
- Protocol has been administratively closed
- All participants have completed the study treatment
- IP had a temperature excursion and can no longer be safely used
- IP is damaged
- PoR has received notification from the CPC that IP is no longer being used in the protocol
- Pharmacy has closed
- Request from the PM for any reason deemed necessary

Once this document has been completed by the PoR, a DAIT IP Destruction form also should be completed and submitted. Follow the form’s accompanying instructions.

2.4.13.3 Transfer of Investigational Product

IPs provided through the CPC or any other sources must not be transferred without prior approval from the PM, MO, PS, and RO. For each incident, such approval will not be granted without the approval of the IP manufacturer and consideration of terms of existing DAIT Clinical Trial Agreements (CTAs) governing use of the IP in the specific trial.

A request for the transfer of IP from one protocol to another protocol must be from a study protocol for which IPs are no longer needed to an active protocol. Once the authorization for the transfer has been granted, shipment instruction with packaging (proper box & packaging material), and temperature monitoring devices such as TempTale (if needed) will be sent to the site to which the IPs were originally shipped. Products must always be sent back to the CPC for further re-distribution and/or auxiliary relabeling (without altering the integrity of the product).

The process will be the same for all three different scenarios if permitted as per the CTA:

2.4.13.3.1 *Different Protocol: IP Transfer Within the Same Clinical Research Site*

2.4.13.3.2 *Different Protocol: IP Transfers to a Different Clinical Research Site*

2.4.13.3.3 *Same Protocol: IP Transfer to a Different Clinical Research Site*

1. A request for the transfer of IP to a different research site or protocol must be from a protocol for which IPs are no longer needed by using the “DAIT IP Transfer” form (*See Form H*).
2. The PM evaluates the need for an IP transfer and contacts the DAIT RO.
3. The DAIT RO determines if a CTA has been executed for the IP and specific trial.
 - i. If the IP is covered under terms of a CTA, the RO will:
 - a) Contact the IP manufacturer for authorization. Authorization from the IP manufacturer must be obtained prior to any transfer.
 - b) Amend the CTA or negotiate a new CTA, as applicable.
 - ii. If the IP is not covered under terms of a CTA, the RO will attempt to communicate with the IP manufacturer’s customer service representative for their opinion regarding such transfer.
4. The PM initiates an “IP Transfer Form,” obtains approval from the RO, and sends it to CPC for IP storage temperature record verification and signature.
5. CPC sends temperature record request email notification to site(s).
6. The PoR from the pharmacy site(s) provides CPC with the IP’s storage temperature records.
7. The CPC reviews storage and chain of custody records and verifies the investigational product/material was stored in a controlled manner under the manufacturer-recommended temperature and that no temperature deviations occurred.
8. The CPC signs the form and sends the original back to the PM.

9. The PM and RO sign the form and send the original back to CPC.
10. The PM also issues an email to the involved site(s), CPC, and the Project team notifying them of this approval.
11. The CPC sends shipping instructions and material along with the original transfer form to site(s) for product transfer.
12. The PoR prepares the IPs following the CPC's instructions and using their shipping material (including a TempTale if provided) to send back to CPC.
13. The PoR signs the original transfer form, keeps a copy for the accountability files, and sends the copied form to the PM.
14. The CPC receives IPs from site(s) and verifies that the IP(s) is in its original container, with the original product label and that the expiration date is current.
15. The CPC may re-label the auxiliary label and ship product(s) to a new site as per PM's direction.
16. The PM and RO receive and sign the transfer form. They send the form to RMC for filing.
17. The RMC receives the form and files in the SECDs.

3 PHARMACY VISITS

3.1 DAIT Authorized Monitor

A DAIT-authorized monitor conducts monitoring visits at the DAIT-funded/sponsored clinical research sites. Monitoring visits are used to: evaluate and assess adherence to the protocol, U.S. Code of Federal Regulations and ICH guidelines; evaluate pharmacy facilities and operations; and perform special assignments and additional assessments, when requested by DAIT. The site coordinator and PI will be notified in advance of a visit and are expected to notify the PoR that a visit will take place. The monitor will assess the pharmacy and any pharmacy storage areas. The PoR should make available any information and pharmacy records requested by the monitor. At the end of each monitoring visit, a pharmacy debriefing is conducted by the monitor, and the PoR should attend this debriefing. The frequency of monitoring visits may vary as determined by the DAIT.

