



GUIDELINES FOR GOOD CLINICAL TRIAL PRACTICE IN ZIMBABWE 2012

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A. GUIDELINES REGULATING CONDUCT OF CLINICAL TRIALS IN HUMAN PARTICIPANTS

1. INTRODUCTION

The guidelines for conducting clinical trials in Zimbabwe were partly derived from the International Conference on Harmonisation Good Clinical Practice (ICH GCP) and from the International Ethical Guidelines for Biomedical Research involving human subjects prepared by the Council for International Organisations of Medical Sciences (CIOMS) in collaboration with World Health Organisation (WHO 2002).

Good Clinical Practice (GCP) is a system of shared responsibilities between clinical investigators, industry/sponsors/monitors, institutions/ethics committees, and government regulators. Each party must understand and execute his/her responsibilities. Clinical research with investigational medicines, biologics and devices is a privilege, which comes with responsibilities for good manufacturing practice (GMP), good laboratory practice (GLP) and good clinical practice (GCP). GCP ensures the protection of clinical trial patients/subjects and that clinical trials produce accurate credible data by defining standards and responsibilities.

According to section 16 of the Medicines and Allied Substances Control Act [Chapter 15:03], "no person shall conduct a clinical trial of any medicine without prior written authorisation of the Authority, granted with approval of the Secretary". This means that all clinical trials of medicines in Zimbabwe must not be initiated until the Medicines Control Authority of Zimbabwe (MCAZ) has with the approval of the Secretary for Health and Child Welfare, authorised the conduct of the trial. Sections 16-24 of the Medicines and Allied Substances Control Act [Chapter 15:03] and Section 43-47 of Statutory Instrument 150 of 1991 stipulate in detail the legal requirements for conducting clinical trials of medicines in Zimbabwe. In addition ethical approval to conduct a clinical trial in humans should be sought from the Medical Research Council of Zimbabwe (MRCZ).

2. SCOPE

These guidelines are for those persons that wish to conduct clinical trials in human beings using medicines in Zimbabwe. They do not include veterinary clinical trials which are covered in a separate guideline.

These guidelines supercede any other guidelines in relation to clinical trials/studies using medicines unless otherwise stated e.g. Conduct of Operational Studies, Bioequivalence/Bioavailability studies, trials for HIV/AIDS vaccines.

The guidelines for conducting clinical trials are based mainly on the guidelines for Good Clinical Practice (GCP) which is an ethical and scientific standard for designing, conducting, recording and



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reporting clinical trials on medicinal products in human beings. These guidelines are directed towards all those involved in clinical trials whether for academic purposes or for the generation of data intended for inclusion in the regulatory submissions for medicinal products.

- 2.1** Compliance with this standard provides public assurance that the rights, safety and well being of subjects are protected, consistent with the principles that have their origin in the Declaration of Helsinki, that clinical trial data are credible.
- 2.2** Before a trial is initiated, foreseeable risks and inconveniences should be weighed against the anticipated benefit for the individual trial subject and society. A trial should be initiated and continued only if the anticipated benefits justify the risks.
- 2.3** The rights, safety and well-being of the trial subjects are the most important considerations and should prevail over the interests of science and society.
- 2.4** The available non-clinical and clinical information on an investigational product should be adequate to support the proposed clinical trial.
- 2.5** Clinical trials should be scientifically sound, and described in a clear, detailed protocol.
- 2.6** A trial should be conducted in compliance with the protocol that has received prior approval of the relevant authorities.
- 2.7** The medical care given to, and medical decisions made on behalf of subjects should always be the responsibility of a qualified physician or, when appropriate of a qualified dentist.
- 2.8** Each individual involved in conducting a trial should be qualified by education, training, and experience to perform his or her respective task(s).
- 2.9** Freely given informed consent should be obtained from every subject prior to clinical trial participation.
- 2.10** All clinical trial information should be recorded, handled, and stored in a way that allows its accurate reporting, interpretation and verification. Laboratory results should be recorded in a flow chart.
- 2.11** The confidentiality of records that could identify subjects should be protected, respecting privacy and confidentiality.
- 2.12** Investigational products should be manufactured, handled, and stored in accordance with applicable good manufacturing practice (GMP). They should be used in accordance with the approved protocol.
- 2.13** Systems with procedures that assure the quality of every aspect of the trial should be implemented.



3. MEDICAL INSTITUTIONS

- 3.1** Clinical trials should be conducted in medical institutions which possess adequate facilities, equipment and a well established organisation so that clinical observation evaluation and necessary procedures or treatments can be adequately and timely performed in the case of an emergency.
- 3.2** A medical institution should establish an Ethics Committee to review and approve proposed clinical trial and to monitor the conduct of the approved trials.
- 3.3** An “**Authorized Institutional Officer**” must be appointed for each medical institution. This person is responsible for the oversight of research and Ethical Committee functions and should be an official of the institution who has the legal authority to act and speak for the institution, and should be someone who can ensure that the institution will effectively fulfill its research oversight function.

The **Authorised Institutional Officer** at a medical **institution** where a clinical trial is conducted should have the following responsibilities:

- 3.3.1** To request the Ethics Committee of the medical institution to provide opinions regarding the proposed clinical trial and to approve the protocol of the trial, and to ensure that the additional approval by the MCAZ was granted.
- 3.3.2** To request the Ethics Committee of the medical institution to provide opinions regarding the revised protocol of the proposed clinical trial and to approve the amendments to the protocol trial, and to ensure that the additional approval by the MCAZ was granted.
- 3.3.3** To request investigators to take necessary measures and procedures in the event of serious adverse drug reactions.



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4. THE ETHICS COMMITTEE (EC)

- 4.1** The Ethics Committee should consist of
- a)** at least 3 professionals in the medical and scientific field with sufficient qualifications and experience.
 - b)** a legal professional
 - c)** a religious or consumer representative who is independent of the institution/trial site.

Only those members who are independent of the investigator/sponsor of the trial should make decisions.

- 4.2** The Ethics Committee should obtain all the information relating to the trial including, protocol, investigators brochure, patient consent forms, insurance for participants, current CV's for investigators and literature detailing rationale for the study.

- 4.3** The Ethics Committee should be asked to consider the following
- a)** the suitability of the investigator for the proposed trial in relation to his/her qualifications, experience, supporting staff, and available facilities, on basis of the information available to the Committee.
 - b)** the suitability of the protocol in relation to the objectives of the study. Its scientific efficiency i.e. the potential for reaching sound conclusions with the smallest possible exposure of subjects, and the justification of predictable risks and inconveniences weighed against the anticipated benefits for the subjects and/or others.
 - c)** the adequacy and completeness of the written information to be given to the subjects, their relatives, guardians and, if necessary. Legal representatives.
 - d)** the means by which initial recruitment is to be conducted and by which full information is to be given, and by which consent is to be obtained. All written information for the subject and/or legal representative must be submitted in its final form.
 - e)** provision for compensation/treatment in the case of injury or death of a subject if attribute to a clinical trial, and any insurance or indemnity to cover the liability of the investigator and sponsor.
 - f)** the extent to which investigators and subjects may be rewarded/compensated for participation.

- 4.4** The Ethics Committee should give its opinion and advice in writing clearly identifying the trial, the documents reviewed and the dates of review.



5. INFORMED CONSENT

- 5.1** The principles of informed consent in the current revision of the Helsinki Declaration should be implemented in each clinical trial.
- 5.2** Information should be given in both oral and written form whenever possible. No participant should be coerced or unduly influenced to participate or continue to participate in a trial. The participant, legal representative or guardian should be given ample opportunity to enquire about the details of the trial and be allowed sufficient time to decide whether or not they wish to participate.
The information should make clear that refusal to participate or withdrawal from the trial at any stage is without any disadvantages for the person's subsequent care.
- 5.3** The participant must be made aware and consent that personal information may be scrutinised during audit by the MCAZ and that personal information will be treated confidentially and will not be publicly available.
- 5.4** None of the information concerning the trial should contain any language that causes the participant/legal representative or guardian waive or appear to waive any legal rights or that releases or appears to release the investigator and/or sponsor from liability for negligence.
- 5.5** The participant must have access to information about procedures for compensation and treatment should he/she be injured/disabled by participating in the trial. The Statutory Instrument (S.I) 150 of 1991 of the Medicines and Allied Substances Control Regulations requires the provision of insurance cover for each per participant.
- 5.6** The language used in the oral and written information about the trial including the informed consent form should be as non-technical as practical and should be understandable to the subject or their representative. Both the English and vernacular version (e.g. Shona/Ndebele) should be made available. Evidence of back translation and who performed it will be required.
- 5.7** Prior to participation in the trial, the written informed consent form should be signed and personally dated by the subject. A witness should sign the consent form to attest that the subject/legal representative gave consent freely. A copy of the signed and dated consent form should be given to the subject/representative before trial commences.



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- 5.8** The informed consent discussion and the written informed consent discussion and the written consent form should include explanations of the following:
- a) That the trial involves research.
 - b) The purpose of the trial.
 - c) The trial treatment(s) and the probability for random assignment to each treatment.
 - d) The trial procedures to be followed, including all invasive procedures.
 - e) The subject's responsibilities.
 - f) Those aspects of the trial that are experimental.
 - g) The reasonably foreseeable risks or inconveniences to the subject and, when applicable, to an embryo, foetus, or nursing infant.
 - h) The reasonably expected benefits. When there is no intended clinical benefit to the subject, the subject should be made aware of this.
 - i) The alternative procedure(s) or course(s) of treatment that may be available to this subject, and their important potential benefits and risks.
 - j) The compensation and/or treatment available to the subject in the event of trial-related injury.
 - k) The anticipated prorated payment, if any, to the subject for participating in the trial.
 - l) The anticipated expenses, if any, to the subject for participating in the trial.
 - m) That the subject's participation in the trial is voluntary and that the subject may refuse to participate or withdraw from the trial, at any time.
 - n) That the subjects' identity will remain confidential whether results of the trial are published or not published. That the MCAZ and other authorised persons will be granted direct access to the subjects' original medical records for verification of trial procedures and data.
 - o) That should any new information that is relevant to the subjects willingness to continue participating in the trial become available it will be conveyed to them in a timely manner.
 - p) The contact persons for further information about the trial or whom to contact in the event of trial-related injury.
 - q) That the subject may be requested to terminate participation in the trial.
 - r) The expected duration of the trial.
 - s) The approximate number of subjects involved in the trial.
- 5.9** The use of placebo alone as trial treatment alone for some subjects is not acceptable where there is known treatment.



6. THE INVESTIGATOR

6.1 Investigators should satisfy the following:

- 6.1.1** The investigator should be qualified by education, training and experience to assume responsibility for the proper conduct of the trial and should provide evidence of such qualifications and experience through up to date Curriculum Vitae. The Investigator should be licensed under the Health Professions Act (Chapter 27.19).
- 6.1.2** The investigator should be thoroughly familiar with the characteristics and appropriate use of the investigational product as described in the protocol, current investigator's brochure, in the product information and in other information sources.
- 6.1.3** Have a clear understanding and willingness to obey the ethical and legal requirements of the trial.
- 6.1.4** To permit monitoring and auditing of the trial and inspection by the MCAZ or appointed representatives.
- 6.1.5** Keep a list of appropriately qualified persons to whom the investigator has delegated significant trial-related duties.
- 6.1.6** The investigator should not have been found guilty of any misconduct under the Health Professions Act and Regulations.
- 6.1.7** The **principle investigator** must be an appropriately qualified and competent person having practical experience within the relevant professional area, who is resident in the country and who is responsible for the conduct of the clinical trial at a clinical site. A principle investigator must have had previous experience as a co-investigator in at least two trials in the relevant professional area.
- 6.1.9** All investigators in a clinical trial as well as the trial monitor must have had formal training in Good Clinical Practice (GCP) within the last three years.
- 6.1.10** Upon signing the application, all parties accept the responsibility that all applicable regulations and requirements will be adhered to. Furthermore, all parties are responsible for ensuring that the trial is based on and implemented according to well – founded ethical and scientific principles, which are expressed in the Helsinki Declaration and its current revisions as well as in the local and international guidelines for GCP.

6.2 Adequate Resources

- 6.2.1** The investigator should have sufficient time to properly conduct and complete the trial within the agreed trial period.
- 6.2.2** The investigator should have adequate number of qualified staff and adequate facilities for the duration of the trial to conduct the trial properly and safely.
- 6.2.3** The investigator should ensure that all persons assisting with the trial are adequately informed about the protocol, investigational product and their trial-related duties and functions.

6.3 Medical Care of Trial Subjects



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6.3.1 A qualified medical practitioner should be responsible for all trial-related medical decisions. The qualified medical practitioner should also be licensed with the Health Professions Council. The medical care given to, and medical decisions made on behalf of the subjects must always be the responsibility of a qualified medical practitioner or when appropriate a qualified dentist registered with the Medical and Dental Practitioners Council.

6.3.2 During and following a subject's participation in a trial, the investigator should ensure adequate medical care is provided to a subject for any adverse events including clinically significant laboratory values related to the trial. The subject should be informed when medical care is needed for inter-current illness for which the investigator becomes aware.

6.4 Other Investigator Responsibilities.

6.4.1 Before initiating a trial the investigator should have the written dated approval from the MCAZ, Medical Research Council of Zimbabwe (MRCZ), and other relevant bodies. **The investigators should sign an agreement to submit periodic reports every 6 months and will be required to request for renewal of authorisation annually on the anniversary of the first approval.**

6.4.2 The investigator should conduct the trial according to the approved protocol.

6.4.3 The investigator should not implement any deviation from or changes to the protocol without prior review and approval of the MCAZ except when the changes involve only logistical or administrative aspects of the trial e.g. monitor or telephone number changes.

6.4.4 The investigator should establish the SOP for investigational products (IP).

- a)** the IP(s) should be kept by a designated person who maintain records of the delivery process and who ensures that the product is processed and stored correctly.
- b)** the designated person should maintain an inventory of the IP at the site, those used by each subject and the return to sponsor or alternative disposition of unused product(s).
- c)** the investigational product(s) should be used only on the subjects participating in the trial.
- d)** the investigator should ensure that the IP are used only in accordance with the approved protocol.
- e)** the investigator should ensure that if there is blinding, it is maintained but there should be criteria establishment for breaking of code.
- f)** the investigator or a person designated by the investigator should explain the correct use of the IP to each subject and should check at appropriate intervals during the trial, that each subject is following the instructions. In the case where the IP is administered to the subject the proper administration should be ensured.

