Quality Medicines for Malawi

PHARMACY GUIDELINES FOR INVESTIGATIONAL DRUGS AND PHARMACY PLAN

A Purpose

These guidelines are principally derived and adapted from guidelines from various internationally recognized sources including within the SADC region. They should be used as a guide to the receipt, use and disposition of study products being investigated in clinical trials in Malawi. They provide guidance to investigators on how to establish and maintain adequate records of study product disposition to comply with statutory requirements and policies of the Pharmacy and Medicines Regulatory Authority.

The pharmacist at each clinical site participating in a clinical trial, who is designated as the Pharmacist of Record, is the primary individual who is expected to;

i. develop and maintain a study product management system, which includes the technical procedures for study product ordering, control, dispensing, and accountability.

ii. In addition, the Pharmacist of Record may be expected to participate in preparation of blinded study products;

iii. preparation of special dosage forms and packaging;

iv. monitoring of adherence to study product treatment regimens by participants;

v. preparation of study product information/data sheets for pharmacy, nursing, and other personnel; data collection and documentation; and

vi. development of research protocols.

B. Responsibilities of Pharmacists

The Pharmacist of Record is responsible for:

i. Establishing internal policies and procedures for the safe and proper use of study products to assure that the study products will be dispensed only to eligible study participants.
ii. Ordering and maintaining records of receipt of protocol-provided study products, dispensing to participants, and disposition of study products.
iii. If any study provided products are received directly from other sources, adequate records showing the receipt, dispensing, dates and quantities must be kept. Records for study drugs that are not provided as part of the protocol must also be maintained.

The pharmacist of Record must:

1 Commit the necessary and appropriate amount of time to meet the pharmaceutical needs and requirements of the clinical trial. Often, protocols are randomized, double-blind trials, which require that a pharmacist to manage the dispensing as well as the preparation of blinded medications. Some of the study products used in the protocols require either special storage conditions or special preparation methods. It is the Pharmacist of Record's responsibility to coordinate all issues related to study product supply. The pharmacist is expected to handle the ordering, receipt, control, dispensing, and accountability of the protocol-provided study products for the Investigator.

2 Provide adequate space, equipment, and supplies for the storage, preparation, packaging, and dispensing of study products including products that require special handling.

3 Provide the proper storage conditions for protocol-provided study products, including segregation, security, temperature, and temperature monitoring, light, moisture, ventilation, and sanitation.

4 To provide adequate security, the study products must be stored in a limited-access area, an area that is locked when not in use. Systems must be in place for identifying and alerting staff that proper storage conditions are not being maintained so that procedures for timely interventions and resolutions can occur. The study products should be accessible only to authorized personnel, such as the Pharmacist of Record or his/her pharmacist-designee. The study products are shipped on a site-specific, investigator-specific, protocol-specific basis, and they should be segregated by protocol when stored with separate supplies for each clinical site and affiliated site. The protocol-provided study products should be packaged in containers designed to maintain the proper storage conditions for the study products during shipment.
If upon arrival, the study product supplies appear to be damaged or the storage conditions have not been maintained (for example, refrigerated

items are not refrigerated upon receipt), the Pharmacist of Record should determine whether the study products may be safely used. The Pharmacist of Record should maintain a record of such determination.

5 Maintain appropriate records of the receipt and disposition of the protocol-specific study products including dates, quantities, batch/lot numbers, use by participants, and amounts returned from any source.

There should be an established method to account for all study products. A Study Product Accountability Record (See example in Annexure I), equivalent computerized record, or other document providing the same information must be used to document the receipt and disposition of all study products by dosage form, strength, batch/lot number and protocol. If other forms, approved by PMRA are to be used, it will be noted in a study specific document. Periodic physical inventories must be conducted to reconcile the quantity on hand with the inventory balances on the accountability record. At a minimum, these inventories are to be performed once per month. These periodic physical inventories should be documented with a date and signature on the accountability record itself. A procedure should be developed to ensure that sufficient supplies of the study product(s) are always available in the institution for the duration of the studies.

