Medicines Control Authority of Zimbabwe

MCAZ/PVCT/GL-01

GUIDELINES FOR CONDUCTING GOOD CLINICAL PRACTICE (GCP) INSPECTIONS IN ZIMBABWE

EFFECTIVE DATE:

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1.0 APPLICATION

The Guidelines for Good Clinical Practice (GCP) Inspection guidelines are for use by MCAZ inspectors and approved clinical trials' study team in Zimbabwe, who require guidance on how inspections are conducted.

2.0 PURPOSE

The Medicines Control Authority of Zimbabwe (MCAZ) has developed the guidelines for regulating the conduct of inspections in clinical trials in human participants in line with the Medicines Allied Substance Control Act (MASCA) Chapter 15:03, Statutory Instrument (SI 150) and other local and international requirements. To achieve compliance, this guideline should be used in conjunction with the Guidelines for Good Clinical Trial Practice in Zimbabwe including other local and international GCP standard requirements.

3.0 BACKGROUND / INTRODUCTION

Good Clinical Practice (GCP) is an international ethical and scientific quality standard for designing, conducting, recording, and reporting trials that involve the participation of human subjects. Compliance with this standard provides public assurance that the rights, safety, and well-being of trial subjects are protected, consistent with the principles that have their origin in the Declaration of Helsinki, and that the clinical trial data are credible.

This guideline sets out the good clinical trial practice that should be followed by applicants and researchers during inspections of **clinical studies in humans** involving the use of registered and unregistered medical products in Zimbabwe, in line with the mandate of Authority to process clinical trial applications, monitor clinical trials from start to finish in accordance with MASCA Chapter 15:03, SI 150. For further information refer to the MASCA [Chapter 15:03], MASCA Statutory Instrument SI 150, Clinical Trial Application Guideline, and Pharmacy Guidelines for Investigational Products available on MCAZ website www.mcaz.co.zw

The guidelines were derived from the International Conference on Harmonization Good Clinical Practice (ICH GCP) and from the International Ethical Guidelines for Biomedical Research involving human subjects prepared by the Council for International Organizations of Medical Sciences (CIOMS) in collaboration with World Health Organization (WHO 2002). It is therefore in line with international best practices as well as the WHO- African Vaccine Regulatory Forum (AVAREF) GCP inspection guidelines.

This guidance should be read in conjunction with other local and international Clinical trial regulations, WHO guidelines and ICH guidance documents relevant to the conduct of clinical trials (e.g., E2A (clinical safety data management), E3 (clinical study reporting), Integrated Addendum to ICH E6(R1): Guideline for Good Clinical Practice E6(R2), E7 (geriatric populations), E8 (general considerations for clinical trials), E9 (statistical principles), and E11 (paediatric populations).

4.0 DEFINITIONS

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

4.2 **Amendment (to clinical trial protocol):** A written description of a change(s) to or formal clarification of a protocol.

4.3 **Applicable Regulatory Requirements:** Any law(s) and regulation(s) addressing the conduct of clinical trials of investigational products and medical products.

4.4 **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, analyzed, and accurately reported according to the protocol, sponsor's standard operating procedures (SOPs), good clinical practice (GCP), and the applicable regulatory requirement(s)..

4.5 **Audit certificate:** A declaration of confirmation by the auditor than an audit has taken place.

4.6 **Audit Report:** A written evaluation by the sponsor's auditor of the results of the audit.

4.7 **Audit Trail:** Documentation that allows reconstruction of the course of events.

4.8 **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 participant(s) being unaware and double-blinding usually refers to the participant(s), investigator(s), and monitor and, in some cases, data analyst(s) being unaware of the treatment assignment(s).

4.9 **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.

4.10 **Certified Copy:** A paper or electronic copy of the original record that has been verified (e.g., by a dated signature) or has been generated through a validated process to produce an exact copy having all of the same attributes and information as the original.