6.5 The investigator should ensure that the subjects have signed and dated the consent form or given their consent in an acceptable form before participating in the trial.



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- 6.6** The investigator should guarantee the confidentiality of the research data, the trial subjects details and information provided by sponsor.
- 6.7** The investigator should ensure that all data is accurately collected and recorded.
- 6.8** The investigator should ensure that all serious adverse events are reported promptly to the MCAZ, sponsor and the Ethics Committee. Proper protection procedures or treatments should be administered to trial subjects with serious adverse events.
- 6.9** The investigator should submit all relevant trial data to the MCAZ and sponsor in a timely fashion for validation, auditing and inspection.

7. SPONSOR



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- 7.1** The sponsor is responsible for implementing and maintaining quality assurance and quality control systems with written SOP's to ensure that trials are conducted and data are generated, recorded and reported in compliance with the protocol, GCP and regulatory requirements.
- 7.2** The sponsor is responsible for selecting investigators according to the availability of adequate clinical trial environment facilities and resources. In addition, the sponsor should ensure that the investigator has sufficient training, qualifications and capability.
- 7.3** The sponsor should agree with investigators on the definition, establishment and assignment of responsibilities specified in the protocol. These responsibilities include data management, unblinding of treatment codes, statistical considerations and preparation of the final clinical report. Prior to the initiation of the clinical trial, the agreement between the sponsor and investigators should be in writing as part of the protocol or in a separate agreement.

The sponsor, in a written document, may agree to transfer all related activities of the clinical trial to the designated research activities of the clinical trial to the designated research institutions. However, all responsibility for the trial lies with the sponsor.

- 7.4** The sponsor should provide an up to date Investigator's brochure, which includes information about the products with respect to their physical, chemical, pharmacokinetic and pharmacodynamic properties obtained from animals as well as human subjects and currently available results of relevant clinical trials.
- 7.5** The sponsor should obtain the investigator's/institutions agreement on the following items:
- a)** the trial is to be conducted in compliance with Good Clinical Practices with the protocol agreed to by the sponsor; and to be in compliance with procedures for data recording/reporting and to permit monitoring, auditing and inspection according to the protocol.
 - b)** The sponsor and all investigators should sign and date the protocol of the trial to confirm the agreement.
- 7.6.** The sponsor should ensure that sufficient safety and efficacy data from non clinical studies and/or clinical trials are available to support human exposure by the route, at the dosages for the duration and in the trial population to be studied.

- 7.7** The sponsor should ensure that the IP's (including active comparator(s) and placebo)



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is manufactured in accordance with Good Manufacturing Practices and are adequately packed and labelled in a manner that protects the blinding if applicable. In addition the labelling should comply with the regulatory requirements.

- 7.8** The sponsor should determine for the IP's, acceptable storage temperature and conditions, storage times, reconstitution fluids and procedures and devices for product infusion if any.
- 7.9** In blinded trials, the coding system for the IP's should include a mechanism that permits rapid identification of the products in case of a medical emergency but does not permit undetectable breaks of the blinding.
- 7.10** If formulation changes are made to the IP or comparator products during the course of the clinical development, the results of pharmaceutical and pharmacokinetic profile of the product should be available to the MCAZ prior to the use of the reformulated IP in clinical trials.
- 7.11** The sponsor should appoint qualified and suitable trained individuals to monitor the trial.
- 7.12** The sponsor should provide insurance or should indemnify the investigator/institution against claims arising from the trial except for claims that arise from malpractice and/or negligence.
- 7.13** The sponsor policies and procedures should address the costs of treatment of trial subjects in the event of trial-related injuries. The sponsor should provide insurance cover for all trial subjects.
- 7.14** The financial aspects of the trial should be documented in an agreement between the sponsor and the investigator/institution.
- 7.15** The sponsor should report to the MCAZ, institutions, all adverse events occurring during the course of the trial. The sponsor should expedite reporting all serious adverse events to the Ethics Committee and the MCAZ and the sponsor and the investigators should immediately undertake appropriate and necessary measures and treatment to protect the trial subjects.
- 7.16** When a trial is prematurely terminated or suspended by the sponsor/investigators, the Ethics Committee and MCAZ/institution should be informed of the decision to terminate/suspend the trial and the reasons thereof by the sponsor/investigators.
- 7.17** Whether the trial is completed or prematurely terminated, the sponsor should submit a report to the MCAZ and institution within 30 (thirty) days.



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- 7.18** The external sponsor should strengthen local capacity for ethical, scientific review, biomedical research and provide healthcare services as described in sections 20, 21 of the International Ethical Guidelines for Biomedical Research involving Human Subjects (CIOMS 2002)

Guideline 20: Strengthening capacity for ethical and scientific review and biomedical research

Many countries lack the capacity to assess or ensure the scientific quality or ethical acceptability of biomedical research proposed or carried out in their jurisdictions. In externally sponsored collaborative research, sponsors and investigators have an ethical obligation to ensure that biomedical research projects for which they are responsible in such countries contribute effectively to national or local capacity to design and conduct biomedical research, and to provide scientific and ethical review and monitoring of such research.

Capacity building may include, but is not limited to, the following activities:

- establishing and strengthening independent and competent ethical review processes/committees.
- strengthening research capacity.
- developing technologies appropriate to health-care and biomedical research.
- training of research and health-care staff.
- educating the community from which research subjects will be drawn.

Guideline 21: Ethical obligation of external sponsors to provide health-care services.

External sponsors are ethically obliged to ensure the availability of:

- health-care services that are essential to the safe conduct of the research;
- treatment of subjects who suffer injury as a consequence of research intervention; and
- services that are a necessary part of the commitment of a sponsor to make a beneficial intervention or product developed as a result of the research reasonably available to the population or community concerned.

8. MONITOR



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- 8.1** Monitor of clinical trial is responsible for monitoring the trial. Monitoring is the act of overseeing the progress of a clinical trial, and ensuring that it is conducted, recorded, and reported in accordance with the protocol, standard operating procedures (SOPs), GCP, and the applicable regulatory requirements.
- 8.1** The Monitor should serve as the primary contact of communication between the sponsor and Investigators.
- 8.2** The Monitors should follow the sponsor's established written Standard Operating Procedures, prior to the initiation of the trial, during the conduct of the trial, and after the conclusion of the trial, to Monitor the Investigator; to verify that the Investigator and the Investigator's staff are performing the specified trial functions in accordance with the approved protocol and any other agreement between the sponsor and Investigators and have not delegated these functions to unauthorised individuals, to verify that all trial data are accurately and completely recorded and reported, and to verify that written informed consent was obtained prior to each trial subject's participation in the trial.
- 8.3.** The Monitor should verify that the space and facilities, including laboratories, equipment, and staff at the investigator's site are adequate; and that the number of the trial subjects recruited are sufficient throughout the trial.
- 8.4.** The Monitor should verify that all staff members of the trial are adequately informed of and understand the detailed procedures of the trial, and are willing to comply with regulatory requirements agreed to on trial approval.
- 8.5** The Monitor should verify if direct and prompt access is available between Investigators and the sponsor at all times during the trial.
- 8.6** The Monitor should verify the accuracy and completeness of CRF entries against the raw data, and inform the Investigator of any CRF entry error, omission or illegibility.
- 8.7** The Monitor should verify that the storage, shipping, disposition, return and record of the use of the investigational products are safe; and properly controlled and documented.
- 8.8** The Monitor should assist the investigator with respect to all the required reports.
- 8.9** The monitor should submit a written monitoring report to the sponsor after each meeting, any other related telephone conversations, and letters to or from the investigator.
- 8.10** The Monitor should assist the investigator in informing the sponsor of trial data and results.

9. CLINICAL TRIAL RECORDS AND REPORTS

- 9.1** The objective of data storage and processing is to record, store and transfer the



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information obtained from the trial subjects during the conduct of the trial, and to transform the data adequately and efficiently for retrospective validation and evaluation of the progress and conduct of the trial.

- 9.2** With respect to blinded clinical trials, the blindness should be completely maintained from the generation of random codes for allocation of treatments to the time of decision for revelation of random codes.
- 9.3** The protocol, documents, case report forms, Informed Consent Forms and other trial-related documents should be retained for at least 10 years by the sponsor; and the trial subjects documents should be retained for at least 10 years by the medical institution. The subject identification codes should be retained by the investigator and the sponsor for at least 10 years.
- 9.4** All records and their duplicates required by the Guidelines should be kept at the trial related sites for the duration of the above-mentioned retention period and should be available at all times for inspection by the MCAZ. The inspector should be allowed to photocopy or duplicate the records by other electronic and/or optical means.
- 9.5** The sponsor must keep all records related to the conduct of a clinical trial in a format that facilitates verification for the purpose of an inspection.
- 9.6** The sponsor must submit requested records within 48 hours if safety concerns arise.
- 9.7** Additionally, the MCAZ can request the submission of additional information within seven days to facilitate an inspection of a site.
- 9.8** The sponsor must maintain complete and accurate records in respect of the use of a drug in a clinical trial, including:
 - 9.8.1** A copy of all versions of the investigator's brochure for the drug;
 - 9.8.2** Records respecting each change made to the investigator's brochure, including the rationale for each change and documentation that supports each change;
 - 9.8.3** Records for all adverse events in respect of the drug that have occurred locally or internationally, including information that specifies the indication for use and the dosage form of the drug at the time of the adverse event;
 - 9.8.4** Records in respect of the enrolment of clinical trial subjects, including information sufficient to enable all clinical trial subjects to be identified and contacted in the event that the use of the drug may endanger the health of the clinical trial subjects or other persons;



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- 9.8.5** Records in respect of the shipment, receipt, disposition, return and destruction of the drug;
- 9.8.6** For each clinical trial site, an undertaking from the principle investigator that is signed and dated by the principle investigator prior to the commencement of his or her responsibilities in respect of the clinical trial, that states that the principle investigator will conduct the clinical trial in accordance with good clinical practices;
- 9.8.7** For each clinical trial site, a copy of the protocol, informed consent form and any amendment to the protocol or informed consent form that have been approved by the Research Ethics Committee and MCAZ for that clinical trial site.
- 9.9 Case Report Form (CRF)**
- 9.9.1** The Investigator should ensure that collection procedures, storage and retrieval of data meets minimum requirements for quality and facilitates verification, validation, audit and inspection. In addition, investigations and findings are accurately and completely documented in the CRF. which should be signed and dated by the authorised individuals.
- 9.9.2** Any change or correction to a CRF, as well as the process of duplicating raw data, should not obscure the original entry. Changes and corrections should be made by crossing out the old entries and should be initiated and dated by the individual who makes the correction. Entry and corrections of the electronic data should only be made by the authorised personnel. Any correction or deletion of electronic data should be documented and recorded. Reasons for the corrections should be given in every case.
- 9.9.3** In addition to the data required by the protocol, other data may be recorded on the CRF and this data should be clearly marked as additional data.
- 9.10 Trial Data**
- 9.10.1** Laboratory values with the normal reference ranges should be recorded or attached to CRF. In addition, the investigator should evaluate and comment on the laboratory values outside acceptable ranges or values that differ importantly from previous values.
- 9.10.2** Adequate security and protection should be provided in the computer system for the accuracy of the database. Any printout of the data, as well as duplicates, must be signed and dated.
- 9.10.3** The Monitor should apply appropriate methods to avoid any omission of



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the data and logically inconsistent data, any missing data identified by computer should be clearly documented and labelled.

9.11 Electronic Data

9.11.1 Validation error free data processing programmes with adequate use documentation should be used.

9.11.2 Adequate security and protection should be provided in the computer system for the accuracy of the data directly entered into the computer database. Any printout of the data, as well as duplicates, must be signed and dated.

9.11.3 Procedures for corrections made at data entry, as well as documentation of corrections in the audit records, should be provided for the electronic data processing and management system or for the network system for remote data entry.

9.12 Validation of Data

9.12.1 The sponsor should be responsible for the accuracy of the transformation of the data during the data processing. The sponsor should compare the original data, observations and findings with the processed and transformed data.

9.12.2 If data transformation is required during data processing, the method of transformation should be validated for what it purports to do. The transformation procedures should be explained in a written document.

9.12.3 The sponsor should maintain a signature list of the individuals who are authorised to make data changes, and institute an adequate security system to prevent any data change by unauthorised personnel.

9.13 Identification of Trial Subjects

9.13.1 The Investigator should keep a detailed and confidential record which can identify the trial subjects at any time.

9.13.2 The sponsor should use an unambiguous identification coding system that allows identification of all the data reported for each subject.

9.14 Progress Reports

Progress reports should be submitted in the recommended format (see Annexe I & II) every 6 months and as determined by the MCAZ.

10. STATISTICAL ANALYSIS



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- 10.1** It is recommended that a biostatistician participates in the planning, execution, analysis and other relevant aspects of clinical trials.
- 10.2 Random allocation and Blinding**
- 10.2.1** The process of random allocation of treatments to the trial subjects should be documented. The sealed random code of each trial subject should be kept by both the Investigator and the sponsor.
- 10.2.2** When a blinded trial is conducted, the circumstances of breaking the random codes should be precisely and clearly stated. The time and reason for revelation of random codes should be clearly and unambiguously recorded on the CRF.
- 10.3** The following issues should be addressed in the statistical analyses.
- 10.3.1** Statistical methods and primary clinical therapeutic end points should be described in the protocol. Any deviation(s) from the original statistical plan specified in the approved protocol should be described and justified in the final report. The possibility and timing of any planned interim analysis should also be described in the protocol. Estimation of the number of subjects planned to be enrolled and the corresponding statistical power of the trial and clinical interpretation should also be described and justified in the protocol.
- 10.3.2** The Investigator and Monitor are responsible for the quality assurance of the data and the statistician is responsible for the reliability and efficiency of data processing and management.
- 10.3.3** The results of statistical analysis should not rely solely on statistical significance but also emphasise the interpretation of the clinical significance, such as estimation of the therapeutic effect and the magnitude of the treatment difference as well as the correspondence intervals.
- 10.3.4** The statistical procedures applied to missing, unused, and surplus data should be described and justified.