A report or post-visit letter is generated for each monitoring visit and is sent by the monitoring group to the site and filed in the SECD file at the DAIT RMC. The report is provided to the PoR, PI, PM, MO, RO, and PS.

3.2 Pharmacy Tours

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

4 GLOSSARY OF TERMS

- **“ALCOA”* Method** – A method used to achieve and maintain data quality.
 - **Attributable:** is it obvious who wrote it?
 - **Legible:** can it be read?
 - **Contemporaneous:** is the information current and in the correct time frame?
 - **Original:** is it a copy; has it been altered?
 - **Accurate:** are conflicting data recorded elsewhere?

*Source: “The Facts About Source Documents” by Stan W. Woollen, Presented at the 1999 Drug Information Association (DIA) Annual Meeting

- **Authorized Prescriber** – A clinician authorized to prescribe in the site’s jurisdiction who is listed on the current FDA Form 1572 (IND studies) or DAIT Investigator of Record Form (IND exempt studies) for a given protocol at the participating site.
- **Back-up Pharmacist** – A licensed/registered pharmacist who performs the day-to-day pharmacy activities and IP management including but not limited to the procurement, storage, preparation, dispensing, and final disposition of IPs for the DAIT-funded/sponsored clinical trial(s), when the Pharmacist of Record is absent.
- **Clinical Products Center (CPC)** – The DAIT contract research organization (i.e., Eminent Services Corporation) that is responsible for labeling, shipment, and (when necessary) manufacturing of clinical trial study therapies.
- **Clinical Research Records** – Original documents, data, and records (e.g., hospital records, clinical and office charts, laboratory notes, memoranda, subjects’ diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial).
- **Clinical Research Site (CRS)** – Discrete locations (i.e., hospitals, outpatient clinics, health maintenance organizations, community health centers, private practices, clinics) where qualified professionals conduct clinical trial research in accordance with Good Clinical Practices (GCP).
- **Clinical Trial/Study** – Any investigation in human subjects intended to discover or verify the clinical, pharmacological, pharmacodynamic, and/or other effects of an IP(s), and/or to identify any adverse reactions to an IP(s), and/or to study absorption, distribution, metabolism, and excretions of an IP(s) with the objective of ascertaining its safety and/or efficacy.
- **Co-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). These individuals are listed on the Form FDA 1572 or the DAIT IoR Form.

- **DAIT Contract Research Organization (DAIT CRO)** – Refers to an entity that assumes, as an independent contractor with the sponsor, one or more of the obligations of a sponsor, as outlined in the Code of Federal Regulations 21 §312. Examples include EMMES, PPD, and Rho.
- **Division of Allergy, Immunology, and Transplantation Clinical Research Information System (DAIT CRIS)** – This is a comprehensive system that supports the Protocol management and tracking of clinical research sites and personnel.
- **DAIT-Funded/Sponsored** – DAIT is providing financial support for trial or study and is responsible for the management, initiation, and oversight for the trial, including submission of the Investigational New Drug Application (IND) to the U.S. Food and Drug Administration (FDA).
- **DAIT Project Team** – The team responsible for a given project. DAIT members include the DAIT Project Manager, the DAIT Medical Officer, and the DAIT Regulatory Affairs Officer and the DAIT PS. Additional team members are added as required for the specific project (i.e., DAIT CRO).
- **Form FDA 1572** – A federal form serving as a statement by the investigator that s/he will abide by the federal guidelines set forth in the Codes of Federal Regulations for the use of drugs in an investigational setting.
- **Good Clinical Practice (GCP)** – The ethical and scientific quality standard for designing, conducting, recording, and reporting trials that involve the participation of human subjects.
- **Good Manufacturing Practice (GMP)** – The regulations set forth to describe current good manufacturing practice for methods to be used in, and the facilities or controls to be used for, the manufacture, processing, packing, or holding of a drug to assure that such drug meets the requirements as to safety and has the identity and strength and meets the quality and purity characteristics that it purports or is represented to possess.
- **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) in diameter.
*Source: <http://en.wikipedia.org/wiki/HEPA>
- **Informed Consent** – A process by which a subject voluntarily confirms his or her willingness to participate in a particular trial, after having been informed of all aspects of the trial that are relevant to the subject's decision to participate. Informed consent is documented by means of a written, signed, and dated informed consent form.
- **International Council for Harmonization (ICH)** – ICH's mission is to achieve greater harmonization worldwide to ensure that safe, effective, and high quality medicines are developed and registered in the most resource-efficient manner.
- **Investigational Product (IP)** – 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, or when used for an unapproved indication, or when used to gain further information about an approved use.