6 Verify in writing on the accountability records when protocol-provided study product supplies are returned, either before or at study completion, that all remaining supplies including returns from participants have been returned. No study supplies are to remain with the site/unit without PMRA authorization. If there are discrepancies between the accountability records and the physical supplies, the pharmacist must attempt to reconcile them. If the attempt to reconcile the differences is unsuccessful, the actions to reconcile must be documented on the accountability records and in a written report.

7 Retain a copy of all records for protocol-provided study product (order forms, receipts for transfers and returns, packing slips, inventory, and accountability records, etc.) during the duration of the study. Protocol-provided study product accountability records and any other unique pharmacy records should be retained until two years after the investigation of the study product is discontinued and the PMRA notified.

Accountability records and any other unique pharmacy information may be archived with case report forms after the protocol database is closed and the study is unblinded, if applicable. Pharmacy records and case report forms should not be archived independently, but should be kept together. When archiving, pharmacy records should be placed in a folder or envelope and clearly marked as pharmacy records.

8 Make the study product accountability records available for inspection and copying by an authorized employee or representative of the PMRA or NHSRC/COMREC upon request.

9 Establish a mechanism to ensure that study products are dispensed only after the written order of the Investigator or upon the order of a licensed clinician directly responsible to the Investigator.

i. Prescriptions shall be written with ink, indelible pencil, typewriter, or computer generated and shall be signed by the authorized clinician.
ii. Prescriptions are to be manually/hand written or with an electronic signature.
iii. Signature stamps are NOT permitted.
iv. Signing blank prescription forms is NOT permitted.
v. It is NOT permitted for an individual who is not an authorized prescriber to sign a prescription with an authorized prescriber's name and then add her/his own name to it in an effort to make it legal. For example, a nurse may not sign a doctor's name to a prescription and then add her/his name to it if she/he is not an authorized prescriber.
vi. Post-dated prescriptions are not permitted.
vii. Only clinicians authorized to prescribe in the site's jurisdiction and who are listed as investigators or sub investigators may write orders for study products.
viii. An agent for the Investigator or sub investigator may prepare prescriptions in advance of a participant's study visit for the SIGNATURE of a practitioner.
ix. The prescribing practitioner is responsible in case the prescription does not conform to any of the following: all essential aspects of the protocol, applicable laws and regulations.

10 Maintain the confidentiality of the participant, the participant's pharmacy file, and the study product accountability record. Maintain the blinding of the participant's treatment assignment to investigators, study nurses, clinic staff and the participant.

11 Establish a communication system with other site staff to assure that the protocol has been approved by the appropriate research ethics committee(s).

12 Establish a system to assure that the participant has signed an informed consent before dispensing protocol-provided study products. This could take the form of either a copy of the signature page of the informed consent

document or a log in which to record who has provided the verbal assurance that the informed consent has been signed or a notation on the prescription.

13 Establish a system to ensure that the current PMRA-approved version of the protocol is being followed when dispensing the protocol-specific drugs. The Pharmacist of Record should have on file a copy of the latest version of the protocol, and any additional versions of the protocol if there are participants being followed on that version. Also, the Pharmacist of Record should receive and retain a copy of all bulletins, clarifications, or Letters of Amendment (LoA) for each protocol.

14 Establish a central system in the pharmacy for maintaining essential information on study agents. An Investigator's Brochure or most current Product Package Insert, which contains current information about the investigational agent as supplied by the manufacturer, is distributed to the clinical sites/centers with the final version of a particular protocol.

15 Prepare written reports (mailed, faxed or e-mailed) of any incidents or matters that could affect the outcome of the study, such as study product preparation and/or administration problems, medication dispensing errors, and participant complaints and/or suggestions for presentation to the Investigator.

The following are examples of incidents that are reportable:

i. A participant was dispensed an incorrect study medication.
ii. A participant was assigned an incorrect participant identification number, incorrect study kit number, or was enrolled in the incorrect clinical trial.
iii. Any unblinding activity by the site pharmacist.
iv. Participants exchanged or shared study medications.
v. Improper storage of study products.
vi. Accountability discrepancies that were not able to be reconciled.
vii. Study products were dispensed or administered to individuals not participating in the protocol.