11. MANAGEMENT OF INVESTIGATIONAL PRODUCTS (IPs)

- 11.1** Clinical trial investigational medicinal products must be manufactured in accordance with Good Manufacturing Practice (GMP) including Good Manufacturing Practice for Investigational Medicinal Products. This implies that the manufacture of the



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investigational product may be subject to control and inspection in the same way as in the case of marketed medicinal products.

- 11.2.** Certificates of analysis (COAs) must be provided for all investigational and comparator products.
- 11.3** Chemistry and manufacturing information provided in the clinical trial application should be presented in a concise manner and should include the following:
 - a. Drug Substance:
 - Names and Source
 - Method of Manufacture
 - Physicochemical Properties and Structure Elucidation
 - Impurities
 - Specifications and Test Methods and Batch Analyses
 - Stability and Packaging
 - b. Dosage Form:
 - Source
 - Developmental Pharmaceutics
 - Formulation and Method of Manufacture and Packaging
 - Specifications and Test Methods and Batch Analyses
 - Stability
- 11.4** If the pharmaceutical or chemical properties of the investigational product have been altered compared to those in use during animal testing or previous clinical trials, such alterations must be described and justified. This, for instance, applies to impurities and degradation products.
- 11.5** Pharmaceutical and/or chemical alterations in an investigational product that is used in an ongoing clinical trial, and that may affect the quality, safety and/or efficacy of the medicinal product must immediately be reported to the MCAZ.
- 11.6** If the composition of the medicinal product is altered, additional bioavailability or bioequivalence studies may be required.
- 11.7** In cases where an extension of the shelf life for the finished medicinal product is desired, an application for this must be submitted to the MCAZ. In such cases stability data or certificates of analysis (CoAs) from reanalysis of the relevant batches must be submitted.
- 11.8** The re-labelling of any remaining packages from previously manufactured batches must be performed in accordance with established written procedures and Good Manufacturing Practices (GMP).



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NB. Trialists may apply for exemption from some of the requirements of this section provided that such exemption shall be provided in writing by the MCAZ.

- 11.9** The management records of the investigational products should document quantities, delivery, receipt, disposition, return, and destruction of the investigational products. The Investigator should not provide the investigational products to any individual who are not trial subjects.
- 11.10** The sponsor should ensure that the investigational products are adequately packaged and labelled for clinical trial use only. In addition, the labelling should comply with the specifications specified in the protocol including at least the following information:
- 11.10.1 A statement indicating that the drug is an investigational drug to be used only by a qualified investigator
 - 11.10.2 The name, number or identifying mark of the drug
 - 11.10.3 The expiration date of the drug
 - 11.10.4 The recommended storage conditions for the drug
 - 11.10.5 The lot number of the drug
 - 11.10.6 The name and address of the sponsor
 - 11.10.7 The protocol code or identification
 - 11.10.8 The name and address of the premises where the clinical trial is to be carried out.
- 11.6** The sponsor should retain the batch samples of the investigational products until at least two years after the approval of a marketing application or after the conclusion of the clinical trial for unapproved marketing application.
- 11.7** Expired investigational products should not be used.
- 11.8** Investigators in the trial should provide information on restrictions on the uses of the IP in any country.
- 11.9** Trial medications must be stored and dispensed by the pharmacy or the pharmaceutical department at the trial site in accordance with good dispensing practices. The general principle is that investigational products used in clinical trials should be handled in the same way as registered medicines.

12. QUALITY ASSURANCE

- 12.1** In order to ensure the conclusion of the trial can be derived sequentially from the raw data, all observations findings, especially the reliability of the trial, should be subjected to re-validation.
- 12.2** Quality control procedure should be enforced to each step of data processing to



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ensure that all data are reliably and correctly processed.

1

- 12.3 It is recommended that the sponsor or the medical institution appoint individuals, who are not involved with the trial, to conduct audits independently.
- 12.4 All relevant documents specified in the guidelines, including application forms, should be made available for inspection and audit by the sponsor or by the MCAZ.
- 12.5 Trial sites, medical institutions, laboratories, and all data (including raw data) and documents should be made available for inspection by the MCAZ.

13. CLINICAL TRIAL PROTOCOL

The contents of a trial protocol should generally include the following topics.

13.1 General Information

- 13.1.1 Protocol title, protocol identifying number, and date. Any amendment(s) should also bear the amendment number(s) and date(s).
- 13.1.2 Name and address of the sponsor and monitor (if other than the sponsor).
- 13.1.3 Name and title of the person(s) authorised to sign the protocol and the protocol amendment(s) for the sponsor.
- 13.1.4 Name, title, address, and telephone number(s) of the sponsor's medical expert (or dentist when appropriate) for the trial.
- 13.1.5 Name and title of the investigator(s) who is (are) responsible for conducting the trial, and the address and telephone number(s) of the trial site(s).
- 13.1.6 Name, title, address, and telephone number(s) of the qualified physician (or dentist, if applicable), who is responsible for all trial-site related medical (or dental) decisions (if other than investigator).
- 13.1.7 Name(s) and address(es) of the clinical laboratory(ies) and other medical and/or technical department(s) and/or institutions involved in the trial

13.2 Background Information

- 13.2.1 Name and description of the investigational product(s).
- 13.2.2 A summary of findings from non clinical studies that potentially have clinical significance and from clinical trials that are relevant to the trial.
- 13.2.3 Summary of the known and potential risks and benefits, if any, to human subjects.
- 13.2.4 Description and justification for the route of administration, dosage, dosage regimen,



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and treatment period(s).

13.2.5 A statement that the trial will be conducted in compliance with the protocol, GMP, GCP and the applicable regulatory requirement(s).

13.2.6 Description of the population to be studied.

13.2.7 References to literature and data that are relevant to the trial, and that provide background for the trial.

13.3 Trial Objectives and Purpose

A detailed description of the objectives and the purpose of the trial.

13.4 Trial Design

The scientific integrity of the trial and the credibility of the data from the trial depend substantially on the trial. A description of the trial design, should include:

13.4.1 A specific statement of the primary endpoints and the secondary endpoints, if any, to be measured during the trial.

13.4.2 A description of the type/design of trial to be conducted (e.g. double-blind, placebo-controlled, parallel design) and a schematic diagram of trial design, procedures and stages.

13.4.3 Use of placebo alone as a trial treatment for trial subject is not acceptable were there is known treatment.

13.4.4 A description of the measures taken to minimise/avoid bias, including:

- a) Randomisation
- b) Blinding

13.4.5 A description of the trial treatment(s) and the dosage regimen of the investigational product(s). Also include a description of the dosage form, packaging, and labelling of the investigational product(s).

13.4.6 The expected duration of subject participation, and a description of the sequence and duration of all trial periods, including follow-up, if any.

13.4.7 A description of the “stopping rules” or “discontinuation criteria” for individual subjects, parts of trial and entire trial.

13.4.8 Accountability procedures for the investigational product(s), including the placebo(s) and comparator(s), if any.

13.4.9 Maintenance of trial treatment randomised codes and procedures for breaking codes.



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13.4.10 The identification of any data to be recorded directly on the CRFs (i.e. no prior written or electronic record of data), and to be considered to be source data.

13.5 Selection and Withdrawal of Subjects

13.5.1 Subject inclusion criteria.

13.5.2 Subject exclusion criteria.

13.5.3 Subject withdrawal criteria (i.e. terminating investigational product treatment/trial treatment) and procedures specifying:

- a) When and how to withdraw subjects from the trial/investigational product treatment.
- b) The type and timing of the data to be collected for withdrawn subjects.
- c) Whether and how subjects are to be replaced.
- d) The follow-up for subjects withdrawn from the investigational product treatment/trial treatment.

13.6 Treatment of Subjects

13.6.1 The treatment(s) to be administered, including the name(s) of all the product(s), the dose(s), the dosing schedule(s), the route/mode(s) of administration, and the treatment period(s), including the follow-up period(s) for subjects for each investigational product treatment/trial treatment group/arm of the trial.

13.6.2 Medication(s)/treatment(s) permitted (including rescue medication) and not permitted before and/or during the trial.

13.6.3 Procedures for monitoring subject compliance.

13.7 Assessment of Efficacy

13.7.1 Specifications of the efficacy parameter

13.7.2 Methods and timing for assessing, recording, and analysing of efficacy parameters.

13.8 Assessment of Safety

13.8.1 Specifications of the efficacy parameter

13.8.2 Methods and timing for assessing, recording, and analysing of efficacy parameters.

13.8.3 Procedures for eliciting reports of and for recording and reporting adverse event and intercurrent illnesses.

13.8.4 The type and duration of the follow-up o subjects after adverse events.



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13.9 Statistics

- 13.9.1** A description of the statistical methods to be employed, including timing of any planned interim analysis.
- 13.9.2** The number of subjects planned to be enrolled. In multi-centre trials, the numbers of enrolled subjects projected for each trial site should be specified. Reason for choice of sample size, including reflections on (or calculations of) the power of the trial and clinical justification.
- 13.9.3** The level of significance to be used.
- 13.9.4** Criteria for the termination of the trial.
- 13.9.5** Procedures for accounting for missing, unused and spurious data.
- 13.9.6** Procedures for reporting any deviation(s) from the original statistical plan (any deviation(s) from the original statistical plan should be described and justified in protocol and/or in the final report, as appropriate).
- 13.9.7** The selection of subjects to be included in the analyses (e.g. all randomised subjects, all dosed subjects, all eligible subjects, valuable subjects).

13.10 Direct Access to Source Data/Documents

The sponsor should ensure that it is specified in the protocol or other written agreement that the investigator(s)/institution(s) will permit trial-related monitoring, audits, Institution Review Boards (IRB)/Institution Ethical Committees (IEC) review, and regulatory inspection(s) providing direct access to source data/documents.

13.11 Quality Control and Quality Assurance of Data and Procedures

13.12 Ethics

Description of ethical considerations relating to the trial.

13.13 Data Handling and Record Keeping

13.14 Insurance of Trial Subjects

- 13.14.1** All subjects must be satisfactorily insured against possible injuries that might arise during the conduct of the clinical trial.
- 13.14.2** For all sponsor-initiated trials, a valid insurance certificate for the duration of the study must be provided prior to study initiation.
- 13.14.3** For investigator-initiated research trials, proof of malpractice insurance that covers clinical trials must be provided.

13.15 Publication Policy



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Publication policy should include a plan for the publication of the results (publishing plan).

14. CLINICAL TRIAL AMENDMENTS

- 14.1** Applications for amendments to clinical trial protocols must be submitted to the MCAZ for approval prior to their implementation.
- 14.2** The applicant must submit the original wording, revised wording, and rationale for the change including a copy of a complete protocol incorporating all amendments.
- 14.3** These amendments must also be presented to the Research Ethics Committee for approval prior to implementation.
- 14.4** Approval must be obtained for the following amendments to the clinical trial protocol:
 - Changes that affect patient selection and monitoring.
 - Changes that affect clinical efficacy and safety requirements (e.g. dosage adjustments, study procedures, etc)
 - Changes that affect patient discontinuation.
 - Changes that result in the extension of the duration of the clinical trial
 - Changes that result to the chemistry and manufacturing information that may affect drug safety and quality (For example: specifications for the drug where the limits of the test are relaxed or deleted; where a new impurity or degradation product has been identified; and, the addition of new raw materials, solvents, reagents, catalysts or any other material used in the manufacture of the drug substance.)

15. DISCONTINUANCE OF A CLINICAL TRIAL BY A SPONSOR

- 15.1** If a clinical trial is discontinued by the sponsor in its entirety or at a clinical trial site, the sponsor must inform the MCAZ no later than 15 days after the date of the discontinuance; and must:
 - 15.1.1** Provide the MCAZ with the reason/s for the discontinuance and its impact on the proposed or ongoing clinical trials in respect of the drug conducted by the sponsor;
 - 15.1.2** As soon as possible, inform all investigators of the discontinuance and of the reasons for the discontinuance, and advise them in writing of any potential risks to the health of clinical trial subjects or other persons.



16. ROLE OF MEDICINES CONTROL AUTHORITY OF ZIMBABWE (MCAZ)

16.1 Approval of Clinical Trial with the Secretary for Health and Child Welfare

No person shall conduct a clinical trial of any medicine without the prior written authorisation of the Authority, granted with the approval of the Secretary for Health and Child Welfare (Section 16 of the Medicines and Allied Substances Control Act [Chapter 15:03])

All clinical trial applications should be submitted to MCAZ for approval with Secretary for Health and Child Welfare.

16.2 Progress Reports

16.2.1 Reports of serious adverse events during the trial must be reported promptly to the MCAZ within 48 hours of occurrence. The serious adverse events (SAE) report form should be completed and detailed, information such as laboratory results submitted to enable causality assessment of the report.

16.2.2 The applicant conducting the clinical trial must submit progress reports to the MCAZ on a **six monthly basis from the date of initiation** of the clinical trial and within 30 days of the completion or termination of the clinical trial.

16.3 Inspection of the Clinical trial

The MCAZ will inspect and monitor the clinical trial periodically or as required depending on the nature of the clinical trial. The inspection will include an official review of trial documents, facilities, records and any other resources that are deemed related to the clinical trial.

16.4 Suspension and or stopping of a clinical trial

If at any stage during the clinical trial of any medicine authorised in terms of section 18 of the Medicines and Allied Substances Control Act [Chapter 15:03], the Authority is satisfied that having due regard to the initial risks, discomforts or other adverse effects caused to persons or animals taking part in the trial it is in the public interest to stop or suspend the trial. It shall seek and obtain forthwith the Secretary's written approval to stop or suspend the trial immediately, and if such approval is obtained, the Authority shall notify in writing the person conducting the trial accordingly.

16.5 Conditions for conduct of clinical trials

Any clinical trial of any medicine authorised in terms of Section 18 of the Medicines and Allied Substances Control Act [Chapter 15:03], shall be subject to such specific and general conditions as the Authority may, with the approval of the Secretary,



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impose and, for the safety of all persons or animals taking part in such trial, the person conducting the trial shall observe strictly all the conditions subject to which the trial is authorised.