- **Investigational Review Board (IRB)** – An independent body constituted of medical, scientific, and nonscientific members whose responsibility is to ensure the protection of the rights, safety, and well-being of human subjects involved in a trial by, among other things, reviewing, approving, and providing continuing review of trials, protocols, and amendments, and of the methods and material to be used in obtaining and documenting informed consent of the trial subjects.
- **Investigator of Record (IoR)** – Also known as the principal investigator (PI). This person is designated by the applicant institution to direct the research and oversees the scientific and technical aspects of the day-to-day management of the research. This person is the signatory for the Form FDA 1572 [Investigational New Drug (IND studies)], or DAIT IoR Form (IND exempt studies).
- **Medical Officer (MO) or Medical Monitor (MM) or Sponsor Investigator** – An individual who both initiates and conducts, alone or with others, a clinical trial, and under whose immediate direction the investigational product is administered to, dispensed to, or used by a subject. The term does not include any person other than an individual (e.g., it does not include a corporation or an agency). The obligations of a sponsor-investigator include both those of a sponsor and those of an investigator.
- **Monitoring** – The act of overseeing the process of a clinical trial and ensuring that it is conducted, recorded, and reported in accordance with the protocol(s), SOPs, GCP, and the applicable regulatory requirements.
- **Pharmacist of Record (PoR)** – A licensed/registered pharmacist who performs the day-to-day pharmacy activities and IP management including but not limited to the procurement, storage, preparation, dispensing and final disposition of IPs for the DAIT-funded and/or DAIT-sponsored clinical trial(s).
- **Principal Investigator (PI)** – A person responsible for the conduct of the clinical trial at a participating site. If a trial is conducted by a team of individuals at a trial site, the investigator is the responsible leader of the team and may be called the principal investigator. See also Subinvestigator.
- **Research Pharmacy** – Any facility, building, or room used by pharmacists to perform one or more of the following functions: storage, preparation, dispensing, and management of IPs (e.g., hospital pharmacy or institutional pharmacy, dispensary, drug storage unit, or drug store).
- **Pharmacy Ancillary Supplies** – Any materials or tools that may be used in a pharmacy to perform and support the day-to-day activities and functions of the pharmacist, such as needles and syringes, oral syringes, prescription vials and lids, gowns, masks, IV solutions, and diluents.
- **Pharmacy Equipment** – Apparatus (device or machinery) that is utilized to ensure the physical and scientific integrity of the IP 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), locking file and storage cabinets, shelving, counting trays for tablets and capsules, graduated cylinders, spatulas, IP containers, fax machines, computers, and printers.

