Medicines Control Authority of Zimbabwe

PHARMACY GUIDELINES FOR INVESTIGATIONAL MEDICAL PRODUCTS

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Approved by Director General: ....10/6/2020.....

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1.0 APPLICATION

This guideline applies to all researchers who conduct clinical trials in human participants in Zimbabwe in terms of the Medicines and Allied Substances Control Act (Chapter 15:03) and regulations.

2.0 PURPOSE

These guidelines should be used as a guide to the receipt, use and disposition of study medical products being investigated in clinical trials in Zimbabwe. They provide guidance to investigators on how to establish and maintain adequate records of study product and disposition of study products to comply with statutory requirements and policies of the Medicines Control Authority of Zimbabwe (MCAZ) including the Medicines Allied Substance Control Act (MASCA) Chapter 15:03 and its Regulations, the Zimbabwe Good Clinical Trial Practice Guidelines, Application Guidelines for Clinical Trial Authorization in Zimbabwe, Good Dispensing Practice Guidelines and Guidelines for the safe disposal of medicines.

3.0 BACKGROUND / INTRODUCTION

These guidelines are principally derived and adapted from guidelines for the Division of AIDS (DAIDS) of the National Institute of Allergy and Infectious Diseases of the National Institutes of Health of the United States of America and the WHO Guidelines for clinical trials pharmacy plan including safe disposal of unwanted pharmaceuticals in and after emergencies. They provide guidance to investigators on how to establish and maintain adequate records of study medical products and disposition/destruction of study products to comply with the MCAZ statutory requirements, policies and other local and international requirements. The guidelines provides guidance on how to prepare a pharmacy plan in line with the MCAZ requirements.

The principal investigator and/or investigator has the overall responsibility for all the medical products and investigational products for the study. The pharmacist at each clinical site/centre participating in a clinical trial, who is designated as the Pharmacist of Record, is the primary individual who is expected to develop and maintain a study product management system, which includes the technical procedures for study product ordering, control, dispensing, and accountability. In addition, the Pharmacist of Record may be expected to participate in; preparation of blinded study products; preparation of special dosage forms and packaging; monitoring of adherence to study product treatment regimens by participants; preparation of study product information/data sheets for pharmacy, nursing, and other personnel; data collection and documentation; and development of research protocols. Researchers and investigators are expected to follow and comply with these pharmacy guidelines for investigational products.

4.0 DEFINITIONS

4.1 **Clinical Trial:** Is defined in the Medicines and Allied Substances Control Act [Chapter 15:03] as follows: "A systematic study in human beings or animals in order to establish the efficacy of, or to discover or verify the effects or adverse reactions of medicines, and includes a study of the absorption, distribution, metabolism and excretion of medicines". This includes any trial for well-known established indication or registered product and academic studies for students in partial fulfilment of tertiary education.

4.2 **Compliance (in relation to clinical trials):** Adherence to all the trial-related requirements, Good Clinical Practice (GCP) requirements, and the applicable regulatory requirements.

4.3 **Documentation:** All records in any form (written, electronic, magnetic optical records, scans, x-rays and electrocardiograms and others) that describe or records the methods, conduct, and/or results of a trial, the factors affecting a trial and the actions taken.

4.4 **Good Clinical Practice (GCP):** A standard for the design, conduct, performance, monitoring, auditing, recording, analyses and reporting of clinical trials that provides assurance that the data and reported results are credible and accurate, and that the rights, integrity and confidentiality of trial participants are protected.

4.5 **Good Manufacturing Practice (GMP):** That part of pharmaceutical quality assurance which ensures that products are consistently produced and controlled to the quality standards appropriate for their intended use and as required by the product specification.

4.6 **Inspection:** The act by a regulatory authority (ies) of conducting an official review of documents, facilities, records, and any other resources that are deemed by the authority (ies) to be related to the clinical trial and that may be located at the site of the trial, at the sponsor's and/or contract research organization's (CROs) facilities, or at other establishments deemed appropriate by the regulatory authority (ies). This maybe include GCP inspection and/or GMP inspection and/or Good Laboratory Practice inspection.