17. FINAL REPORTS

- 17.1** Not later than 30 days after the completion of a clinical trial, the person who conducted the trial shall compile and submit to the Secretary through the Authority (MCAZ) a preliminary report on the ethical evaluation of the trial.
- 17.2** In addition to the report referred to above, the person who conducted the trial shall, not later than 90 days after the completion of the trial, compile and submit to the Secretary through the Authority (MCAZ) a comprehensive report or any serious or adverse effects or reaction established by the trial. Section 24 of the Medicines and Allied Substances Control Act [Chapter 15:03] refers.

NB: Final report content should also include information on the checklist and flow diagram of the CONSORT (Consolidated Standards of Reporting Trials). The CONSORT statement was intended to improve the report on a randomised-controlled



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trial (RCT), enabling readers to understand a trial's conduct and to assess the validity of its results.

The MCAZ has adopted use of the CONSORT statement for reporting of all clinical trials and operational research studies. *Please see summary of the CONSORT statement, checklist table 1 and flow diagram 1 below:*

The CONSORT Statement: Revised Recommendations for Improving the Quality of Reports of Parallel-Group Randomised Trials, David Moher, MSc; Kenneth F. Schulz, PhD; and Douglas Altman, DSc, for the CONSORT Group.

To comprehend the results of a randomised controlled trial (RTC), readers must understand its design, conduct, analysis, and interpretation. That goal can be achieved only through complete transparency from authors. Despite several decades of educational efforts, the reporting of RCTs needs improvement. Investigators and editors developed the original CONSORT (Consolidated Standards of Reporting Trials) statement to help authors improve reporting by using a checklist and flow diagram. The revised CONSORT statement presented in this paper incorporates new evidence and addresses some criticisms of the original statement.

The checklist items pertain to the content of the Title, Abstract, Introduction, Methods, Results and Discussion. The revised checklist includes 22 items selected because empirical evidence indicates that not reporting the information is associated with biased estimates of treatment effect or because the information is essential to judge the reliability of relevance of the findings. We intended the flow diagram to depict the passage of participants through an RCT. The revised flow diagram depicts information from four stages of a trial (enrolment, intervention allocation, follow-up, and analysis). The diagram explicitly includes the number of participants, for each intervention group, that are included in the primary data analysis. Inclusion of these numbers allows the reader to judge whether the authors have performed an intention-to-treat analysis.

In sum, the CONSORT statement is intended to improve the reporting of an RCT, enabling readers to understand a trial's conduct and to assess the validity of its results.

Ann Intern Med, 2001; 134:657-662. Also published in JAMA (April 18, 2001 and The Lancet (April 14, 2001)

Annexe I: Checklist of Items to Include When Reporting a Randomised Trial

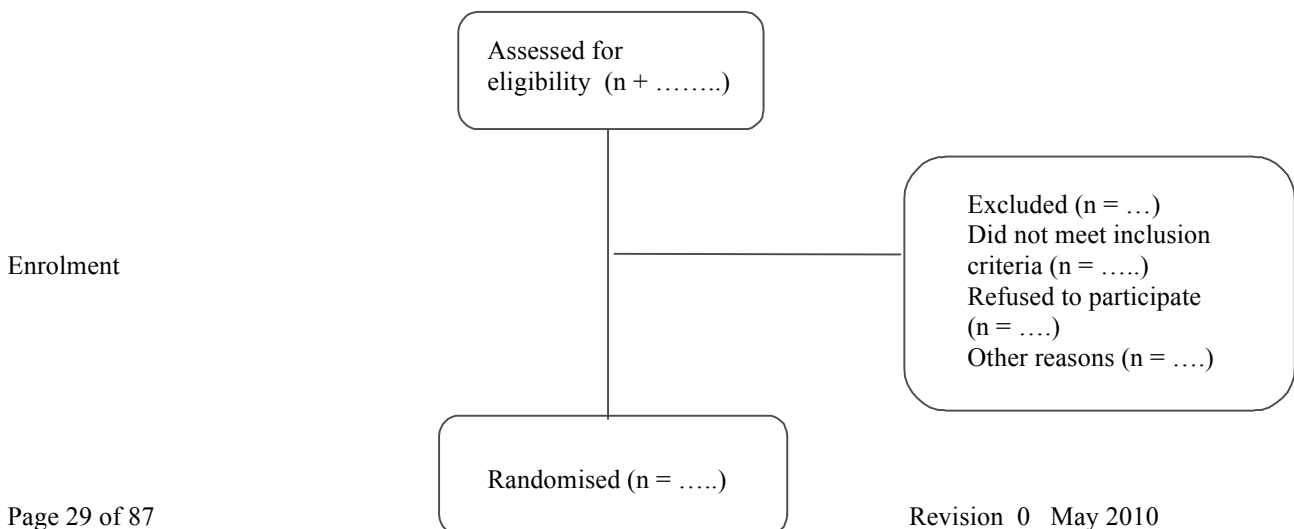
Paper Section & Topic	Item Number	Descriptor	Reported on Page Number
Title and Abstract	1	How participants were allocated to intervention (e.g. "random allocation," "randomised", or "randomly assigned")	
Introduction Background	2	Scientific background and explanation of rationale	
Methods Participants Interventions	3	Eligibility criteria for participants and settings and locations where the data were collected.	
Objectives	4	Precise details of the interventions intended for each group and how and when they were actually administered.	
Outcomes	5	Specific objectives and hypothesis	
Sample Size	6	Clearly defined primary and secondary outcome measures and, when applicable any methods used to enhance the quality of measurements (e.g. multiple observations, training of assessors.)	
Randomisation	7	How sample size was determined and, when applicable, explanation of any interim analyses and stopping rules.	
	8	Method used to generate the random allocation sequence, including details	



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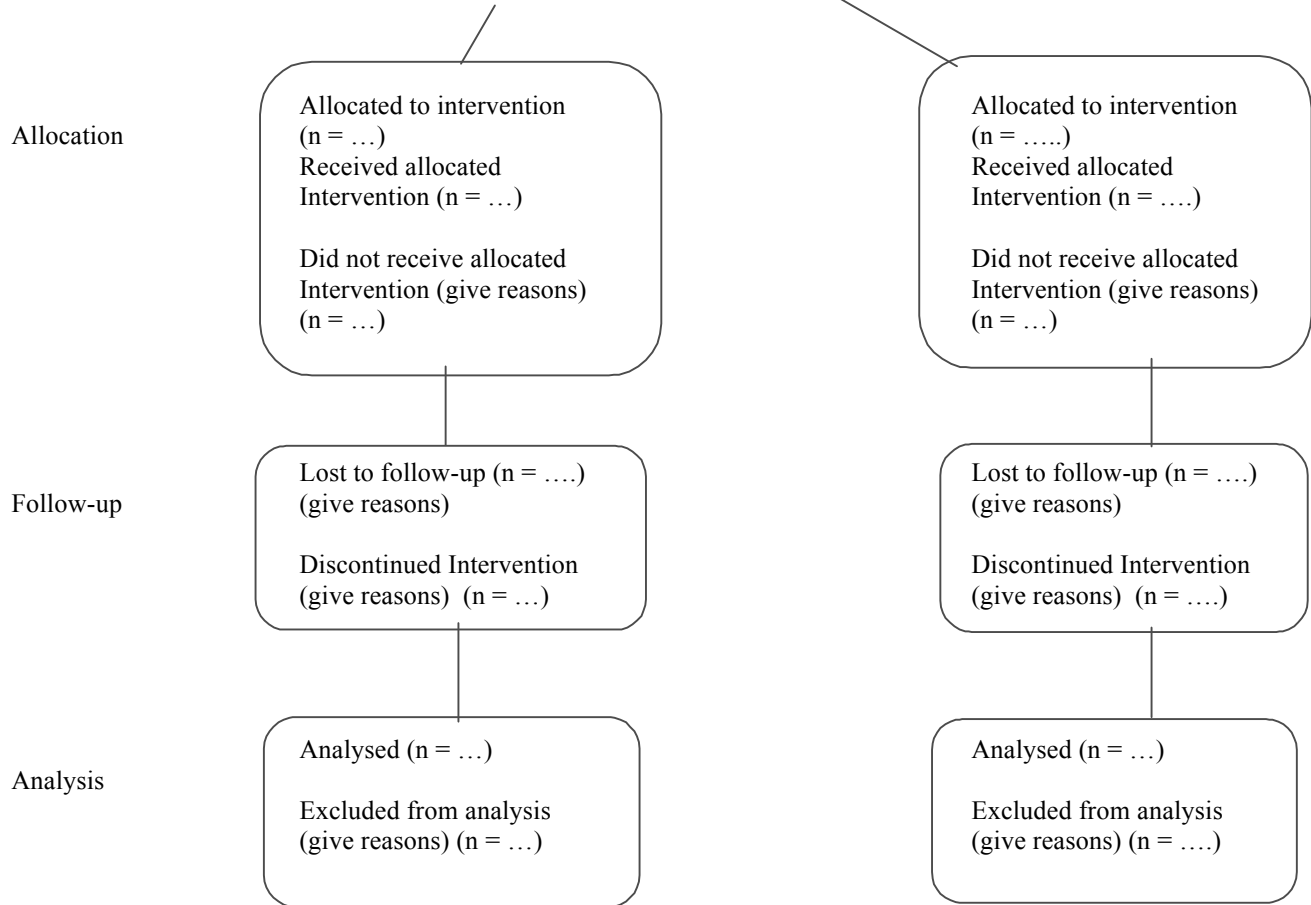
Sequence generation Allocation Concealment	9	of any restriction (e.g. blocking, stratification). Method used to implement the random allocation sequence (e.g. numbered containers or central telephone), clarifying whether the sequence was concealed until interventions were assigned.
Implementation	10	Who generated the allocation sequence, who enrolled participants, and who assigned participants to their groups.
Blinding (masking)	11	Whether or not participants, those administering the interventions and those assessing the outcomes were blinded to group assignment. If done, how the success of blinding was evaluated.
Statistical methods	12	Statistical methods used to compare groups for primary outcome(s): methods for additional analyses, such as sub group analyses and adjusted analyses.
Results Participant Flow	13	Flow of participants through each stage (a diagram is strongly recommended). Specifically, for each group report the number of participants randomly assigned, receiving intended treatment, completing the study protocol, and analysed for the primary outcome. Describe protocol deviations from study as planned together with reasons.
Recruitment	14	Dates defining the periods of recruitment and follow-up.
Baseline Data	15	Baseline demographic and clinical characteristics of each group.
Numbers analysed	16	Number of participants (denominator) in each group included in each analysis and whether the analysis was by "intention to treat". State the results in absolute numbers when feasible (e.g. 10 of 20, not 50%).
Outcomes and estimation	17	For each primary and secondary outcome, a summary of results for each group and the estimated effect size and its precision (e.g. 95% confidence interval).
Ancillary Analyses	18	Address multiplicity by reporting any other analyses performed, including subgroup analyses and adjusted analyses, indicating those prespecified and those explanatory.
Adverse events	19	All important adverse events or side effects in each intervention group.
Discussion Interpretation	20	Interpretation of the results, taking into account study hypotheses, sources of potential bias or imprecision, and the dangers associated with multiplicity of analyses and outcomes.
Generalisability	21	Generalisability (external validity) of the trial findings.
Overall evidence	22	General interpretation of the results in the context of current evidence.

Annexe II; Flow diagram of the progress through the phases of a randomised trial (enrolment, intervention allocation, follow-up, and data analysis).





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18. APPLICATION FOR AND APPROVAL OF CLINICAL TRIALS

18.1 Application forms MC10 to conduct a clinical trial in Zimbabwe are available from the MCAZ on request or on the website www.mcaz.co.zw

18.2 Completed MC10 application forms in duplicate should be submitted together with all relevant information including cover sheet, checklist, and application fee to the:

***The Director-General
Medicines Control Authority of Zimbabwe
106 Baines Avenue
P O Box 10559
Harare
Zimbabwe***



MEDICINES CONTROL AUTHORITY OF ZIMBABWE

Tel: +263 4 736981-5 or +263 4 708255 or +263 4 792165

Fax: +263-4-736980

E-mail: mcaz@africaonline.co.zw

- 18.3** The application fees for conducting a clinical trial are subject to change from time to time as determined by the Authority. These are available on request or on the website
- 18.4** If after due consideration, the Authority is satisfied that the application should be granted, it shall consult with, and obtain from the Secretary written approval of the clinical trial, and thereafter issue written authorisation in the prescribed form to the applicant to conduct the trial.
- 18.5** Any person who is aggrieved by a decision of the Secretary not to grant written approval for the conduct of a clinical trial may appeal to the Minister, whose decision shall be final.

19. SERIOUS ADVERSE EVENTS (SAEs) REPORTING

19.1 Responsibilities of Sponsors, Investigators, & Clinical Sites

The sponsor of a clinical trial and investigators participating in a clinical trial are responsible for proper reporting of Serious Adverse Events (SAEs). The purpose of reporting SAEs is to better understand the toxicity and safety of investigational products. Reporting and monitoring of SAEs is required to alert the MCAZ, sponsor, and clinical investigators of real and potential volunteer safety issues. The MCAZ will carefully review the SAE Report and use this information to monitor the investigational product's toxicity profile and volunteer safety.

Serious adverse events data provide the MCAZ and investigators with an early toxicity profile of an investigational product. The toxicity profile is an early warning system of potentially serious events which may occur with the use of an investigational product. This information might also be used during the application for registration of a new medicine



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review to determine if a product is safe for marketing. If a product is approved the safety information reported by the clinical sites during the clinical trial phase of product development will have contributed to the “adverse reaction” section of the Product Package Insert.

The Serious Adverse Events (SAE) Form must be completed and submitted to MCAZ as soon as possible (within 24-48 hours) after the site becomes aware of an event. MCAZ may need to contact the clinical site for additional information regarding the SAE. MCAZ will maintain all SAE reports confidential on file and in a regulatory database.

19.2 Follow-up Information

For the circumstances listed below, or as requested by MCAZ, clinical sites are required to submit follow-up information as soon as it becomes available. Additional information may include copies of diagnostic test results, laboratory reports, or medical record progress notes. All additional information should be clearly marked as update information and should include the Protocol Number and Volunteer ID Number.

19.2.1 Changes to Relationship Assessment

The clinical site obtains new information which changes the site investigator’s assessment of the relationship between the event and Investigational Product.

19.2.2 Updated Death Information

The clinical site obtains new information from the Death Certificate or autopsy results after an SAE Form is submitted. This pertains to deaths initially reported with limited or preliminary information.