- **Protocol** – A document that describes the objective(s), design, methodology, statistical considerations, and organization of a trial. The protocol usually provides the background and rationale for the trial, but these could also be provided in other protocol-referenced documents.
- **Protocol Deviations** – Lack of adherence to that which is outlined in the protocol. Any action that was not outlined in the protocol.
- **Quality Assurance (QA)** – All those planned and systemic actions that are established to ensure that a trial is performed and the data are generated, documented (recorded), and reported in compliance with GCP and the applicable regulatory requirement(s).
- **Quality Management (QM)** – The operational techniques and activities undertaken within the quality assurance system to verify that the requirements for quality of the trial-related activities have been fulfilled.
- **Randomization** – The process of assigning trial subjects to treatment or control groups using an element of chance to determine the assignments in order to reduce bias.
- **Regulatory Management Center (RMC)** – The organization under contract to the DAIT, NIAID, NIH Office of Regulatory Affairs that provides regulatory support for all DAIT-funded clinical studies and trials.
- **Standard Operating Procedures (SOPs)** – Written instructions governing pharmacy operations for conducting the DAIT-sponsored/funded clinical trials and to assure compliance with all applicable laws and regulations.
- **Sponsor** – Refers to the Division of Allergy, Immunology, and Transplantation (DAIT) of the National Institute of Allergy and Infectious Diseases (NIAID), which is responsible for the initiation, management, and/or financing of all DAIT clinical trials.
- **Sponsor Essential Clinical Documents (SECD)** – Those documents which: (i) individually and collectively permit evaluation of the conduct of a clinical study and the quality of the data produced; and (ii) are required by ICH and local regulatory health authorities, to be reviewed and held by the Sponsor of the specific clinical study. Also referred to as a Trial Master File or TMF.
- **Study Materials** – Any materials other than study medications that are distributed in relation to a clinical trial as decided upon by the project team. These could include over the counter medications, FDA-approved medications, blood tubes, reagents, saline, etc.
- **Subinvestigator** – Any individual member of the clinical trial team designated and supervised by the principal investigator at a participating site to perform critical trial-related procedures and/or to make important trial-related decisions (e.g., associates, residents, research fellows). See also Principal Investigator.

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

- **Room Temperature** – The temperature prevailing in a working area.
- **Controlled Room Temperature** – A temperature maintained thermostatically that encompasses the usual and customary working environment of 20°C to 25°C (68°F to 77°F); that results in a mean kinetic temperature calculated to be not more than 25°C; and that allows for excursions between 15°C and 30°C (59°F and 86°F) that are experienced in pharmacies, hospitals, and warehouses. Provided the mean kinetic temperature remains in the allowed range, transient spikes up to 40°C are permitted as long as they do not exceed 24 hours. Spikes above 40°C may be permitted if the manufacturer so instructs. Articles may be labeled for storage at “controlled room temperature” or at “up to 25°C,” or other wording based on the same mean kinetic temperature. The mean kinetic temperature is a calculated value that may be used as an isothermal storage temperature that simulates the non- isothermal effects of storage temperature variations.
- **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). An article for which storage in a cool place is directed may, alternatively, be stored in a refrigerator, unless otherwise specified in the individual monograph.
- **Cold** – Any temperature not exceeding 8°C (46°F). A refrigerator is a cold place in which the temperature is maintained thermostatically between 2°C and 8°C (36°F and 46°F).
- **Refrigeration** – “Controlled cold temperature” is defined as temperature maintained thermostatically between 2°C and 8°C (36°F and 46°F), that allows for excursions in temperature between 0°C and 15°C (32°F and 59°F) that may be experienced during storage, shipping, and distribution such that the allowable calculated mean kinetic temperature is not more than 8°C (46°F). Transient spikes up to 25°C (77°F) may be permitted if the manufacturer so instructs and provided that such spikes do not exceed 24 hours unless supported by stability data or the manufacturer instructs otherwise.
- **Freezer** – A place in which the temperature is maintained thermostatically between -25°C and -10°C (-13°F and 14°F).

* Source: May 1, 2012 USP35-NF30– The Official Compendia of Standards – General Notices R-1

5 REFERENCES

1. Code of Federal Regulations, Title 21, Part 312
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2. USA Food and Drug Administration
<http://www.fda.gov>
3. International Conference on Harmonisation, Guidance for Industry, E6 Good Clinical Practice: Consolidated Guidelines
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4. The Joint Commission International (JCI) on Accreditation of Healthcare Organizations
<http://www.jointcommission.org>
5. United States Pharmacopoeia/National Formulary Storage Temperatures
<http://www.usp.org/USPNF>
6. U.S. Office of Personnel Management: Federal Holidays
http://www.opm.gov/Operating_Status_Schedules/fedhol/index.asp
7. Human Subjects Research Requirements SOP
<http://grants.nih.gov/grants/policy/hs/index.htm>
8. Requirements for Source Documentation in DAIT Funded and/or Sponsored/ funded Clinical Trials
<https://www.niaid.nih.gov/sites/default/files/documents/dait-sourcedocpolicy.pdf>