4.7 **Investigator:** An individual responsible for the conduct of the clinical trial at a trial site. If it is conducted by a team of investigators at a trial site, the leader of the team may be called principal investigator (see definition below).

4.8 **Investigational (Study) Product:** A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial including a product with a marketing authorisation when used or assembled 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.

4.9 **Investigator's Brochure:** A compilation of the clinical and nonclinical data on the investigational product(s) which is relevant to the study of the

investigational product(s) in human participants.

4.10 **Participant /Trial participant:** An individual who participates in a clinical trial, either as a recipient of the investigational product(s) or as a control.

4.11 **Pharmacy:** Any licensed premises used to perform one or more of the following functions: storage, preparation, dispensing and management of study products.

4.12 **Pharmacist of Record:** A licensed/registered pharmacist who performs the day to day pharmacy activities and study product management including but not limited to the procurement, storage, preparation, dispensing and final disposition of study products.

4.13 **Pharmacy plan:** A document created by the pharmacist of record for each clinical research site which addresses the control and use of investigational products.

4.14 **Principal Investigator:** A person responsible for the conduct of the clinical trial at a trial site who is a medical practitioner, or dentist or other qualified person, resident in the country and a member of good standing of a professional medical association. If a trial is conducted by a team of investigators at a trial site, the principal investigator is the responsible leader of the team.

4.15 **Protocol:** A document that describes the objective(s), design, methodology, statistical considerations and the organisation of a trial. The protocol usually also gives the background and rationale for the trial, but these could be provided in other protocol referenced documents.

4.16 **Product Defect:** A product that is not of the correct quality, safety or efficacy as defined by its manufacturer which may pose risk to the users.

4.17 **Quality Assurance (QA):** Systems and processes established to ensure the trial is performed and the data generated, documented and reported in compliance with GCP and appropriate regulatory requirements.

4.18 **Recall:** A process for withdrawing or removing a product from the pharmaceutical distribution chain because of defects in the product, complaints of serious adverse reactions to the product and/ or concerns that the product is or may be counterfeit.

4.19 **Sponsor:** An individual, company, institution or organisation which takes responsibility for the initiation, management and/or financing of a trial. This excludes an individual company, institution or organisation which has been requested to provide money for a trial and does not benefit in any way from the results of the trial.

4.20 **Standard Operating Procedure (SOP):** A detailed, written instruction for

the management of clinical trial. They provide a framework enabling the efficient implementation and performance of all the functions and activities for a particular trial.

4.21 **Study Product Disposal:** Is the discarding of study product which may be expired, leftovers or unwanted.

4.22 **Trial Site:** The location(s) where trial-related activities are actually conducted.

5.0 GUIDELINES

These guidelines are divided into seven main sections namely, Responsibilities of the Pharmacist of Record, Pharmacy Plan, Study Product Accountability, Dispensing Study Products, Importation and Management of Investigational Products, Study Product Transfers and Disposal of Study Products.

5.1 RESPONSIBILITIES OF PHARMACIST OF RECORD

5.1.1 The Pharmacist of Record is responsible for:

5.1.1.1 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.

5.1.1.2 Ordering and maintaining records of receipt of protocol-provided study products, dispensing to participants, and disposition of study products.

5.1.1.3 Maintaining records of any study provided products received directly from other sources including adequate records showing the receipt, dispensing, dates and quantities of the medicines. Records for study medicines that are not provided as part of the protocol should also be maintained.

5.1.2 The Pharmacist must:

5.1.2.1 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 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.

5.1.2.2 Ensure that adequate space, equipment, and supplies for the storage, preparation, packaging, and dispensing of study products is available, including for products that require special handling. He or she must make sure that study product handling, storage and dispensing is in line with the Medicines Allied Substance Control Act (MASCA) Chapter 15:03 and its Regulations and MCAZ Good Dispensing Guidelines.