19.2.3 HIV Disease Progression

The clinical site should only submit an Update SAE Form for HIV disease progression as follow-up to a previously reported HIV infection. This would include changes in immunologic status, new onset of opportunistic infection (OI) or progression of HIV infection to a severe or life-threatening status.

19.3 Recurrent Events

Serious Adverse Event (SAEs) recurring in the same volunteer on a particular protocol are only reportable to MCAZ under the following circumstances:

1. Recurrent episode is attributed to a NEW ETIOLOGY, or
2. Recurrent episode has progressed to a higher reportable toxicity grade level.

19.4 Means of Reporting Serious Adverse Event (SAEs)

Serious Adverse Events (SAEs) that meet reporting requirements must be reported on the completed SAE forms and submitted to the MCAZ by MCAZ office fax, e-mail or hand delivered to the offices on the following address:



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Medicines Control Authority of Zimbabwe (MCAZ)
106 Baines Avenue
P O Box 10559
Harare

Tel: +263-4-736981-5
Fax: +263-4-736980
E-mail: mcaz@africaonline.co.zw

19.5 INSTRUCTIONS FOR COMPLETING THE SERIOUS ADVERSE EVENT (SAE) FORM

HEADER INFORMATION

- Box:** Do Not Write in this Box. This is for MCAZ Office use only.
- Site Report Date:** Enter the date the SAE Form was completed by the site.
- Site Awareness Date:** Enter the date the site first became aware OR was first notified of the SAE.
- Event Previously Reported:** Tick the appropriate response that indicates whether or not this event has been previously reported on an SAE form.
- Clinical Site:** Print the name of the clinical trial title reference
- Telephone Number:** Provide the most appropriate telephone number should the MCAZ Office need to contact the site to obtain additional information
- Completed by:** Print the name and title of the person filling out the SAE Form
- Protocol Number:** Enter the trial protocol number that this volunteer is currently enrolled in
- Volunteer ID Number:** Enter the volunteer ID Number used in the trial to identify the trial volunteer
- Age:** Enter the age of the volunteer and circle the appropriate units
- Sex:** Enter the appropriate sex of the volunteer.



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ITEM 1 Enter one (1) primary reason this SAE is being reported

ITEM 2

Reportable SAE: Enter a key word, laboratory parameter, diagnosis or cause of death on the line provided i.e. the SAE

Toxicity Grade: Enter a toxicity grade (1-5) to indicate the severity of the event being reported. There are defined as 1= mild, 2= moderate, 3= severe, 4= life-threatening, 5= death

ITEM 3

SAE Onset Date: Enter the date when the SAE first occurred at this toxicity grade level. (For SAEs, which are lab abnormalities, use the specimen collection date).

Study Week: Enter the week of study (counting from enrolment) during which the event occurred.

ITEM 4

Visit Number: Enter the visit number when the SAE was first assessed.

If Unscheduled Visit:

Record the two digit Visit Code for the most recent scheduled visit if applicable.

Note: Use this code even when that scheduled visit was not completed.

Use the guide below to complete the third box (after the decimal point).

Num Visit Type

1. First Unscheduled Visit after the most recent scheduled visit.
2. Second Unscheduled Visit after the most recent scheduled visit.

Identified Post-Study: If this serious Adverse Event has been identified by the site in the Post-Study period, then Study Week and Visit Number do not need to be completed.

ITEM 5

A. Vaccine Products: Sequentially list the dates of all immunizations received by the volunteer. For protocols where a “dose” of vaccine product consists of sequential immunizations, include the schedule of administration in item #7 or in an attached summary.

B. Non-Vaccine Products:

Start Date: Enter the Initial Date that the volunteer began taking the Investigational Product.

Date Last Administered: Enter the Last Date that the volunteer received the Investigational Product. If the volunteer is being continued on the Investigational Product, this date field should be left blank.

Dose, route schedule at SAE onset: Enter the dose, route and schedule that was administered at the time of the SAE onset.

ITEM 6

Check the appropriate response that represents the management of the study treatment as a result of the SAE.

ITEM 7

Summarize the event in the space provided, or attach a narrative summary. Include all relevant information and details surrounding the event. Also include the **outcome of the SAE** i.e. if patient recovered or not, or fatal.



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- Death, Cancer, Congenital anomaly/Birth defect, Permanent disability/Incapacity, Overdose or error in administration, HIV Infection, Immune dysfunction, Grade 3 or 4 event, Grade 1 or 2 event, Recurrent event, Other, Other

2. REPORTABLE SAE (Use Key Word, Diagnosis, Cause of Death, Lab Parameter) TOXICITY GRADE (1-5) defined as 1= mild, 2= moderate, 3= severe, 4= life-threatening, 5= death

3. SAE ONSET DATE: DDMMYY STUDY WEEK: Yes No

4. VISIT NUMBER: IDENTIFIED POST-STUDY: Yes No

5. INVESTIGATIONAL PRODUCT

A. VACCINE PRODUCTS (List ALL immunization date -DDMM\YYYY)

- 1-8 numbered blank lines for vaccine products

B. NON-VACCINE PRODUCTS

Start Date: DDMMYY Date Last Administered or Tx End Date: DDMMYY

Dose, route, schedule at SAE onset:

6. MANAGEMENT OF STUDY TREATMENT (Check One Response)

- Continued, Temporarily withheld, Off Investigational Product at SAE onset or treatment course completed, Reduced dose or schedule, Permanently discontinued

7. EVENT SUMMARY

Include clinical history of event, associated signs and symptoms, alternative aetiologies being considered, medical management, test results, and relevant past medical history below, or attach summary.

Blank lines for event summary

OUTCOME OF SAE:

Blank line for outcome of SAE

8. CONCOMITANT MEDICATIONS

List ALL non-study Concomitant Medications being taken one month prior to SAE onset below, or attach a copy of the medication profile.

- 1-6 numbered blank lines for concomitant medications



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9. RELEVANT LABORATORY TESTS

Complete the table below, or send copies of data forms or other laboratory slips with equivalent information.

Laboratory Test	Abnormal Result	Site Normal Range	Collection Date (DD\MM\YYYY)	Lab Value Previous or subsequent to this event	Collection Date (DD\MM\YYYY)

10. PHYSICIAN ASSESSMENT AND SIGNATURE

Relationship of SAE to Investigational Product: (Check <u>One</u> Response)	
<input type="checkbox"/> Definitely	<input type="checkbox"/> Probably
<input type="checkbox"/> Possibly	<input type="checkbox"/> Not Related
Physician Signature: _____ Signature indicates review and approval of data provided	Date: ____ \ ____ \ ____ - ____ D D M M Y Y Y Y
Physician Name Printed: _____	

B. APPENDICES

APPENDIX 1: REQUIREMENTS WHEN SUBMITTING AN APPLICATION TO CONDUCT A CLINICAL TRIAL:

- I. Covering letter*
- ii. Cover sheet*
- iii. Checklist*
- iv. Completed Application form (MC10) to be submitted in triplicate*
- v. All documents and electronic copies to be submitted in duplicate*
- vi. Final version of the Clinical Trial Protocol*
- vii. Patient Information leaflet and Informed Consent form*
- viii. Investigators Brochure and/or Package Insert*
- ix. Signed investigator(s) CV(s) in required format*
- x. Signed declaration by Principal investigator(s)*
- xi. Signed joint declaration by Sponsor/National Principal investigator*



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- xii. *Signed declaration by Co- or Sub-investigators*
- xiii. *Signed declaration by regional monitor and/or study co-ordinator*
- xiv. *Indemnity and Insurance Certificate and/or*
- xv. *Proof of Malpractice insurance of trialist(s)*
- xvi. *Ethics Committee(s) approval or*
- xvii. *Copy of letter submitted to Ethics Committee(s)*
- xviii. *Diskettes to be submitted in Microsoft Word format*
- xix. *Financial declaration by Sponsor and Principle investigator*
- xx. *Electronic copies to be submitted in Microsoft Word format*



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**APPENDIX 2: CHECKLIST OF REQUIRED DOCUMENTATION
ACCOMPANYING APPLICATION FOR APPROVAL OF CLINICAL TRIAL**

To be completed by Applicants for all Clinical Trials

COVER SHEET

Study Title:

Protocol No:

Version No: **Date of Protocol:**

Study Drug:

Ref number (if applicable):

Ref number(s) of comparator drug(s) (if applicable):

Ref number(s) of concomitant drug(s) (if applicable):

Date(s) MCC approval of previous protocol(s):

Sponsor:

Applicant:

Contact Person:

Address:

Telephone Number: **Fax Number:**

Cell Number:

E-mail address:

FOR OFFICIAL USE

Date original application received:

Tracking No:

Application fee paid:

Signature: **Date:**

ACKNOWLEDGEMENT OF RECEIPT OF APPLICATION (Contact details to be completed by the applicant). Whole cover sheet to be faxed to applicant once details in block above are completed.

Contact Details: Name: **Fax No.:**

Receipt of new application is hereby acknowledged. **Date:**

Signature (of recipient): **Name:**

CHECKLIST



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- COVERING LETTER
 - FULLY COMPLETED APPLICATION (SECTIONS 1–3)
 - PROTOCOL (INCLUDING RELEVANT QUESTIONNAIRES, ETC.)
 - PATIENT INFORMATION LEAFLET(S) AND INFORMED CONSENT(S)
 - INVESTIGATORS BROCHURE AND / OR ALL PACKAGE INSERT(S)
 - INVESTIGATOR'S CV(S) IN REQUIRED FORMAT
 - SIGNED DECLARATION(S) BY INVESTIGATOR(S)
 - CV(S) AND SIGNED DECLARATION(S) BY STUDY CO-ORDINATOR AND/OR MONITOR
 - CERTIFICATE(S) OF ANALYSIS
 - INSURANCE CERTIFICATE
- AND IF NECESSARY:**
- LETTER ENDORSING GENERIC INSURANCE CERTIFICATE
 - ETHICS APPROVAL
- OR**
- COPY OF LETTER APPLYING FOR ETHICS COMMITTEE APPROVAL
 - COPY/IES OF RECRUITMENT ADVERTISEMENT(S) (IF APPLICABLE)
 - FINANCIAL DECLARATION (SPONSOR AND NATIONAL PI)

Electronic versions of the application form (Sections 1 –3), the protocol, the investigator's brochure and/or other relevant documents:

- LABELLED DISKETTE/CD-ROM (MSWORD OR RICH TEXT FORMAT)

List of files submitted on diskette/CD-ROM:

NB: INCOMPLETE APPLICATIONS WILL NOT BE PROCESSED



APPENDIX 3: DECLARATION BY APPLICANT

I/We, the undersigned have submitted all requested and required documentation, and have disclosed all information which may influence the approval of this application.

I/We, the undersigned, hereby declare that all information contained in, or referenced by, this application is complete and accurate and is not false or misleading.

I/We, the undersigned, agree to ensure that if the above-said clinical trial is approved, it will be conducted according to the submitted protocol and all applicable legal, ethical and regulatory requirements.

Applicant (local contact)

Date

National Principal Investigator /
National Co-coordinator /
Other (state designation)

Date



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APPENDIX 4: APPLICATION FORM MC10

MEDICINES AND ALLIED SUBSTANCES CONTROL ACT [CHAPTER 15:03]
APPLICATION FOR AUTHORISATION TO CONDUCT A
CLINICAL TRIAL
(To be submitted in triplicate)

- 1. Particulars of applicant
If an individual: Full names
Date and place of birth
Qualifications
Address (Home)
(Business)
If a company: Name of company
Physical Address
Registered office
Postal Address
Telephone Number
Position of person in the company who is making the application on behalf of the company
State the main field of manufacture of the company if applicable
2. State the name of the drug, its chemical composition, graphic and empirical formulae, animal pharmacology, toxicity and teratology as well as any clinical or field trials in humans or animals, or any other relevant information and supply reports, if any
3. State any adverse or possible reactions to the drug
4. State therapeutic effects of the drug
5. (a) Has the drug been registered in the country of origin? YES/NO* If YES a valid certificate of registration in respect of such drug issued by the appropriate authority established for the registration of drugs in the country of origin shall accompany this application.
If NO state details
(b) Have clinical trials been conducted in the country of origin" YES/NO*
If YES state details
If NO give reasons why



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(c) Has an application for registration of the drug been made in any other country? YES/NO*
If YES state details including the date on which the application was lodged.

.....

(d) Has the drug been registered in any other country? YES/NO*

If YES state details

(e) Has the registration of the drug been rejected, or refused, deferred or cancelled in any country? YES/NO*

If YES, state details

(f) What is the status of the drug in Zimbabwe?

Tick (✓) whichever is appropriate

Registered

Unregistered

Application for registration has been submitted

Three stacked empty boxes for tick marks.

6. State the name(s), address(es) and telephone number(s) and qualifications of the person(s) who will conduct the trial

Table with 4 columns: Name, Qualifications, Address and telephone number (Business), Address and telephone number (Home). Includes dotted lines for data entry.

7. State the name, physical address and telephone number of the institution or places where the trial will be conducted.....

8. State the purpose of the trial and the reasons thereof

9. State the time period for the trial

10. Description of the type of trial (e.g. controlled, open) trial design (e.g. parallel groups, crossover technique), blind technique (e.g. double blind, simple blind) randomisation (e.g. method and procedure) or any other type of trial

11. Description of participants (e.g. age group of persons or animals, type or class of persons or animals, sex, etc).....

12. Criteria for inclusion or exclusion of participants



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- 13. Number of participants expected to take part and a justification thereof (e.g. based on statistical considerations)
14. Administration route, dosage, dosage interval and period for the drug being tested and the drug being used as a control
15. Control groups (placebo, other therapy, etc)
16. (a) State whether any other drug will be given concomitantly, YES/NO*
(b) State whether a person already on another drug will be given the experimental drug at the same time or whether the participant will be taken off the other drug:
17. Recording of effects: give a description of the methods of recordings and times of recordings
18. State clinical and laboratory tests, pharmacokinetic analysis, etc, that are to be carried out
19. State the method of recording adverse reactions and provisions for dealing with same and other complications
20. State antidote
21. State the procedure for the keeping of participants lists and participants records for each participant taking part in the trial
22. State where the trial code will be kept and how it can be broken in the event of an emergency
23. State the measures to be implemented to ensure that safe handling of drugs and to promote and control compliances with the prescribed instructions
24. Evaluation of results, state the description of methodology (e.g. statistical methods)
25. State how the persons or owners of animals are to be informed about the trial



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26. State how staff involved are to be informed about the way the trial is to be conducted and about the procedures for drug usage and administration and what to do in an emergency.