4.11 **Clinical Trial [MASCA]:** Is defined in the Medicines and Allied Substances Control Act [Chapter 15:03] as follows: "A systematic study in human beings or animals in order to establish the efficacy of, or to discover or verify the effects or adverse reactions of medicines, and includes a study of the absorption, distribution, metabolism and excretion of medicines". This also includes any trial for vaccines/biologics or unregistered/registered product, and academic medicines studies in humans by undergraduate and/or postgraduate students in partial fulfilment of academic requirements, and 'off label use'. If in doubt please consult MCAZ on whether a study constitutes a clinical trial or not in terms of MASCA Chapter 15:03.

4.12 **Clinical Trial [ICH: E6 (R2)]:** Any investigation in human subjects intended to discover or verify the clinical, pharmacological and/or other pharmacodynamic effects of an investigational product(s), and/or to identify any adverse reactions to

an investigational product(s), and/or to study absorption, distribution, metabolism, and excretion of an investigational product(s) with the object of ascertaining its safety and/or efficacy. The terms clinical trial and clinical study are synonymous.

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

4.14 **Confidentiality:** Prevention of disclosure, to other than authorized individuals, of a sponsor's proprietary information or of a participant's identity and/or medical records.

4.15 **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.

4.16 **Co-ordinating Investigator:** An investigator assigned the responsibility for the co-ordination of investigators at different centers participating in a multicenter trial.

4.17 **Contract Research Organization (CRO):** A scientific body (commercial or academic) contracted by a sponsor to perform some of the sponsors trial related duties and function

4.18 **Direct Access:** Permission to examine, analyze, 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 participants' identities and sponsor's proprietary information.

4.19 **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 the 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.

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

4.21 **Ethics Committee:** An independent body consisting of medical, scientific, legal, and religious and consumer group representatives whose responsibility is to verify that the rights, safety, and well-being of human participants involved in a trial are protected. An Ethics Committee provides public assurance of that protection by, among other things, reviewing 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 participants. The Committee is independent of the investigator, sponsor and relevant authorities. Ethical Committee may also be referred to as Institutional Review Board (IRB).

4.22 **Good Clinical Practice (GCP):** Good Clinical Practice (GCP) is an international ethical and scientific quality standard for designing, conducting, recording and reporting trials that involve the participation of human subjects. Compliance with this standard provides public assurance that the rights, safety, and well-being of

trial subjects are protected, consistent with the principles that have their origin in the Declaration of Helsinki, and that the clinical trial data are credible. ICHE6 (R2)

4.23 Good Clinical Practice (GCP) Grading:

4.23.1 Minor: These are conditions, practices or processes that would not be expected to adversely affect the right, safety or well-being of the subjects and/or the quality and integrity of data. Observations classified as minor, indicate the need for improvement of conditions, practices and processes. Many minor observations might indicate a bad quality and the sum might be equal to a major finding with its consequences.

4.23.2 Major: These are conditions, practices or processes that might adversely affect the rights, safety, or wellbeing of the subjects and/or the quality and integrity of data. Major observations are serious findings and are direct violations of GCP principles. Possible consequences may include data being rejected and/or legal action required. Observations classified as major, may include a pattern of deviations and/or numerous minor observations.

4.23.3 Critical: These are conditions, practices or processes that adversely affect the rights, safety, or wellbeing of the subjects and/or the quality and integrity of data. Critical observations are considered to be totally unacceptable and possible consequences.

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

4.25 Good Laboratory Practice (GLP): The principles of Good Laboratory Practice (GLP) define a set of rules and criteria for a quality system concerned with the organisational process and the conditions under which clinical, non-clinical health and environmental safety studies are planned, performed, monitored, recorded, reported and archived.

4.26 Independent Data-Monitoring Committee (IDMC) / Data and Safety Monitoring Board (DSMB) / Safety Monitoring Committee (SMC) or Data Monitoring Committee (DMC): 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.