The Pharmacist of Record's report of an incident must include:

i. All participant identification numbers such study identification numbers.

ii. Clinical site/center name and center/site number.

iii. A description of the incident or problem.

iv. The reason(s) for the incident.

v. Resolution and/or follow-up of the incident.

vi. A description of the steps that have been taken to ensure that similar incidents do not happen again.

vii. A statement of whether the incident resulted in a reportable adverse event report.

16 Plan, develop, and implement a systematic process for quality assurance monitoring and problem-solving activities. The quality and appropriateness of the investigational pharmacy service should be internally reviewed and evaluated. When problems are identified, the actions that are taken to resolve the problems should be appropriately documented and reported. Internal quality assurance monitoring should be performed at specified periodic intervals.

17 Monitor labeled expiration dates and discard expired products. Expired product must be removed from active stock and placed in quarantine separated from active stock until discarded.

18 Obtain and maintain a prescriber sample signature list.

19 Submit a Notification of Change in Pharmacist whenever there is a change in pharmacy personnel or contact information. Curriculum vitae for a new Pharmacist of Record or primary back-up pharmacist should be forwarded to PMRA.

PHARMACY PLAN

The pharmacist at each clinical trial site, designated as the Pharmacist of Record, is the primary individual who is expected to develop and maintain an investigational product control system, which includes the technical procedures for product ordering, control, dispensing, and accountability. In addition, the Pharmacist of Record is responsible for the establishment of internal policies and procedures for the safe and proper use of investigational products. The Pharmacist of Record will perform the day to day dispensing and accountability activities.

A pharmacy plan shall be created by the pharmacist of record for each clinical research site, addressing the control and use of Investigational Products. The pharmacy plan for a clinical research site must be submitted to the PMRA for approval prior to the receipt and distribution of study medication.

If a Pharmacist of Record will be responsible for dispensing activities at more than one clinical site, provide a separate pharmacy plan for each clinical research site.

A Background

1 Name, Address of the clinical research site this pharmacy plan is for.

2 Name, degree, title or position, site mailing address, Internet address (if any), telephone, and fax numbers of the Pharmacist of Record who is responsible for this pharmacy plan?

3 Provide delivery address where study products are to be delivered.

4 Name, degree, title or position of the Back-up Pharmacist who will assume these responsibilities when the Pharmacist of Record is not available.

5 Does the pharmacy have written policies and procedures for handling investigational products? If yes, attach.

6 Describe the system for organizing protocol information, [for example, the current PMRA-approved version of the protocol (and amendments if applicable), participant treatment assignment lists, order forms, packing slips, accountability records, written prescriptions, return records, letters and memos from PMRA, Investigator's Brochures, etc.], the process for keeping this information up to date, where it will be located and who will have access.

7 How will the Pharmacist of Record be informed of the PMRA approval of a protocol? How will the Pharmacist of Record verify that s/he is working with the current PMRA approved version of a protocol?

8 How will authorized prescribers be identified for a protocol so as to prevent the unauthorized prescribing of investigational products?

9 What procedures will be followed by the Pharmacist of Record to maintain confidentiality of a participant's pharmacy file and the investigational product accountability records?

10 Does the pharmacy utilize a computerized investigational drug system (e.g. accountability/inventory, study information and/or medication order entry)? If so, describe.

11 Will the Pharmacist of Record be involved in participant consultation/counseling?

B Investigational Drug Control

Each of the following questions must be answered.

1 Room Temperature Storage

a) Where will investigational products be stored?
b) Who will have access to investigational products?
c) How will access to investigational products be limited to only those listed in b) above?
d) If prescriptions are prepared prior to a participant's visit, where will they be stored?
e) Is the access limited in this storage area?
f) At what temperature range is the storage area(s) maintained?
g) How often is the storage area(s) monitored for temperature control?
h) Is there documentation of the temperature monitoring of the storage area(s)?

2 Refrigerated Storage in the Pharmacy

a) Is refrigeration available? Yes? No?
b) Where is the refrigerator located?
c) How large is the refrigerator? Indicate whether cubic feet or cubic meters.
d) Who will have access to the refrigerator?
e) How will access to the refrigerator be limited?
f) At what temperature is the refrigerator maintained?
g) How often is the refrigerator monitored for temperature control?
h) Is there documentation of the temperature monitoring of the refrigerator`?