.....

27. State whether there are any ethical or moral considerations relating to the trial, giving details

.....

.....

28. State the name and address of the company who will insure all the participants in the proposed trial ++

.....

29. State the amount of insurance in respect of each participant

30. State the quantity of the drug for which exemption is required if the drug is not registered

.....

31. Particulars of persons who will take part in the clinical trial +++

.....

	Name	Occupation	Address	Date and Place of birth
--	-------------	-------------------	----------------	--------------------------------

1.

2.

3.

32. Particulars of animals that will take part in the clinical trials.

Kind and breed of animal

.....

Age of animal, if known

Name and addresses of owners of animals

	Name	Address
--	-------------	----------------

1.

2.

3.



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33. Attached is a sample of the drug, together with methods of analysis and storage conditions.

Date
Signature of applicant

Countersignature of medical superintendent or senior medical officer if the clinical trial is to be conducted in a hospital or a medical institution. ⁺⁺⁺⁺

Date

Notes

**Delete the inapplicable*

- +, item 21: Records should permit easy identification of individual participants.
- ++, item 28: A letter from the insurance company shall be attached to the application indicating the insurance company's consent to the proposed insurance and a copy of the proposed insurance policy.
- +++ , item 31: The consent of each person or the guardian of such person who will participate in the trial is required to be attached to the application in Form D.C. 17.
The consent of each owner of an animal which will participate in the trial is required to be attached to the application in Form D.C. 18.
- ++++, This item should be countersigned by a veterinary surgeon if the trial is to be conducted in a veterinary hospital.

FOR OFFICIAL USE ONLY

1. Director-General's comments on the application

2. Authority' comments on the application

3. Application approved/disapproved by the Secretary.

Comments

Date
Secretary for Health

APPENDIX 5: ADMINISTRATIVE AND SUPPLEMENTARY DETAILS



MEDICINES CONTROL AUTHORITY OF ZIMBABWE

Title:

Protocol Number/identification:

Date of final protocol:

Part 1: CONTACT DETAILS

(NAME/ADDRESS/TEL/CELL/FAX/E-MAIL)

1.1 Applicant: (as in Section 1)

1.2 Sponsor: (as in Section 1)

1.3 If no sponsor, person or organisation initiating, managing, and / or funding the clinical trial:

1.4 Local Contact Person for correspondence:

1.5 National Principal Investigator/Coordinator: (or equivalent person)

1.6 International Principal Investigator: (if applicable)

1.7 Regional Monitor:

1.8 Study Coordinator:

Part 2: DETAILS OF INVESTIGATIONAL PRODUCT (S)

2.1 Name(s) and details of investigational product(s) to be used in trial:

[A summary of the chemistry and manufacturing data, formulation, composition, excipients and strength should be provided. Complete chemistry and manufacturing data should be included in the investigator's brochure. Product(s) registration number(s) and date(s) of registration, if applicable, should be included]

2.2 Name(s) and details (as above) of comparator product(s) and product registration number(s) and date(s) of registration if applicable:

[As in 2.1, where applicable. Package inserts for registered comparator products should be included]

2.3 Name(s) and details (as above) of concomitant medication(s) including rescue medications which are required in the protocol, and product registration number(s) if applicable:

[As in 2.1, where applicable. Package inserts for registered products should be included]

2.4 Estimated Quantity of Trial Material (each drug detailed separately) for which exemption will be required:

2.5 If any of the above drugs are marketed locally, explain whether locally-sourced products will be used in the trial:

2.6 Details of receipt of drugs from supplier, packaging, storage and shelf-life and dispensing:

2.7 Date (or envisaged date) of application for registration of trial medication:

*[Provide an explanation if registration is **not** envisaged]*



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2.8 Registration status of trial medication, for the indication to be tested in this trial, in other countries:

[i.e. Country: date registered / date applied for / date registration refused / date registration withdrawn by applicant / date registration cancelled by regulatory authority) [Attach as an appendix if necessary]

Part 3: DETAILS OF TRIALIST (S) AND TRIAL SITE (S)

3.1 Details of Investigator(s):

[Designation and title of principal investigators / investigators] Include Name/Address/Tel/Cell/Fax/E-Mail]

3.2 Current work-load of Investigator(s):

[Number of studies currently undertaken by trialist(s) as principal and/or co- or sub-investigator, and the total number of patients represented by these studies. Time-commitments of researcher(s) in relation to clinical trial work and non-trial work]

Recommended format for Investigator work-load:

Investigator (Name and designation):			
Total number of current studies (all stages) on specified date	Number	Date	
Total number of patients / participants for which responsible on specified date	Number	Date	
ESTIMATED TIME PER WEEK [168 hours denominator]		Hours	%
Clinical trials	Clinical work (patient contact)		
	Administrative work		
Organisation (Practice / university / employer)	Clinical work		
	Administrative work		
Teaching	Preparation / evaluation		
	Lectures / tutorials		



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Writing up work for publication / presentation			
Reading / sourcing information (e.g. internet searches)			
Other (specify)			

3.3 Details of Trial Site(s):

[Name of site, physical address, contact details, contact person, etc]

3.4 Capacity of Trial Site(s):

[Number of staff, names, qualifications, experience -- including study coordinators, site facilities, emergency facilities, other relevant infrastructure]

Part 4: PARTICIPANTS (TRIAL SUBJECTS)

4.1 Number of local participants:

4.2 Total number of participants worldwide:

4.2 Total enrolment in each local site/centre:

[If competitive enrolment, state minimum and maximum number per site.]

4.3 Volunteer base from which local participants will be drawn:

4.4 Retrospective data indicating potential of each site to recruit required number of participants within envisaged duration of trial:

[Attach as an appendix if necessary]

Part 5: OTHER DETAILS

5.1 Provide an explanation if the trial is to be conducted locally only and not in the host country of the applicant / sponsor:

5.2 Estimated duration of trial:

5.3 Details of other Regulatory Authorities to which applications to conduct this trial have been submitted, but approval has not yet been granted. Include date(s) of application:

5.4 Details of other Regulatory Authorities which have approved this trial. Include date(s) of approval and number of sites per country:

5.5 Details of other Regulatory Authorities or Research Ethics Committees which have rejected this trial, if applicable, and provide reasons for the rejection:

5.6 Details of and reasons for this trial having been suspended at any stage by other Regulatory Authorities, if applicable:

5.7 Details if this trial is being undertaken in other SADC countries, any other country in Africa, or any country where there is no regulatory control of clinical trials:

5.8 Previous studies using this agent which have been approved by the MCAZ:

Approval number:

Study title:

Protocol number:



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Date of approval:
Principal Investigator:
Date(s) of progress report(s):
Date of final report:

5.9 If any sub-studies are proposed as part of this protocol, indicate whether these will also be conducted locally. If not, please explain:

Part 6: ETHICS

- 6.1 Research Ethics Committee responsible for each site, date of approval or date of application:
[Attach copy of response(s) made by, and/or conditions required by Research ethics Committee(s) if available]
- 6.2 State which Good Clinical Practice (GCP) guidelines are being followed:
- 6.3 Details of capacity building component of the trial, if any:
- 6.4 Details of GCP training of investigators, monitors, study co-ordinators in terms of conducting this trial:
- 6.5 Detailed safety and monitoring plan for each site: *[Attach as an appendix if necessary]*
- 6.6 Details of trial insurance:[e.g. insurer, policy holder, policy number, insurance cover, period of validity]
- 6.7 Details of possible conflict of interest of any person(s)/organisation(s) who/which will be involved in the trial:
- 6.8 Remuneration to be received by investigators, trial participants or others:
[Indicate breakdown of costs to be covered, if applicable. Indicate compensation to be received by participants for travel and incidental expenses.]

Part 7 – APPLICANT’S REPORT / PRESENTATION

***[Please use Black 12 point Arial Font, using MSWord for the electronic version]
[The following section should be fully completed]***

1. Title:
2. Protocol Number/Identification:



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3. Summary of the Rationale for study:
[Provide a brief description of the rationale and relevance of the study, e.g. why should this trial be undertaken at all?]
4. Summary of the Background Information:
[Provide a brief statement on each of the following:]
5. Disease / problem
6. Local relevance (e.g. local epidemiology)
7. Properties of trial drug (e.g. pharmacological / chemical / pharmaceutical)
8. Pre-clinical findings: (e.g. laboratory / animal / toxicity / mutagenicity, etc)
9. Clinical findings (e.g. pharmacokinetics, safety, tolerability, efficacy)
10. Objectives of study:
[These should be clearly listed and justified]
11. Study design:
[These should be clearly described and each component justified. Include study phase, use of placebo, dosages, randomisation, blinding, duration of treatment, etc.]
12. Trial Participants:
[Number of participants; ability to enrol required number within stated time, etc]
13. Criteria for selection, eligibility and enrolment:
[Inclusion and exclusion criteria listed and justified]
14. Treatment modalities and regimens, drug accountability:
[These should be clearly explained and justified for all participant groups/arms, e.g. route of administration, dose, etc. Clearly describe drug accountability]
15. Outcome measurements/variables:
[These should be clearly stated and justified]
16. Adverse events:
[Measures to monitor assess and report all adverse events should be clearly stated and justified]
17. Statistical measures:
[Provide a clear and justified description of the following:]
 - Determination of sample size
 - Statistical method(s) and analysis of quantitative measures
 - Statistical method(s) and analysis of qualitative measures
 - Data processing (e.g. how, where, when, who)
 - Interim analysis and stopping rules if applicable
18. Ethical Issues:
[The following additional information, in respect of the proposed trial, is required:]
 - Comment on which GCP guidelines are being followed



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- Comment on choice of investigators
- Comment on need for, appropriateness of, and relevance of GCP training / updating / for staff involved in this trial
- Comment on capacity building element of trial
- Comment on resources of sites and sponsor
- Comment on monitors and monitoring plan
- Indicate how additional staff (monitors, pharmacists, nursing staff, etc.) will maintain patient confidentiality, follow the protocol, and abide by ethical and regulatory requirements
- Comment on insurance and indemnity measures
- Comment on appropriateness of Patient Information Leaflet and Informed Consent
- Comment on availability and completeness of separate Patient Information leaflets and Informed Consent forms for any proposed archiving of biological specimens for later research or for genetics research.
- Comment on ethics of the publication policy
- Comment on treatment and/or management of participants and their disease condition(s) after completion of trial
- Comment on ethics committee capacity to monitor site and conduct of trial
- Provide an explanation if minimum recommended compensation for participants is not being provided.

19. Other relevant information not included above:

20. Are references adequate and dates of references current?

21. Are there discrepancies between the protocol and investigator's brochure or package inserts?
Are there specific explanation(s) for these discrepancies?

22. Other comments on this trial.

For office use:

Reviewer's questions and concerns to be considered and/or forwarded to applicant:

Reviewer's recommendation:

Declaration of conflict of interests by reviewer (if applicable):

Signature of reviewer

Date:

APPENDIX 6: RECOMMENDED FORMAT FOR CVS OF INDIVIDUALS PARTICIPATING IN CLINICAL TRIALS

1. Study Title:

2. Protocol Number:

3. Designation:



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[e.g. National Principal Investigator, Investigator (Principal, Co- or sub-), Study Co-ordinator, Regional Monitor, Local Monitor, Clinical Research Associate]

4. Personal Details

Name:

Work Address:

Telephone Number:

Fax Number:

Cell-phone Number:

e-mail address:

5. Academic and Professional Qualifications

6. Professional registration number

7. Current personal medical malpractice insurance details

8. Relevant related work experience (brief) and current position

9. Participation in clinical trials research in the last three years

[Study title, protocol number, designation. If multiple trials, only list those with relevance to this application, or in the last year]

10. Peer-reviewed publications in the past 3 years

11. Date of last GCP training

[As a participant or presenter]

12. Any additional relevant information supporting abilities to participate in conducting this trial

[Briefly]

Signature:

Date:

APPENDIX 7: JOINT DECLARATION BY SPONSOR (OR REPRESENTATIVE) AND PRINCIPAL INVESTIGATOR (OR NATIONAL PRINCIPAL INVESTIGATOR) CONCERNING SUFFICIENT FUNDS TO COMPLETE STUDY

Title:

Protocol:



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I, <full name>, representing <sponsor or representative>

And

I, <full name>, Principal Investigator/National Principal Investigator

Hereby declare that sufficient funds have been made available to complete the above-identified study.

Signed

Date

SPONSOR (or alternative)

Name

Address

Contact details

Signed

Date

PRINCIPAL INVESTIGATOR (or National PI)

Name

Address

Contact details

APPENDIX 8: DECLARATION BY PRINCIPAL INVESTIGATOR

Name:

Title of Trial:



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Protocol:

Site:

1. I am familiar with internationally accepted standards of Good Clinical Practice (GCP) and understand the responsibilities and obligations of the Principle Investigator within the context of this study.
2. I have notified the MCAZ of any aspects of the above with which I do not / am unable to, comply. (If applicable, this may be attached to this declaration.)
3. I have thoroughly read, understood, and critically analysed the protocol and all applicable accompanying documentation, including the investigator’s brochure, patient information leaflet(s) and informed consent form(s).
4. I will conduct the trial as specified in the protocol and in accordance with Good Clinical Practice (GCP).
5. To the best of my knowledge, I have the potential at the site(s) I am responsible for, to recruit the required number of suitable participants within the stipulated time period.
6. I will not commence with the trial before written authorisations from the relevant Research Ethics Committee(s) as well as the MCAZ have been obtained.
7. I will obtain informed consent from all participants or if they are not legally competent, from their legal representatives.
8. I will ensure that every participant (or other involved persons), shall at all times be treated in a dignified manner and with respect.
9. Using the broad definition of conflict of interest below, I declare that I have no financial or personal relationship(s) which may inappropriately influence me in carrying out this clinical trial. [*Conflict of interest exists when an investigator (or the investigator’s institution), has financial or personal associations with other persons or organizations that may inappropriately influence (bias) his or her actions.*]*
*Modified from: Davidoff F, et al. Sponsorship, Authorship, and Accountability. (Editorial) JAMA Volume 286 number 10 (September 12, 2001)
10. I have* / have not (delete as applicable) previously been the principal investigator at a site which has been closed due to failure to comply with Good Clinical Practice. (*Attach details.)
11. I have* / have not (delete as applicable) previously been involved in a trial which has been closed as a result of unethical practices. (*Attach details)
12. I will submit all required reports within the stipulated time-frames.