5.1.2.3 Ensure provision for the proper storage conditions for protocol-provided study products, including segregation, security, temperature, and temperature monitoring, light, moisture, ventilation, and sanitation. 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 or back up Pharmacist. The study products are shipped on a site specific, investigator-specific, protocols specific basis, and they should be segregated by protocol when stored with separate supplies for each clinical site/canter 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 or discarded. The Pharmacist of Record should maintain a record of such determination.

5.1.2.4 He or she should ensure that there is an established method to account for all study products. 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 by dosage form, strength, lot number and protocol. If other forms, approved by MCAZ 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. Verify in writing on the accountability records when protocol-provided study product supplies are returned, including returns from participants, either before or at study completion. No study supplies are to remain with the site/unit without MCAZ authorisation. 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.

5.1.2.5 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. 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

5.1.2.6 Make the study product accountability records available for GCP inspection and copying by an authorized employee or representative/inspector of the MCAZ or Medical Research Council of Zimbabwe (MRCZ), upon request.

5.1.2.7 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.

5.1.2.8 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.

5.1.2.9 Establish a communication system with other site staff to assure that the protocol has been approved by the MCAZ and appropriate medical ethics committee(s) e.g., Institutional Review Board(s)

5.1.2.10 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.

5.1.2.11 Establish a system to ensure that the current MCAZ-approved version of the protocol is being followed when dispensing the protocol-specific products. 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. In addition, the Pharmacist of Record should receive and retain a copy of all bulletins, clarifications, or letters of amendment (LoA) for each protocol.

5.1.2.12 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, should be distributed to the clinical sites/centres with the final version of a particular protocol.

5.1.2.13 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.

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

i. All participant identification such study identification numbers.
ii. Clinical site/centre name and centre/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 or deviation report.

5.1.2.15 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

5.1.2.16 Monitor labelled expiration dates and discard expired products in line with the set procedures. Expired products must be removed from active stock and placed in quarantine separated from active stock until discarded.

5.1.2.17 Obtain and maintain a prescriber sample signature list/logo

5.1.2.18 Submit a notification of change of the Pharmacist of Record whenever there is a change in pharmacy personnel or contact information. Cover letter detailing the changes, curriculum vitae, valid persons license for the new Pharmacist of Record or primary back-up pharmacist and revised Pharmacy Plan (if applicable) should be forwarded to the MCAZ for approval

5.1.2.19 Should record and report product defects in line with the Guidelines for the Notification of a Medicinal Product Problem/Defect and Recall Procedure. SOP for handling product defects and recalls should be available.

5.2 PHARMACY PLAN

5.2.1 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 MCAZ for approval prior to the receipt and distribution of study medication and should be included in the application to conduct a clinical trial submitted to MCAZ.

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.

5.2.2 The following information should be included in a Pharmacy Plan:

5.2.2.1 Background

i. Name, Address of the clinical research site this pharmacy plan is for.
ii. Copy of valid MCAZ research pharmacy premises license should be attached.
NB. All research pharmacies should be inspected by MCAZ inspectorate and approved in line with the requirements.
iii. 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. Copy of valid MCAZ persons licence should also be attached
iv. Name, degree, title or position of the Back-up Pharmacist who will assume these responsibilities when the Pharmacist of Record is not available.
v. Provide delivery address where study products are to be delivered
vi. Does the pharmacy have written policies and procedures for handling investigational products? If yes, attach.
vii. Describe the system for organizing protocol information, (for example, the current MCAZ 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 MCAZ, Investigator's Brochures, etc.), the process for keeping this information up to date, where it will be located and who will have access.
viii. How will the Pharmacist of Record be informed of the MCAZ approval of a protocol? How will the Pharmacist of Record verify that s/he is working with the current MCAZ approved version of the protocol?
ix. How will authorized prescribers be identified for a protocol so as to prevent the unauthorized prescribing of investigational products?

x. 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?
xi. Does the pharmacy utilize a computerized investigational medicine system (e.g. accountability/inventory, study information and/or medication order entry)? If so, describe.
xii. Will the Pharmacist of Record be involved in participant consultation/counselling?

5.2.2.2 Investigational product control

Each of the following questions must be answered.