3 Refrigerated Storage in the Clinic

a) If study products that require refrigeration are prepared in advance for a participant's collection (pick up) at the clinic, will refrigeration be available in the clinic? Yes? No?

b) How is access to the refrigerator in this area limited?

4 Freezer Storage in the Pharmacy

a) Is a -20 to -10° C (-4 to 14°F) freezer available? Yes? No`?
b) If yes, where is the freezer located`?

c) How large is the freezer? Indicate whether cubic feet or cubic meters.
d) Who will have access to the freezer?
e) How will access to the freezer be limited?
f) At what temperature is the freezer maintained?
g) How often is the freezer monitored for temperature control?
h) Is there documentation of the temperature monitoring of the freezer?

5 Minus 70° Freezer Storage Space Availability

a) Is -70°C freezer storage space available? Yes? No?
b) If yes, where is this -70°C freezer storage space located?
c) How many cubic feet or cubic meters are available?
d) Who will have access to the -70°C freezer storage space?
e) How will access to the -70°C freezer storage space be limited?
f) At what temperature is the -70°C freezer storage space maintained?
g) How often is the -70°C freezer monitored for temperature control?
h) Is there documentation of the temperature monitoring of the -70° C freezer?

6 The Pharmacist of Record is required to keep complete written records (accountability records) of all study drugs that are received and of all study drugs that are dispensed to participants. The count or quantity of study drugs that you have at your site must match the quantity on the accountability records at all times. How often will the study drugs on the shelves and in the refrigerator/freezer be counted and compared with the accountability record?

C Investigational Drug Dispensing

1 An authorized prescriber must sign a written prescription at the time that a participant is registered/randomized to the protocol, or when there is a change in treatment, in order for the pharmacist to dispense medications. How will the Pharmacist of Record receive this written prescription? (If electronic prescriptions are used describe this process).

2 Describe how an initial written study medication order will be prepared and dispensed at this institution. Will these medications be prepared in the in-patient or outpatient pharmacy? (If both, describe both procedures).

3 How will it be documented that the informed consent was signed prior to dispensing the investigational product(s)?

4 How will the Pharmacist of Record be informed that subsequent prescriptions/refills need to be prepared? How will study products be delivered to the participant for follow-up visits?

5 Written prescriptions must be used to notify the Pharmacist of Record when a study drug dose is changed. How will the Pharmacist of Record receive the written prescription that notifies that a dose has been changed?

6 Is a biological safety cabinet or an isolator available for preparing study products? Yes? No?

7 How will the Pharmacist of Record dispense study products? (Check all that apply)

- Directly to participants.
- Deliver study products to other healthcare providers who will distribute it to participants.
- Through other procedures (describe).

8 How will the Pharmacist of Record receive study drugs returned by the participant? (Tick all that apply)

- Directly from participants.
- From other healthcare providers.
- Through other procedures (describe).

D Study Product Accountability

A Study Product Accountability Record, equivalent computerized record, or other document providing the same information must be used to document the receipt and disposition of all study products received. Accountability records must also be kept for any other protocol-supplied study product that is received from some other source such as directly from a pharmaceutical company. The accountability record is to be used for recording data on the dispensing of the protocol and lot specific study products. Information to be recorded on the accountability record includes:

i. Prescription number
ii. date dispensed
iii. participant identification number or study kit identification number
iv. study identification number
v. quantity dispensed or received from or returned
vi. current balance
vii. pharmacist's initials
viii. comments

The sample accountability record utilizes a single lot per page method. This is the recommended method. The name of the manufacturer and the lot number are recorded in the top portion of the form. In instances where more than one lot of a specific product is on inventory, it will be necessary to have a separate accountability record for each lot of that product.

The inventory balance documented on this form should match the actual study product inventory on hand at all times.

Make an entry with the date and pharmacist's initials in the accountability form every time that a physical inventory is conducted and reconciled with

the accountability records. When the recorded balance and the actual inventory are not equal, the discrepancy and the reason for the discrepancy should be documented on the study product accountability record. After documentation of discrepancy, the balance may be adjusted to match the actual inventory level.