Signature:

Date:

Witness:

Date:

APPENDIX 9: DECLARATION BY CO- AND SUB-INVESTIGATORS

Name:

Title of Trial:



MEDICINES CONTROL AUTHORITY OF ZIMBABWE

Protocol:

Principal Investigator's Name:

Site:

Designation:

1. I am familiar with internationally accepted standards of Good Clinical Practice (GCP) and understand the responsibilities and obligations of the Investigator within the context of this study.
2. I will carry out my role in the trial as specified in the protocol and in accordance with Good Clinical Practice (GCP).
3. I will not commence with my role in the trial before written authorisations from the relevant Research Ethics Committee(s) as well as the MCAZ have been obtained.
4. If applicable to my role in the trial, I will ensure that informed consent has been obtained from all participants or if they are not legally competent, from their legal representatives.
5. I will ensure that every participant (or other involved persons, such as relatives) shall at all times be treated in a dignified manner and with respect.
6. Using the broad definition of conflict of interest below, I declare that I have no financial or personal relationship(s) which may inappropriately influence me in carrying out this clinical trial.
7. *[Conflict of interest exists when an investigator (or the investigator's institution), has financial or personal relationships with other persons or organizations that inappropriately influence (bias) his or her actions.]**
8. I have not previously been involved in a trial which has been closed due to failure to comply with Good Clinical Practice.
9. I will submit all required reports within the stipulated time-frames.

Signature:

Date:

Witness:

Date:

**Modified from: Davidoff F, et al. Sponsorship, Authorship, and Accountability. (Editorial) JAMA Volume 286 number 10 (September 12, 2001)*

APPENDIX 10: DECLARATION BY REGIONAL MONITOR

Name:

Title of Trial:



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Protocol:

Site:

1. I am familiar with internationally accepted standards of Good Clinical Practice (GCP) and understand the responsibilities and obligations of the clinical trial Monitor within the context of this study.
2. I have notified the MCAZ of any aspects of the above with which I do not / am unable to, comply. (If applicable, this may be attached to this declaration.)
3. I will carry out my responsibilities as specified in the trial protocol and accordance with Good Clinical Practice (GCP)
4. Using the broad definition of conflict of interest below, I declare that I have no financial or personal relationship(s) which may inappropriately influence me in carrying out this clinical trial.
5. [*Conflict of interest exists when an investigator (or the investigator's institution), has financial or personal relationships with other persons or organizations that inappropriately influence (bias) his or her actions.*]*
6. *Modified from: Davidoff F, et al. Sponsorship, Authorship, and Accountability. (Editorial) JAMA Volume 286 number 10 (September 12, 2001)
7. I have* / have not (delete as applicable) previously been the monitor at a site which has been closed due to failure to comply with Good Clinical Practice. (*Attach details.)
8. I have* / have not (delete as applicable) previously been involved in a trial which has been closed as a result of unethical practices. (*Attach details)
9. I will submit all required reports within the stipulated time-frames.

Signature:

Date:

Witness:

Date:

APPENDIX 11: APPLICATION FOR CLINICAL TRIAL PROTOCOL Amendment Form 1

Reference/tracking number for this correspondence: _____

APPLICATION FOR APPROVAL OF:



MEDICINES CONTROL AUTHORITY OF ZIMBABWE

- PROTOCOL AMENDMENT
- INCREASE IN NUMBER OF PATIENTS PARTICIPATING
- CHANGES IN DOSE / REGIMENT OF STUDY DRUG

Study title:

Protocol number:

Date:

1. APPLICANT

- 1.1 Name/address/telephone/fax number of Applicant wishing to conduct trial:
- 1.2 Name/address/telephone/fax number of CRO representing sponsor as Applicant or Local Sponsor Company details (if applicable):
- 1.3 Name, designation and qualifications of person representing the Applicant (Local Contact Person for all further correspondence)
- 1.4 National Coordinator name, address, telephone/fax number
- 1.5 International Principal Investigator name, address, telephone/fax number
- 1.6 Name of sponsor

2. TRIAL PARTICULARS (original application)

- 2.1 Trial Approval Number:
- 2.2 Date of Approval of original protocol:
- 2.3 Number of local Investigators approved for this trial:
- 2.4 Number of local sites approved for this trial:
- 2.5 Number of participants approved for this trial:

3. AMENDMENT PARTICULARS

(Please list requests for approval)

Does the applicant wish to increase the number of local subjects participating in this trial?

- Yes
- No

Does the applicant wish to change the dose / regimen of the study drug?

- Yes
- No



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Does this amendment request require a new consent form to be signed by the participant?

Yes

No

If “Yes” please submit new PIL together with this application.

3.1 Protocol Amendment Number:

3.2 Version Number and Date of Protocol Amendment (for each document submitted):

3.3 General motivation for the proposed Amendment: *[List all of the issues included in the amendment and provide the rationale for each amendment]*

3.4 Details of the proposed Protocol Amendment: *[For each amendment, provide a brief motivation and clearly highlight changes to the original protocol; this can be done either as “old text” replaced with “new text” or with the old text deleted with a line through it and the new text in bold and underlined]*

3.5 Will this Amendment apply to all approved investigators/sites:

YES

NO

If NO: Specify the investigator(s) / site(s) for which the Amendment will apply:

4. ETHICS COMMITTEE APPROVAL

4.1 Have the Research Ethics Committee(s) responsible for each centre to which this amendment applies been notified?

4.2 Research Ethics Committee(s) responsible:

4.3 Date of application to Ethics Committee:

4.4 Date of approval by Ethics Committee:

I/We, the undersigned, agree to conduct / manage the above-mentioned trial under the conditions as stated in this application. (The person(s) undertaking legal responsibility to sign this form).

Applicant (local contact)

Date

APPENDIX 12:APPLICATION FOR ADDITIONAL INVESTIGATOR (S), CHANGE OF INVESTIGATOR (S) OR ADDITIONAL CLINICAL TRIAL SITES, Amendment form 2

Reference/tracking number for this correspondence: _____

APPLICATION FOR APPROVAL OF:



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- CHANGES IN INVESTIGATOR (S) AT APPROVED SITE (includes additional investigators)
- ADDITIONAL SITE(S)

Study title:

Protocol number:

Date:

1. APPLICANT

- 1.1 Name/address/telephone/fax number of Applicant wishing to conduct trial
- 1.2 Name/address/telephone/fax number of CRO representing sponsor as Applicant or Local Sponsor Company details (if applicable)
- 1.3 Name, designation and qualifications of person representing the Applicant (*Local Contact Person for all further correspondence*)
- 1.4 National Coordinator name, address, telephone/fax number
- 1.5 International Principal Investigator name, address, telephone/fax number
- 1.6 Name of sponsor

2. TRIAL PARTICULARS (original application)

- 2.1 Trial Approval Number:
- 2.2 Date of Approval of original protocol:
- 2.3 Number of local investigators approved for this trial:
- 2.4 Number of local sites approved for this trial:
- 2.5 Number of participants approved for this trial:

3. INVESTIGATOR DETAILS

- 3.1 Name and address of additional Investigator(s) / Changes to Investigators: *[Proof of GCP training must be provided for investigators who have not previously participated in clinical trials]*
- 3.2 Summarise other ongoing/planned studies at this site involving this investigator: *[Provide details of studies, including numbers of subjects, whether the investigator is involved in research in a full-time or part-time capacity, and any other detail that may effect the capacity of the site at any one time]*



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- 3.3 Details of Ethics Committee(s) who will approve investigator(s):
- 3.4 Date of application to Ethics Committee:
- 3.5 Date of approval by Ethics Committee:
- 3.6 Is CV for additional Investigator(s) attached? YES / NO
- 3.7 Is the Declaration of Intent attached? YES / NO

4. CAPACITY OF THE SITE

4.1 Describe how the site is structured so as to be able to take on the work for which this application is being made: *[Give details of support staff, facilities, back up and any other relevant infrastructure]*

5. RATIONALE FOR APPLICATION

5.1 Briefly explain the reason for the new investigator/s or site(s):

I/We, the undersigned, agree to conduct / manage the above-mentioned trial under the conditions as stated in this application. (The person(s) undertaking legal responsibility to sign this form).

Applicant (local contact)

Date



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PHARMACY GUIDELINES FOR INVESTIGATIONAL DRUGS (FEBRUARY 2010)

A. Purpose



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These guidelines are principally derived and adapted from guidelines from 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. These guidelines should be used as a guide to the receipt, use, and disposition of study products being investigated in clinical trials in Zimbabwe. These guidelines 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 Medicines Control Authority of Zimbabwe (MCAZ) including the Zimbabwe Clinical Trial Practice Guidelines.

The pharmacist at each clinical site/center 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.

B. Responsibilities of Pharmacists

The Pharmacist of Record is responsible for:

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



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for each clinical site/center 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.

4. Maintain appropriate records of the receipt and disposition of the protocol-specific study products including dates, quantities, lot numbers, use by participants, and amounts returned to 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, 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.

5. 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 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.
6. 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 MCAZ 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.

7. Make the study product accountability records available for inspection and copying by an authorized employee or representative of the MCAZ or Medical Research Council of Zimbabwe (MRCZ), upon request.
8. Establish a mechanism to ensure that study products are dispensed only after the



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written order of the Investigator or upon the order of a licensed clinician directly responsible to the Investigator.

- Prescriptions shall be written with ink, indelible pencil, typewriter, or computer generated and shall be signed by the authorized 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 of a participant's study visit for the SIGNATURE of a practitioner.
 - 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.
9. 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.
10. Establish a communication system with other site staff to assure that the protocol has been approved by the appropriate medical ethics committee(s) e.g., Institutional Review Board(s)
11. 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.
12. Establish a system to ensure that the current MCAZ-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.

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.



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14. 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:

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

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

- All participant identification numbers such study identification numbers.
- Clinical site/center name and center/site number.
- A description of the incident or problem.
- The reason(s) for the incident.
- Resolution and/or follow-up of the incident.
- A description of the steps that have been taken to ensure that similar incidents do not happen again.
- A statement of whether the incident resulted in a reportable adverse event report.

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.
16. 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.
17. Obtain and maintain a prescriber sample signature list.
18. 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 the MCAZ.

GUIDELINES FOR PHARMACY PLAN AND PHARMACIST OF RECORD

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



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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.

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 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.
7. 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 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?



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- 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?



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- 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 investigational products/study drugs that are received and of all investigational products/study drugs that are dispensed to participants. The count or quantity of investigational products/study drugs that you have at your site must match the quantity on the accountability records at all times. How often will the investigational products/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)?



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- 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).

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 MCAZ of a change in the Pharmacist of Record or Back-up Pharmacist.

Permanent: _____ Temporary _____ Date From: _____ Date To: _____

Site Name: _____ MCAZ Trial Number(s) _____

Name of PREVIOUS Pharmacist of Record: _____

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



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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.

Date

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 MCAZ

II. 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:

- Prescription number
- date dispensed
- participant identification number or study kit identification number
- study identification number



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- quantity dispensed or received from or returned
- current balance
- pharmacist's initials
- 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: 1.

Draw a single line through the incorrect information.

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

3. 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 MCAZ.

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 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.

D Study Product Transfers

1. Guidelines for Dispensing Study Products



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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. BSA 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 MCAZ-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



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(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).
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.
8. 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 a Participant 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 MCAZ 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,



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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 MCAZ

- a. 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 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 MCAZ must be maintained with the study protocol records.



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**APPENDIX 13: Requirements Importation for importation
and release of Investigational medicinal
for clinical trials conducted in Zimbabwe**

Guidelines Reference No. 3

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REQUIREMENTS FOR IMPORTATION AND RELEASE OF INVESTIGATIONAL MEDICINAL PRODUCTS

1. Introduction

Investigational medicinal products which are unregistered medicines may only be brought into the country after ethical approvals are in place, the clinical trial application has been approved and a letter of authorisation has been issued by the NRA.

The NRA of the producing country should be responsible for assurance of compliance with GMP for the manufacture and lot release of clinical batches and vaccines.



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They should take all appropriate measures to ensure that the holder of the authorisation referred to above has permanently and continuously at his disposal the services of at least one qualified person who is responsible in particular for ensuring:

- a) in the case of investigational medicinal products that each batch has been manufactured and checked in accordance with internationally accepted standards of good manufacturing practice for medicinal products for human use, in accordance with the product specification file, and that each production batch has been checked in accordance with the information submitted in the application for authorisation;
- b) in the case of an investigational medicinal product which is a comparator product from a third country, and which has a marketing authorisation, where the documentation certifying that each production batch has been manufactured in conditions at least equivalent to the standards of good manufacturing practice referred to the above cannot be obtained, that each production batch has undergone all relevant analyses, tests or checks necessary to confirm its quality in accordance with the information submitted in the application for authorisation.

Insofar as the provision laid down in (a) or (b) above are complied with, investigational medicinal products shall not have to undergo any further testing if they are imported into the country in which the clinical trial is to be conducted, together with batch release certificate signed by the qualified person.

In all cases, the qualified person must certify in a register or equivalent document that each production batch satisfied the provisions as stated above. The said register or equivalent document should be kept up to date as operations carried out and shall remain at the disposal of the agents of the competent authority for a period of not less than five years.

2. Scope

This guideline applies to all investigational medicinal products, including vaccines, which do not have marketing authorisation in the country of intended use. All procedures should apply to the placebo product, if applicable to the relevant clinical trial. During the period of validity of the trial authorisation any subsequent importations should be subject to the same procedures.

3. Responsibilities of the Sponsor

The sponsor should not supply an investigational medicinal product until the sponsor obtains all required documentation (e.g. approval from the appropriate ethics committee and regulatory authority(ies)).



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The sponsor should ensure that the investigational product(s) (including active comparator(s) and placebo, if applicable) is characterised as appropriate to the stage of development of the product(s), is manufactured in accordance with any applicable GMP and is coded and labelled in a manner that protects the blinding, if applicable.