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

ii. Refrigerated Storage in the Pharmacy
- Is refrigeration available? Yes? No?
- Where is the refrigerator located?
- How large is the refrigerator? Indicate whether cubic feet or cubic meters.
- Who will have access to the refrigerator?
- How will access to the refrigerator be limited?
- At what temperature is the refrigerator maintained?
- How often is the refrigerator monitored for temperature control?
- Is there documentation of the temperature monitoring of the refrigerator`?

iii. Refrigerated Storage in the Clinic
- 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?
- How is access to the refrigerator in this area limited?

iv. Freezer Storage in the Pharmacy
- Is a -20 to -10° C (-4 to 14°F) freezer available? Yes? No?
- If yes, where is the freezer located?
- How large is the freezer? Indicate whether cubic feet or cubic meters.
- Who will have access to the freezer?
- How will access to the freezer be limited?

- At what temperature is the freezer maintained?
- How often is the freezer monitored for temperature control?
- Is there documentation of the temperature monitoring of the freezer?

v. Minus 70° Freezer Storage Space Availability
- Is -70°C freezer storage space available? Yes? No?
- If yes, where is this -70°C freezer storage space located?
- Who will have access to the -70°C freezer storage space?
- How many cubic feet or cubic meters are available?
- How will access to the -70°C freezer storage space be limited?
- At what temperature is the -70°C freezer storage space maintained?
- How often is the -70°C freezer monitored for temperature control?
- Is there documentation of the temperature monitoring of the -70° C freezer?

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

5.2.2.3 Investigational product dispensing

5.2.2.3.1 A prescription must be signed by the authorised prescriber upon prescribing treatment to the participant. When there is a change in treatment, the pharmacist should be made aware of the changes in order for the pharmacist to dispense the medications. Written prescriptions must be used to notify the Pharmacist of Record when a study medicine dose is changed. Describe how the Pharmacist of Record will receive written prescriptions? (If electronic prescriptions are used describe this process.)

5.2.2.3.2 Describe the process of preparing and dispensing medicines at the in-patient/ out-patient pharmacy.

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

5.2.2.3.4 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?

5.2.2.3.5 Is a biological safety cabinet, an isolator or laminar cabinet available for preparing study products? Yes / No? If yes describe how it will be handled and special precautions which may be required. **NB this may need to be inspected by MCAZ first before dispensing of the study products.**

i. 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).

ii. How will the Pharmacist of Record receive study products returned by the participant? (Tick all that apply)
- Directly from participants.

- From other healthcare providers.
- Through other procedures (describe).

Pharmacist of Record Signature _____ Date _____

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

5.3 STUDY PRODUCT ACCOUNTABILITY

5.3.1 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:

5.3.1.1 Prescription number
5.3.1.2 date dispensed
5.3.1.3 participant identification number or study kit identification number
5.3.1.4 study identification number
5.3.1.5 quantity dispensed or received from or returned
5.3.1.6 current balance
5.3.1.7 pharmacist's initials
5.3.1.8 comments

5.3.2 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

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

5.3.3.1 Draw a single line through the incorrect information.

5.3.3.2 Initial, date, and state reason for change (if necessary)

5.3.3.3 Insert the correction.

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

5.3.4 It is required that the prescription for the corresponding entry in the Study Medicine Accountability Record be maintained and be easily retrievable for review MCAZ during GCP inspections.

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/log 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/inspectors of the MCAZ.

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 MCAZ notified.

5.4 DISPENSING STUDY PRODUCTS

5.4.1 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

5.4.2 Prescriptions

5.4.2.1 Prescriptions shall be written with ink, indelible pencil, typewriter, or computer generated and shall be signed by the clinician.

5.4.2.2 Prescriptions are to be manually/hand written or with an electronic signature.

5.4.2.3 Signature stamps are NOT permitted.

5.4.2.4 Signing blank prescription forms is NOT permitted.

5.4.2.5 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.

5.4.2.6 Post-dated prescriptions are not permitted.

5.4.2.7 Only clinicians authorized to prescribe in the site's jurisdiction and who are listed as investigators or sub investigators or as study clinicians may write orders for study products.

