DUKE UNIVERSITY MEDICAL CENTER CLINICAL TRIALS UNIT
Clinical Research Site Pharmacy
Policies and Procedures

A. Background

1. Clinical Research Sites

The Duke University Medical (DUMC) Clinical Trials Unit (CTU) has three Clinical Research Sites (CRS): Duke Adult, Duke Pediatrics and the Kilimanjaro Christian Medical Center (KCMC) in Moshi, Tanzania. The DUMC Clinic 2J Pharmacy serves the Duke Adult and Duke Pediatric sites, and the KCMC Pharmacy Department serves the KCMC site. The Pharmacists of Record (PoR) for these pharmacies work closely together and communicate regularly. Pharmacy operations are standardized whenever possible between the sites.

2. Communication:

a) Periodic electronic conferences between site pharmacists will be conducted via Yahoo messenger (IM). The purposes of these conferences are to keep abreast of new information and protocol changes, to follow-up on action items, to problem solve, to coordinate and collaborate on activities, to build relationships, and to review the results of pharmacy audits.
b) Pharmacists also communicate via email, fax and telephone as needed.
c) Electronically transmitted documents will be password protected.
d) Pharmacists will conduct cross-site visits as appropriate.
e) Documentation of conferences will follow CTU source documentation SOP's.

3. System for organizing protocol information

All sites organize protocol information in the same way: through use of protocol notebooks containing the following sections (new materials placed uppermost in each section):

a) Protocol

Includes the current IRB approved version of the protocol and amendments. The pharmacist is notified of protocol changes in two ways: the study coordinator notifies the site pharmacist of DAIDS approval by giving the pharmacist a copy of the approval email from DAIDS and the CRPMC sends the site pharmacist a new Drug Supply Statement for each version of the protocol for which the site is approved. The pharmacist places the active version of the protocol in the study binder and shreds the old version of the protocol. All previous versions are available through the regulatory coordinator who stores these documents in compliance with DIADS, GCP, and site specific SOPs.

b) Pharmacy Procedures

Pharmacy procedures specific to the protocol.

c) Forms and Labels

Preprinted medication labels and forms to be used in the study.

d) Pharmacist's Prescription List

Provided by the Division of AIDS for each study: lists the patient's treatment assignment based on the Study Identification Number. Additional treatment assignment lists are added as they are received from DAIDS.

e) Drug Supply Statement

Protocol specific statement provided after DAIDS approval of each new version of the protocol: lists ordering information for all medications supplied for the study by DAIDS. New drug supply statements are added as they are received from DAIDS.

f) Prescriber Information

Copy of the signed FDA form 1572 or DAIDS Investigator of Record Agreement and a Prescribers List and Signature Log (names and signatures of providers authorized to prescribe

medications for the study).

g) Shipments

Completed order forms and packing slips for each shipment stapled together and filed after the drug shipment has been received, verified and entered on drug accountability records.

h) Return Records

Records of all medications returned to DAIDS.

i) Correspondence

Letters and memos to and from DAIDS and other study-specific correspondence.

j) Drug Accountability Records

A separate record is kept for each medication and lot number received for the study.

k) Subject Specific Tabs

Patient specific information including a copy of the signed signature page of the informed consent, written prescriptions, copies of the subject enrollment and treatment assignment, a chronological list of treatment assignments with start and stop dates for each medication, patient teaching notes, and pharmacist's notes.

The protocol notebooks are stored in the Pharmacy in locked cabinets to which only the ACTG pharmacist and technician have access to maintain integrity of any blinded study treatments. Emergency unblinding will be performed per instructions in each study protocol. Investigator's Brochures, package inserts and safety memos are stored with regulatory files of the site. The pharmacist has access to these files. The site coordinator will forward a copy of all emails regarding Investigator Brochures, package inserts and safety memos to the pharmacist for review.

4. Participant Consultation and Counseling

At the Duke Adult site, the pharmacist is responsible for ensuring that all participants are adequately counseled when they receive their first supply of study medication with information on proper use and storage of each medication and possible side effects and adherence. The pharmacist provides written materials that explain proper use and storage of each medication, the possible side effects and contact information for the study team at the site. This counseling can be done by the pharmacist or by someone delegated by the pharmacist and will be documented. At the Duke Pediatric site, the study nurse is responsible for medication and compliance counseling at the entry visit.

After the initial counseling, the pharmacists will continue to serve as a resource at the Duke Adult and Duke Pediatric sites and will be available to the participant and the study nurse to provide further counseling and consultation as needed. The pharmacists at KCMC dispense medications to the patient and provide counseling at each study visit. The pharmacist will notify the study nurses if there is a problem with adherence based on estimated measurements/accurate counts of returned medication.