The sponsor should determine for the investigational medicinal product(s) acceptable storage temperatures, storage conditions (e.g. protection from light), storage times, reconstitution fluids and procedures, and devices for product infusion, if any.

The sponsor should:

- ensure timely delivery of investigational product(s) to the investigator(s);
- maintain records that document shipment, receipt, disposition, return and destruction of the investigational product(s);
- maintain a system for retrieving investigational product(s) and documenting this retrieval (e.g. for deficient product recall, reclaim after trial completion, expired product reclaim);
- maintain a system for the disposition of unused investigational product(s) and for the documentation of this disposition.

The sponsor should also:

- take steps to ensure that the investigational product(s) are stable over the period of use; This data should be available on request and for inspection purposes. If non-compliance with the specifications becomes evident in the stability studies during the period of use in the clinical trial, the sponsor should notify the investigators and arrange to take appropriate steps;
- maintain sufficient quantities of the investigational product(s) used in the trial to reconfirm specifications, should this become necessary, and maintain records of batch sample analysis and characteristics. To the extent stability permits, samples should be retained either until the analyses of the trial data are complete or as required by the applicable regulatory requirement(s), whichever represents the longer retention period.

4. Labelling and Packaging

The labelling of investigational medical products should comply with the relevant NRA requirements. The particulars should appear in at least the official language of the country on the outer packaging or, where there is no outer packaging, on the immediate packaging.

The particulars should include at least the following information:

- state clearly that it is clinical trial material.
- the product name or unique code.
- Storage temperature and conditions.
- expiry date.



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- sponsor contact details.

Investigational medicinal products should be packaged to prevent contamination and unacceptable deterioration during transport and storage.

The investigational product(s) should be stored as specified by the sponsor, and in line with Good Pharmacy Practice (GPP) and Good Manufacturing Practice (GMP), and the NRA regulations and conditions (if applicable).

In blinded trials the coding system for the investigational product(s) should include a mechanism that permits rapid identification of the product(s) in case of a medicinal emergency, but does not permit undetectable breaks of the blinding.

5. Importation and Release

Shipping of investigational products should be conducted according to instructions given by or on behalf of the sponsor in the shipping order.

A pre-clearance inspection should be carried out at the port of entry by the NRA. This should include the shipping documentation and overall physical condition of the consignment. (See point 6 below).

If specific storage conditions are essential to ensure the quality of the product, e.g. maintenance of cold chain in the case of vaccines, a device that will confirm that storage temperatures were not exceeded during transport should be included with the shipment.

6. Documentation

Documentation that should accompany each consignment of Investigational Medicinal Product should enable the NRA at the port of entry to release the product to the investigator(s) responsible for conducting the clinical trial in the country.

The documentation should include at least:

- the COAs of each batch of the investigational product(s) as well as comparator(s), if relevant.
- a copy of NRA letter of approval of clinical trial.
- a copy of a valid Certificate of Manufacture issued by the competent Regulatory Authority in the country of origin.
- a copy of a valid WHO certificate of a pharmaceutical product issued by the competent Regulatory Authority in the country of origin.

The Cover Sheet should be completed by the Sponsor and should accompany each consignment of investigational medicinal products. *See Annex 1*



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The Check-list may be used by the sponsor to ensure that the required documents are attached and correct, but a blank document should be submitted with the Cover Sheet for use by the relevant NRA staff responsible for authorising the importation of the IMP. *See Annex 2*

7. Definitions and Abbreviations

- CoA: Certificate of Analysis
- GMP: Good Manufacturing Practices
- IMP: Investigational Medicinal Product
It is a pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical trial, including products already with a marketing authorisation but used or assembled (formulated or packaged) in a way different from the authorised form, or when used for an authorised indication, or when used to gain further information about the authorised form.
- NRA: National Regulatory Authority.
- Sponsor: An individual, company, institution or organisation which takes responsibility for the initiation, management and/or financing of a clinical trial.

ANNEX 1

COVER SHEET (to be completed by the sponsor)	
IMPORTATION AND RELEASE OF INVESTIGATIONAL MEDICINAL PRODUCTS	
Fees (if applicable)	
Study Title and phase of the study	
Protocol Number	
Study Drug	
Unique Code Number	



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NRA approval reference number of clinical trial	
NRA reference number(s) of comparator drug(s) (if applicable)	
NRA reference number(s) of concomitant drug(s) (if applicable)	
Sponsor	
Applicant	
Trial site(s)	
Sponsor Contact	
Address	
Telephone number	
Fax number:	
Cell number:	
Email address	
Batch number(s) and expiry date:	
Study drug	
Comparator drug(s)	
Quantities	
Blinding done or not	
Recommended storage temperature	

ANNEX 2

CHECK-LIST of required documentation

To be supplied by the sponsor for use by the NRA staff responsible for authorising the importation of the IMP

IMPORTATION AND RELEASE OF INVESTIGATIONAL MEDICINAL PRODUCTS			
Checklist of required documentation			
Are the following documents attached and correct, as indicated:		YES	NO
1	Copy of the NRA letter of approval of clinical trial		
2	Certificate(s) of Analysis (CoA) Study drug		



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	Comparator (if applicable)		
3	Does the CoA reflect at least the following information:		
	Product name or code		
	Name of company/sponsor		
	Batch number		
	Expiry date		
	Date of issue		
	Signature, qualification and title of responsible person		
	Results of physical and analytical tests		
4	Copy of valid Certificate of Manufacture issued by the competent Regulatory Authority in the country of origin.		
5	WHO certificate of a pharmaceutical product issued by the competent Regulatory Authority in the county of origin.		
6	Device/Proof of maintenance of cold chain (if applicable)		
7	<i>Labelling: Outer packaging, immediate container</i> Does the label clearly indicate		
7.1	That the product is clinical trial material e.g. "For use in clinical trial only".		
7.2	Product name or unique code (if blinded) <i>Does this concur with the information on the Cover Sheet</i>		
7.3	Storage temperature <i>Does this concur with the information on the Cover Sheet</i>		
7.4	Storage conditions (e.g. protection from light)		
7.5	Batch number <i>Does this concur with the information on the Cover Sheet</i>		
7.6	Date of Manufacture		
7.7.	Expiry date <i>Does this concur with the information on the Cover Sheet</i>		
7.8	Sponsor contact details <i>Does this concur with the information on the Cover Sheet</i>		
8	Is the physical condition of the consignment acceptable?		

C. GLOSSARY

1.1 Adverse Event (AE)

Any undesirable experience occurring to a subject during a clinical trial, whether or not considered related to the investigational product(s). An unexpected AE is an experience not reported in the current Investigators Brochure or elsewhere.

1.2 Serious Adverse Events (SAE) means any untoward medical occurrence that at any dose results in death, is life threatening, requires inpatient hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability/incapacity or is a congenital anomaly/birth defect (ICH definition 1997).



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1.3 Adverse Drug Reaction (ADR)

A response to a drug which is noxious and unintended, and which occurs at doses normally used in man for the prophylaxis, diagnosis, or therapy of disease or for the modification of physiological action for clinical trials, an adverse reaction which occurs as a result of medicine overdose will be considered as an ADR.

For a new medicinal product or its new intended usages, this includes all unintended responses to any dose. For marketed products, the event is that which occurs at doses normally used in man for prophylaxis, diagnosis of therapy or disease or for modification of physiological function.

A causal relationship between a medicinal product and an adverse event is at least a reasonable possibility.

1.4 Applicable Regulatory Requirement(s)

Any law(s) and regulation(s) addressing the conduct of clinical trials of investigational products

1.5 Audit (of a trial)

A systematic and independent examination of trial related activities and documents to determine whether the evaluated trial related activities were conducted, and the data were recorded, analysed and accurately reported according to the protocol, sponsor's Standard Operating Procedures (SOPs), Good Clinical Practice (GCP) and the applicable MCAZ requirements.

Audit must be conducted by the sponsor but independent of units responsible for clinical research or through an external contractor.

1.6 Audit certificate is a declaration of confirmation by the auditor that an audit has taken place.

1.7 Audit Report is a written evaluation by the sponsor's auditor of the results of the audit.

1.8 Audit Trail is documentation that allows reconstruction of the course of events.

1.9 Blinding/Masking

A procedure in which one or more parties to the trial are kept unaware of the treatment assignment(s). Single-blinding usually refers to the subject(s) being unaware and double-blinding usually refers to the subject(s), investigator(s) monitor and in some cases data analyst(s) being unaware of the treatment assignment(s).

1.10 Case Report Form (CRF)

A printed, optical or electronic document designed to record all of the protocol required information. There should be assurance of accurate input and presentation and it should allow verification.

1.11 Clinical Trial

Is defined in the Medicines and Allied Substances Control Act [Chapter 15:03] as
“Clinical trial” means 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”.



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This includes any trial for well-known established indication or registered product, academic studies for students in partial fulfillment of tertiary education.

It excludes the treatment of an individual patient by a medical practitioner with an unregistered or registered medicine outside of the approved conditions of registration of such a medicine. This would usually require special approval by the MCAZ for example section 75.

If in doubt the final designation on whether a study constitutes a trial rests with the MCAZ

1.12 Confidentiality

Prevention of disclosure, to other than authorised individuals, of a sponsor's proprietary information or of a subject identity and/or medical records.

1.13 Contract

A written, dated and signed agreement between the investigator(s), institutions and sponsor that sets out any arrangements on delegation and distribution of tasks and obligations and if appropriate on financial matters. The protocol may serve as a basis for a contract.

1.14 Co-ordinating Investigator

An investigator assigned the responsibility for the co-ordination of investigators at different centres participating in a multicentre trial.

1.15 Contract Research Organisation (CRO)

A scientific body (commercial or academic) contracted by a sponsor to perform some of the sponsors trial related duties and function

1.16 Direct Access

Permission to examine, analyse, verify and reproduce any records and reports that are important to evaluation of a clinical trial. Any party with direct access should take reasonable precautions to maintain confidentiality of subjects' identities and sponsor's proprietary information.

1.17 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.

These include protocol, copies of submissions and approval from MCAZ, investigators Curriculum Vitae, consent forms, monitor reports, audit certificates, reference ranges, raw data, laboratory results, completed CRF and the final report.

1.18 Essential Documents

Documents which individually and collectively permit evaluation of the conduct of a study and the quality of data produced.

1.19 Ethics Committee



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An independent body consisting of medical scientific, legal, special scientific religious and consumer group representatives whose responsibility is to verify that the safety, integrity and well being of human subjects participating in a particular trial are protected.

An Ethics Committee should provide public assurance by review and approving/providing favourable opinion on the trial protocol, the suitability of the investigators, facilities and the methods and material to be used in obtaining and documenting informed consent of the trial subjects. The Committee is independent of the investigator, sponsor and relevant authorities. Ethical Committee may also be referred to as **Institutional Review Board (IRB)**.

1.20 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 are credible and that the rights integrity and confidentiality of trial subject's are protected.

1.21 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.

1.22 Independent Data-Monitoring Committee (IDMC) or (Data and Safety Monitoring Board/Committee (DSMB/C), Data Monitoring Committee)

An independent data-monitoring committee that may be established by the sponsor to assess at intervals the progress of a clinical, the safety data, and the critical efficacy endpoints, and to recommend to the sponsor whether to continue, modify, or stop a trial.

1.23 Informed Consent

The voluntary confirmation of a subject's willingness to participate in a particular trial and the documentation thereof. The subject is informed of all aspects of the trial that include the objectives, potential benefits and risks and inconveniences, and the subjects rights and responsibilities.

1.24 Inspection

The act by the MCAZ of conducting an official review of documents, facilities, records and any other resources that are deemed 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 (CRO's) facilities, or at other establishments deemed appropriate by the MCAZ..

1.25 Institution (medical)

Any public or private entity or agency or medical or dental facility where clinical trials are conducted.

1.26 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)**.

1.27 Investigators Brochure



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A collection of data consisting of all the information known prior to the clinical trial concerning the clinical and non clinical data on the investigational product(s). There should be adequate data to justify the nature, scale and duration of the proposed trial.

1.28 Investigational 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.

1.29 Monitor

A person appointed by the sponsor or CRO to oversee the progress of a clinical trial and of ensuring that it is conducted, recorded and reported in accordance with the SOP's, GCP and the applicable regulatory requirements.

1.30 Multicentre Trial

A clinical trial conducted according to one single protocol but at more than one site. It is carried out by more than one investigator.

1.31 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.

1.32 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.

1.33 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.

1.34 Randomisation

The process of assigning trial subjects to treatment or control groups using an element of chance to determine the assignments in order to reduce bias.

1.35 Raw Data

Original and certified copies of documents, data and records (e.g. hospital records, clinical and office charts, laboratory notes, memoranda, pharmacy dispensing records, recordings from automated instruments, X-rays, microfilm) related to a clinical trial.

1.36 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



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organisation which has been requested to provide money for a trial and does not benefit in any way from the results of the trial.

1.37 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.

1.38 Subject Identification Code

A unique identifier assigned by the investigator to each trial subject to protect the subject's identity and used in lieu of the subject's name when the investigator reports adverse events and/or other trial related data.

1.39 Subject/Trial subject

An individual who participates in a clinical trial, either as a recipient of the investigational product(s) or as a control.

D. REFERENCES:

- 1) E6 (CPMP/ICH/135/95) Harmonised Tripartite Guideline 1997
- 2) E8 (CMP/ICH/291/95) General Considerations for Clinical Trials
- 3) International Ethical Guidelines for Biomedical Research involving Human Subjects. CIOMS 2002. (Prepared by the Council for International Organisations of Medical Sciences (CIOMS) in collaboration with the World Health Organisation (WHO).
- 4) The World Medical Association's Declaration of Helsinki. Revised Declaration of Helsinki (2010)
- 5) CONSORT statement - Ann Intern Med., 2001; 134:657-662. Also published in JAMA (April 18, 2001) and The Lancet (April 14, 2001)
- 6) Medicines and Allied Substances Control Act (MASCA) [Chapter 15:03]
- 7) MASCA [Chapter 15:03] Statutory Instrument (SI) 150 of 1991
- 8) MASCA [Chapter 15:03] Statutory Instrument Fee Schedule (SI) 178 of 2008