5.4.2.8 An agent for the Investigator or sub investigator may prepare prescriptions in advance for the signature of a practitioner.

5.4.2.9 The prescribing practitioner is responsible in case the prescription does not conform in all essential aspects of the protocol, to the law and regulations.

5.4.2.10 Obtain and maintain a prescriber sample signature list/log

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

5.4.2.12 Medication orders or prescriptions should include:

i. Participant name (or initials)
ii. Date
iii. Protocol number
iv. Personal Identification number or other participant identifier
v. Study Identification number, randomised number, or study identification number
vi. Body surface Area or height and weight when necessary
vii. Age of participant
viii. Medication prescribed.
ix. Quantity or instructions to indicate amount to be dispensed
x. Directions for participant
xi. Any special instructions regarding dose reduction, dose escalation, etc.
xii. Prescriber's signature

5.4.3 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).

5.4.4 The study product must be dispensed in accordance with the current MCAZ-approved protocol.

5.4.5 The study products must be labelled 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 labelling 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."

5.4.6 Labels should include:

i. Name, address, and phone number of dispensing site
ii. Participant name or coded identification
iii. Dispensing date
iv. Directions
v. Prescribing Investigator's name
vi. Participant and/or study identification number
vii. Protocol number
viii. Number of dosing units dispensed
ix. Name of investigational product or protocol-provided product, if appropriate (i.e. if un-blinded study and confidentiality is not an issue)

5.4.7 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.

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

5.5 IMPORTATION AND MANAGEMENT OF INVESTIGATIONAL PRODUCTS

5.5.1 All study investigational products and other trial related medical products shall be approved for importation, exportation or destruction by the MCAZ. Approval to import or export products for clinical trials shall only be granted to clinical research entities whose study has been approved by The Authority. Applicants are required to submit an application for authorisation to import investigational products. The application shall contain the following:

5.5.1.1 A cover letter stating the full name and address of the innovator and /or manufacturer, the study Sponsor and the recognized clinical research entity, the name/description of the investigational product, placebo and quantity to be imported;
5.5.1.2 The **quantity** and **source** of each investigational product and trial related products to be imported;
5.5.1.3 Shipment documents and invoices of the product purchased/ to be purchased indicating quantities;
5.5.1.4 A certificate of analysis of investigational products for all batches of each product to be imported;
5.5.1.5 Lot Release certificate(s) (where applicable) for all batches to be imported.

5.5.2 On submission of the above, an application for an import permit will be processed within five (5) working days.

5.5.3 The investigational product shall be appropriately labeled with the approved labels to indicate that samples are for the conduct of clinical trials only. The label shall bear the following as the basic information:

5.5.3.1 For Clinical Trial purposes ONLY
5.5.3.2 Trial name
5.5.3.3 Expiry date (if applicable)
5.5.3.4 Dosage (if applicable)
5.5.3.5 Investigational Product identity number.

5.5.4 Products imported may be inspected by officials of the Authority at the port of entry before they are released to the recognized clinical research entity.

5.5.5 For investigational products purchased locally, the Principal Investigator shall document the source, proof of purchase, quantities purchased and Certificate of Analysis for each batch of Investigational Products. Copies of all documents on investigational products, whether purchased locally or imported shall be kept on site for verification and accountability during GCP inspections.

5.6 STUDY PRODUCT TRANSFERS

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 MCAZ.

5.6.1 Notification of Pharmacist of Record

5.6.1.1 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:

i. The participant's name, participant identification, and a study specific number.
ii. The name and telephone number of the physician responsible for the study participant at the second institution.
iii. The name and telephone number of the pharmacist responsible for distributing the study product at the second institution.
iv. 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.
v. 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.
vi. An estimate of the participant's length of stay in the second institution.
vii. 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.

5.6.2 Notification to the Pharmacist at the Second Institution

5.6.2.1 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.

5.6.2.2 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.

5.6.3 Notification to the MCAZ should include at least the following information:

5.6.3.1 The clinical trial Pharmacist of Record must inform the MCAZ when a study product is redistributed to another health institution. This notification should be in written form.