If error corrections are needed, the following must be followed:

i. Draw a single line through the incorrect information.
ii. Initial, date, and state reason for change (if necessary)
iii. Insert the correction.

- Never use pencil to write entries.
- Never use "white-out" or correction ink
- Never obliterate entries that require correction
- Never destroy original documents, even if they require error correction.

It is required that the prescription for the corresponding entry in the Study Drug Accountability Record be maintained and be easily retrievable for review by PMRA.

Identification of the dispensing pharmacist is always necessary when there is an audit or review of the study product accountability records and prescriptions. A list of pharmacists' signatures and initials to identify each dispensing pharmacist must be available. Upon request, the list of pharmacists' signatures and initials must be made available to authorized representatives of the PMRA.

Study Product Accountability Records, shipment invoices and return receipts should be maintained in the pharmacy until the study is completed. When the database for the study has been closed, the records should be stored, either in the pharmacy or with other study records from the clinic; until two years after the study of the study product is discontinued and the PMRA notified.

E Study Product Transfers

I Guidelines for Dispensing Study Products

1 A mechanism must be established to ensure that study products are dispensed only upon the written order of the Investigator or upon the order of a licensed clinician directly responsible to the Investigator

2 Prescriptions

- Prescriptions shall be written with ink, indelible pencil, typewriter, or computer generated and shall be signed by the clinician.
- Prescriptions are to be manually/hand written or with an electronic signature.

- Signature stamps are NOT permitted.
- Signing blank prescription forms is NOT permitted.
- It is NOT permitted for an individual who is not an authorized prescriber to sign a prescription with an authorized prescriber's name and then add her/his own name to it in an effort to make it legal. For example, a nurse may not sign a doctor's name to a prescription and then add her/his name to it if she/he is not an authorized prescriber.
- Post-dated prescriptions are not permitted.
- Only clinicians authorized to prescribe in the site's jurisdiction and who are listed as investigators or sub investigators may write orders for study products.
- An agent for the Investigator or sub investigator may prepare prescriptions in advance for the SIGNATURE of a practitioner.
- The prescribing practitioner is responsible in case the prescription does not conform in all essential aspects of the protocol, to the law and regulations.
- Obtain and maintain a prescriber sample signature list

3 The prescribing clinician is responsible for ensuring that the prescription conforms to the protocol and all applicable laws and regulations.

4 Medication orders or prescriptions should include:

a) Participant name (or initials)
b) Date
c) Protocol number
d) Personal Identification number or other participant identifier
e) Study Identification number, randomised number, or study identification number
f) Body surface Area or height and weight
g) Medication prescribed.
h) Quantity or instructions to indicate amount to be dispensed
i) Directions for participant
j) Any special instructions regarding dose reduction, dose escalation, etc.
k) Prescriber's signature

5 A method must be established to verify that a valid, signed consent form was signed by participant prior to dispensing the supply of the protocol-provided product(s).

6 The study product must be dispensed in accordance with the current PMRA-approved protocol.

7 The study products must be labeled properly to ensure their safe administration and use by the research staff and participants. Prepare prescription labels in a format that complies with all applicable labeling

requirements especially the Medicines and Allied Substances Control (General) Regulations and that maintains participant confidentiality. It is the site pharmacists' responsibility to know the requirements for their jurisdiction. Prescription labels for study products should be distinguishable from other labels by an appropriate legend. "Investigational Product" or "For Investigational Use Only."

Labels should include:

a) Name, address, and phone number of dispensing site
b) Participant name or coded identification
c) Dispensing date
d) Directions
e) Prescribing Investigator's name
f) Participant and/or study identification number
g) Protocol number
h) Number of dosing units dispensed
i) Name of investigational product or protocol-provided product, if appropriate (i.e. if unblinded study and confidentiality is not an issue)

8 Instructions should be provided to the participant and/or the appropriate nursing service personnel if they advise the participant on the correct use of the study product.

9 If for any reason a study product is mailed to a participant, it must be packaged and labeled properly. Some method of documenting the receipt of the study product by the participant must be used.