B. Study Product Control

1. Study Product Ordering from the CRPMC:

All study products are ordered from the Clinical Research Products Management Center (CRPMC) on a DAIDS Study Product Request Form. This form is sent via FAX or email to the CRPMC.

2. Procedure for Importing Study Products into Tanzania
   a) The local Investigator of Record submits the protocol to the Ethical Committee at KCMC.
   b) The Ethical Committee grants approval of the protocol.
   c) The protocol is submitted to the National Institute of Medical Research in Tanzania.

d) The National Institute of Medical Research grants approval.
e) Any study products that are not on the Tanzania Formulary will require a waiver from the Tanzania Food and Drug Authority (TFDA).
f) Once approval is received from the National Institute of Medical Research and, if necessary, a waiver is obtained from TFDA, the Site Pharmacist at KCMC orders the study product from the supplier.
g) The supplier sends the pharmacist at KCMC a copy of the packing slip showing the date of arrival in Tanzania.
h) The KCMC pharmacist contacts the inspectorate pharmacist at TDFA who must accompany the KCMC pharmacist to the airport and inspect the study products before they can be picked up. After the study is approved, waivers are obtained and the first shipment is received, this procedure repeats for each study product shipment beginning with step g.

3. Receiving Study Product: The site pharmacist is responsible for checking the accuracy of each shipment and communicating immediately with the staff at the CRPMC it there are any discrepancies between what was ordered, what is reflected on the packing slip, and what is received. The pharmacy staff person who checks in the order signs and dates the packing the slip and puts the products away in proper storage areas according to the storage requirements specified by DAIDS or the manufacturer.
4. Storage of Study Products:
   a) Room Temperature Storage: Investigational products are stored in locked cabinets in each pharmacy to which only the pharmacists and pharmacy technicians have access. The room temperature is maintained between 15 and 30 ° C.
   b) Refrigerated Storage: All pharmacies have refrigerated storage space. The temperature in the refrigerators is maintained between 2 and 8° C. Access to the refrigerators is limited to pharmacy staff.
   c) Freezer Storage: There is a –20 to -10° C freezer in the Clinic 2J pharmacy. Access to the freezer is limited to CRS pharmacy staff. The CRS pharmacy staff also have access to a -70° freezer in the Investigational Drug Service area of the Pharmacy Department. Access to this area is limited to Investigational Drugs Service staff. IDS staff escort the CRS pharmacy staff when they need access to the freezers. Any CRS study products stored in these freezers will be stored in separate containers from other study product and clearly labeled as CRS study product with contact information for the site pharmacist on the container. Minus 70° C storage space is available to pharmacy staff at KCMC. The freezer is located in the KCMC laboratory, and only laboratory personnel have access to these freezers. KCMC pharmacy staff must be escorted by laboratory personnel each time they need access to the freezers. Any CRS study products stored in these freezers will be stored in locked containers separate from laboratory products and clearly labeled as CRS study product with contact information for the site pharmacist on the container.
   d) Power Loss: Refrigerators and Freezers at Duke and KCMC are connected to an emergency generator backup power system. At Duke the system is activated automatically if the main power is interrupted. At KCMC the generators are being set up to come on automatically. Until the system operates automatically, the engineer on duty will turn on the generator in case of power interruption.
   e) Temperature Monitoring: At Duke, room, refrigerator and freezer temperatures are checked daily when the pharmacy is open and recorded on a manual temperature log. In addition the room, refrigerator and freezer temperatures are monitored by a constant temperature monitoring, data logging, and alarm system. If the temperature varies outside the defined range, an alarm will go off in the hospital BAS (central monitoring) room. This room is manned 24 hours a day, seven days a week. BAS personnel will immediately notify CRS pharmacy personnel via an ordered call list using pagers, telephones or cell phones. CRS pharmacy personnel will take action to either correct the malfunction or move product to an area of appropriate temperature. At KCMC, the room and refrigerator temperatures are

checked three times daily when the pharmacy is open and recorded on temperature logs. A 24-hour recording device that records the temperature on a paper chart monitors each KCMC pharmacy storage area. The chart is changed once a week and the charts are kept in a notebook for three years. At KCMC a Sensaphone temperature monitoring and alarm system is being used. If the temperature varies out of range an audible alarm will sound and the system will automatically and immediately call the cell phones of up to eight CRS pharmacy personnel to notify them of the problem. If an alarm is activated, CRS pharmacy personnel will take action to either correct the malfunction or move product to an area of appropriate temperature.

f) Accountability Records and Inventory: Drug Accountability Records at each site will be maintained on the DAIDS Study Accountability Record. These records will be kept in the Drug Accountability Section of each protocol notebook. A separate record will be used for each product and lot number. The records will track prescription number, date, SID, PID, quantity dispensed or received, balance, pharmacist's initials, and comments. A perpetual inventory will be kept so that the balance recorded with each entry will match the inventory on the shelf at that time. In addition, a physical inventory of each study will be conducted monthly, and the inventory will be recorded on the accountability record.