5.6.3.2 Product Details and Quantities of the products transferred

5.6.3.3 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.

5.6.3.4 A copy of this notification to MCAZ must be maintained with the study protocol records.

5.6.3.5 The rationale for the study product redistribution (e.g. Left over after study completion)

5.7 DISPOSAL OF STUDY MEDICAL PRODUCTS

5.7.1 Principles

Expired, Contaminated, Left overs or unwanted study products must be disposed off safely, without harming people and the environment. Improper disposal of study products may lead to contamination of water supplies or local sources used by nearby communities or wildlife posing significant risk to the public health and the environment.

These study products may be destroyed using safe methods upon authorization by the MCAZ and the study Sponsor. As such, an official request to dispose of the study products, indicating the type , quantity of each product to be destroyed and the method of destruction shall be made to the Authority. The reason for the disposal must be indicated in the letter. The destruction process maybe be supervised by MCAZ Officers and representatives of other relevant agencies where applicable and a destruction certificate/letter confirming destruction shall be issued. Records of study medical products disposal should be kept in the pharmacy file.

NB: To destroy dangerous drugs (Narcotics) permission must be sought from the Secretary of Health and Child Welfare in line with the dangerous Drugs Act (Chapter 15:02).

5.7.2 Recommended methods of disposal.

These methods have been adapted from the WHO Guidelines for safe disposal of unwanted pharmaceuticals in and after emergencies and the MCAZ Guidelines for the safe disposal of expired medicines.

5.7.2.1 Return to donor or manufacturer

Wherever practical the possibility of returning unusable study product for safe disposal by the manufacturer should be explored; particularly medicines which present disposal problems, such as anti-neoplastics. For unwanted, unrequested donations, especially those that arrive past or unreasonably near their expiry date it may be possible to return them to the donor for disposal.

5.7.2.2 Landfill

This is the most widely used method. The appropriate landfill is ideally an evacuated pit isolated from watercourses and above the water table. To landfill means to place waste directly into a land disposal site without prior treatment or preparation. Since antibiotics may lead to unwanted exposure to resistance-forming organisms in the environment, they should not be landfilled.

5.7.2.3 Waste encapsulation

This is immobilizing the pharmaceuticals in a solid block within a plastic or steel drum. They are filled to 75% capacity with solid and semi-solid pharmaceuticals, and the remaining space is filled by pouring in a medium such as cement or cement/lime mixture, plastic foam or bituminous sand.

This is let to set over a few days. The drum is sealed and placed at the bottom of the landfill and covered with other waste.

Encapsulation of antineoplastic medicines requires a slightly different technique. The medicines must be destroyed in a two-chamber incinerator, which operates at a high temperature of at least 1200°C in the secondary chamber, and is fitted with gas cleaning equipment.

5.7.2.4 Waste immobilization: Inertization

This involves the removal of the packaging (cardboard, paper, plastic) grinding the medicines, mixing with water, cement and lime to a paste. This paste is then disposed of amongst the other waste and sets as solid pieces. Pills need to be removed from their blister packs. Worker protection in the form of protective clothing and masks is required as there may be a dust hazard.

5.7.2.5 Sewer

This could be used on some liquids and intravenous fluids after diluting with water then flushing in small quantities down the sewer. The intravenous fluids referred to here are harmless solutions of salts, amino acids, lipids, glucose etc. Large quantities of disinfectants must not be flushed into the sewer as they could kill the bacteria in the sewage works necessary for the biological treatment of the sewage. In the same way such large quantities should not be discharged into rivers, as they could be fatal to aquatic life. Quantities of not more than 50 litres per day may be acceptable. In instances where there are no sewers the liquids could be diluted (except for cytotoxics, narcotics and antibiotics) with copious amounts of water then poured into large courses of water provided they are immediately dispersed and diluted by the flowing river water. It is not acceptable to discharge waste whether diluted or not into slow moving or stagnant surface waters.