II Dispensing Participant Specific Study Products to another Institution that Is Not Participating in the approved clinical trial

When a participant is to remain on protocol, but is to receive the study product at another institution, appropriate arrangements for the dispensing of participant specific study products must be made. Also appropriate notification must be made to the sponsor and the PMRA of the second institution that will be receiving the study product.

1 Notification of Pharmacist of Record

The Investigator should notify the Pharmacist of Record in writing that the study product should be redistributed to another institution for a specific participant. This written notification should include:

a) The participant's name, participant identification, and a study specific number.

b) The name and telephone number of the physician responsible for the study participant at the second institution.
c) The name and telephone number of the pharmacist responsible for distributing the study product at the second institution.
d) A copy of the second institution's IRB approval of the protocol. If approval is not required, a copy of the IRB notification is sufficient documentation. Also, in the approval document or notification to the IRB, the procedures for how the study product will be handled should be outlined. For example, the procedures could state that the study product will be provided to the pharmacist at the second institution for storage, preparation, and dispensing; or that the study product will be prepared or dispensed by the clinical network/program Pharmacist of Record for administration in the second institution.
e) A detailed outline of the method of study product transport in detail. For example, the research nurse will transport the study product to the second institution; or the pharmacist at the second institution will pick up the study product at the clinical trial pharmacy, or the study product will be transported by special courier and delivered to the pharmacist at the second institution.
f) An estimate of the participant's length of stay in the second institution.

g) A description of the participant discharge procedure and notification process for informing the clinical trial Pharmacist of Record. The participant/protocol follow up procedures also should be outlined.

2 **Notification of Pharmacist at Second Institution**

a) The clinical trial Pharmacist of Record should contact the pharmacist at the second institution and should provide appropriate study product handling and disposition instructions to him or her. At the least, a copy of the protocol, a copy of the participant's informed consent, and study product storage, handling, and any special preparation and administration instructions should be provided. Also, specific details for study product accountability, re-supply, and return of unused study product should be worked out between the two pharmacists.
b) The clinical trial Pharmacist of Record is responsible for ensuring that the study product is handled properly and all disposition is appropriately documented. A copy of the study product accountability instructions and study product information provided to the pharmacist at the second institution must be maintained by the clinical network/program Pharmacist of Record. Upon request by the sponsor, this information must be made available for review.

3 **Notification of the PMRA**

a) The clinical trial Pharmacist of Record must inform the PMRA when a study product is redistributed to another health institution. This notification should be in written form and should include at least the following information:
b) A statement that the study product was distributed to a second institution per written authorization by the Investigator. The statement should give the complete name of the second institution and the Investigator, the clinical trial number under which the study product is being dispensed, and the date.
c) The rationale for the study product redistribution
d) A copy of this notification to PMRA must be maintained with the study protocol records.

Pharmacist of Record Signature _____ Date _____

NOTE: Pharmacy plans will not be approved without the Pharmacist of Record's dated signature and an attached copy of the Pharmacist of Records curriculum vitae. A copy of the completed Pharmacy Plan must be kept on file in the pharmacy.

Temporary/Permanent Notification of Change in Pharmacist of Record or Back-Up Pharmacist

This memo serves to notify the PMRA of a change in the Pharmacist of Record or Back-up Pharmacist.

Permanent: _____ Temporary _____ Date from: _____ Date to: _____

Site Name: _____ PMRA Trial Number(s) _____

Name of PREVIOUS Pharmacist of Record: _____

The following information may be provided as an attachment, (See CV requirement below)

Name of NEW Pharmacist of Record or Back-up Pharmacist: _____

Degree, Title, Position: _____
Mailing Address: _____
_____
_____
Telephone number: _____

Fax number: _____

Please complete the following:

_____ (Initial here) I agree to comply with all the information contained in the Previous or Revised Pharmacy Plan. If the pharmacy plan was revised, please attach.

Sign and date: _____ _____
Signature of NEW Pharmacist of Record or Back-up Pharmacist.

Send:

1) This completed form, signed and dated
2) A copy of the C.V. for the New Pharmacist of Record
3) The Revised Pharmacy Plan (if applicable) to PMRA