C. Investigational Product Dispensing

1. Prescriptions: The CRS Clinical Research Nurse notifies the CRS pharmacist when a patient is scheduled for study entry. Once the patient is successfully randomized to study treatment, the study nurse or data manager delivers a prescription signed by an authorized prescriber listed on the FDA form 1572 to the pharmacist along with a signed copy of the patient's informed consent. The pharmacist cannot dispense study medication until he has received both the prescription and copy of the informed consent. The study nurse or data manager also provides the pharmacist with a copy of the "Network Subject Enrollment System Results" with the patient's assigned PID and SID number that the pharmacist uses to look up the patients assigned treatment in the Network Pharmacists Prescription List. The pharmacist dispenses the first supply of study medication to the patient.
2. Dispensing the Initial Supply of Study Medication: The pharmacist fills enough of each of the assigned study medications to last until the patient's next scheduled study visit. The medications are prepared in the clinic pharmacy at each site. The medications are dispensed in the original container or in prescription vials or bottles that meet DAIDS and the product manufacturer's requirements for storage such as air-tightness, humidity-control and child-proof-closures. The products are labeled according to DAIDS, national and local guidelines. Each label contains the following information: name, address, and phone number of the Pharmacy, patient name, dispensing date, directions, prescriber's name, SID number, number of dosing units dispensed, name and strength of drug, prescription number and the legend "Caution: New Drug. Limited by Federal Law to Investigational Use". For blinded studies the bottles are labeled with the name of the active protocol drug and the statement "or placebo" (e.g. zidovudine or placebo).
3. Subsequent Prescriptions/Refills: Pharmacists are notified ahead of time of patients' return clinic visits by the study nurse. Either the patient or the study nurse comes to the pharmacist to pick up the medication and to return unused study medication and/or empty containers.
4. Prescriptions For A Dose Change: At the Duke Adult and Duke Pediatric sites, a new prescription is required for any change in the patient's regimen. At KCMC a new prescription is required for each dispensing of study product. Prescriptions must be signed by an authorized prescriber listed on the FDA form 1572.
5. Dispensing of Study Product: The pharmacist dispenses the initial supply of any study medication and the pharmacist or designate counsels the patients on proper use and storage of the medication and of the

possible adverse effects. For refills at the Duke Adult and the Duke Pediatric sites, either the patient or the study nurse comes to the pharmacy to pick up the study medication. The pharmacist is available to answer questions from the patient or the study nurse and to help with patient teaching or adherence counseling. At the KCMC site, the pharmacist dispenses all refills directly to the patient.

6. Drugs Returned by the Patient: Either the subject or the study nurse will deliver study drug returns to the pharmacist. All drugs returned by patients will be returned to the CRPMC.
7. Biological Safety Cabinets: All three pharmacies have access to a biological safety cabinet for preparation of study products that require preparation in such a cabinet.

D. Study Product Returns

Study products provided by the CRPMC will be returned to the CRPMC when the protocol is completed or terminated, the study product has been dispensed to the participant and was retuned to the site, it has expired, it has been stored improperly and can no longer be safely used, return has been requested by a DAIDS pharmacist, return has been requested by a CRPMC recall letter. All returns will be documented on the DAIDS Study Product Return Form and will be sent to the CRPMC via certified carrier so the shipment can be tracked. A copy of each Study Product Return Form is kept in the Protocol Notebook.

E. Quality Assurance

1. Perpetual Inventories are maintained for each study product supply and lot number. Physical inventories of all study products are also performed monthly and documented on the Study Accountability Record.
2. Confirmation of the participant's signature on the informed consent is obtained before the first supply of study medication is dispensed to the patient.
3. Prescriptions signed by the IoR or a sub-investigator on the FDA form 1572 must be received before the first supply of study medication is dispensed to the patient.
4. When problems in the pharmacy operations are identified, actions to correct the problem will be documented and reported to the IoR and DAIDS. Written reports will be sent to inform the IoR and DAIDS of any incidents or matter that could affect the outcome of the study. This report will be written so as not to unblind the investigators or other study personnel.