5.7.2.6 Incineration

Very few local incinerators meet emission control standards. It is however acceptable to use two chamber incinerators that operate at a minimum temperature of 850°C (medium temperature). Most municipal and hospital incinerators belong in this category for the destruction of solid medicines. The destruction at lower temperatures or in open containers will cause aerosol forms of the medicines to be released into the air. Paper and cardboard packaging, if they are not to be recycled, may be burnt. Polyvinyl chloride (PVC) plastic however must not be burnt. High temperature incinerators typically found at cement kilns, thermal power stations or foundries and operate at temperatures above 850°C are the best.

5.7.2.7 Chemical decomposition

This could be done following the manufacturers recommendation followed by landfill. This chemical inactivation is normally tedious and time consuming and large stocks of chemicals must be available. It could however be used for small quantities of cytotoxics and antibiotics.

Summary of pharmaceutical categories and disposal methods for study products

Category	Disposal methods	Comments
Solids **Semi-solids** **Powders**	Landfill Waste encapsulation Waste inertization Medium and high temperature incineration (cement kiln incinerator)	No more than 1% of the daily municipal waste should be disposed of daily in an untreated form (non-immobilized) to a landfill.
Liquids	Sewer High temperature incineration (cement kiln incinerator)	Antineoplastics not to sewer.
Ampoules	Crush ampoules and flush diluted fluid to Sewer	Antineoplastics not to sewer.
Anti-infective medicines	Waste encapsulation Waste inertization Medium and high temperature incineration (cement kiln incinerator)	Liquid antibiotics may be diluted with water, left to stand for several weeks and discharged to a sewer.
Antineoplastics	Return to donor or manufacturer Waste encapsulation Waste inertization Medium and high temperature incineration (cement kiln incinerator) (chemical decomposition)	Not to landfill unless encapsulated. Not to sewer. No medium temperature incineration.
Controlled medicines	Waste encapsulation Waste inertization Medium and high temperature incineration (cement kiln incinerator)	Not to landfill unless encapsulated.
Aerosol canisters	Landfill Waste encapsulation	Not to be burnt: may explode.
Disinfectants	To sewer or fast–flowing watercourse: small quantities of diluted disinfectants (max. 50 litres per day under supervision)	No undiluted disinfectants to sewers or water courses. Maximum 50 litres per day diluted to sewer or fast–flowing watercourse. No disinfectants at all to slow moving or stagnant watercourses.
PVC plastic, glass	Landfill	Not for burning in open containers.

Paper, cardboard	Recycle, burn, landfill

NOTE: For further details about the disposal methods and procedures please refer to the WHO Guidelines for safe disposal of unwanted pharmaceuticals in and after emergencies and the MCAZ Guidelines for the safe disposal of expired medicines.

6.0 KEY RELEVANT DOCUMENTS

6.1 Medicines and Allied Substances Control Act (MASCA) [Chapter 15:03] and its Regulations.

6.2 Application Guidelines for Clinical Trial Authorisation in Zimbabwe Rev 0_May 2020.

6.3 Guidelines for Good Clinical Trial Practice in Zimbabwe Revision 1_June 2020

6.4 e-CT application and registry system- External User Manual Guide Rev 0_June 2020

6.5 e-PV Pharmacovigilance electronic reporting system-External User Manual Rev 0_June 2020

6.6 WHO Guidelines for safe disposal of unwanted pharmaceuticals in and after emergencies.

6.7 MCAZ Guidelines for the safe disposal of expired medicines.

6.8 MCAZ Good Dispensing Practice Guidelines.

6.9 MCAZ Notification of a Medicinal Product Problem/Defect and Recall Procedure Guidelines.

6.10 Requirements for Pharmacy Activities at DAIDS Supported Clinical Research Sites Conducting Trials Outside of the HIV/AIDS Clinical Trials Networks.

7.0 HISTORY

Revision Number	Date Approved	Date Reviewed: May 2020
0	March 2016	Reason for Change and Amendments To align with the local and international standards The following changes/amendments were done from **Revision 0** to **Revision 1**
1	June 2020	i. Addition of importation and disposal of study products sections ii. Requirement for the Pharmacist of Record to report product defects reports and recalls iii. Alignment to the new MCAZ template for guidelines