4.27 Impartial Witness: A person, who is independent of the trial, who cannot be unfairly influenced by people involved with the trial, who attends the informed consent process if the participant or the participant's legally acceptable representative cannot read, and who reads the informed consent form and any other written information supplied to the participant.

4.28 Informed Consent: A process by which a participant voluntarily confirms his or her willingness to participate in a particular trial, after having been informed of all aspects of the trial that are relevant to the subject's decision to participate and includes the objectives, potential benefits, risks and inconveniences, and the participant's rights and responsibilities. Informed consent is documented by means of a written, signed and dated informed consent form.

4.29 Inspection and/or GCP inspection: The act by a regulatory authority(ies) of conducting an official review of documents, facilities, records, and any other

resources that are deemed by the authority(ies) to be related to the clinical trial and that may be located at the site of the trial, at the sponsor's and/or contract research organisation's (CROs) facilities, or at other establishments deemed appropriate by the regulatory authority(ies).

4.30 **Institution (medical):** Any public or private entity or agency or medical or dental facility where clinical trials are conducted.

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

4.32 **Investigators Brochure:** A compilation of the clinical and nonclinical data on the investigational product(s) that is relevant to the study of the investigational product(s) in human subjects There should be adequate data to justify the nature, scale and duration of the proposed trial.

4.33 **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.

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

4.35 **Joint review:** This process involves a joint assessment of the application by the Authority (MCAZ) with the relevant ECs/IRBs and other receiving national drug regulatory agencies.

4.36 **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.

4.37 **Monitoring Plan:** A description of the methods, responsibilities and requirements for monitoring the trial.

4.38 **Multicenter 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.

4.39 **Nonclinical Study:** Biomedical studies not performed on human subjects.

4.40 **Pandemic:** an emergency occurring worldwide or over a wide area crossing international boundaries and affecting a large number of people The act by a regulatory authority(ies) of conducting an official review of documents, facilities, records, and any other resources that are deemed by the authority(ies) to be related to the clinical trial and that may be located at the site of the trial, at the sponsor's and/or contract research organisation's (CROs) facilities, or at other establishments deemed appropriate by the regulatory authority(ies).

4.41 **Participant Identification Code:** A unique identifier assigned by the investigator to each trial participant to protect the participant's identity and used in lieu of the participant's name when the investigator reports adverse events and/or other trial related data.

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

4.43 **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 team of investigators at a trial site conducts a trial, the principal investigator is the responsible leader of the team.

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

4.45 Quality Management System: The sponsor should implement a system to manage quality throughout all stages of the trial process. Sponsors should focus on trial activities essential to ensuring human subject protection and the reliability of trial results. Quality management includes the design of efficient clinical trial protocols and tools and procedures for data collection and processing, as well as the collection of information that is essential to decision making. The methods used to assure and control the quality of the trial should be proportionate to the risks inherent in the trial and the importance of the information collected. The sponsor should ensure that all aspects of the trial are operationally feasible and should avoid unnecessary complexity, procedures, and data collection. Protocols, case report forms, and other operational documents should be clear, concise, and consistent. The quality management system should use a risk-based approach as described below.

4.45.1 Critical Process and Data Identification: During protocol development, the sponsor should identify those processes and data that are critical to ensure human subject protection and the reliability of trial results.

4.45.2 Risk Identification: The sponsor should identify risks to critical trial processes and data. Risks should be considered at both the system level (e.g., standard operating procedures, computerized systems, personnel) and clinical trial level (e.g., trial design, data collection, informed consent process).

4.45.3 Risk Evaluation: The sponsor should evaluate the identified risks against existing risk controls by considering:

i. The likelihood of errors occurring.
ii. The extent to which such errors would be detectable.
iii. The impact of such errors on human subject protection and reliability of trial results.

4.45.4 Risk Control: The sponsor should decide which risks to reduce and/or which risks to accept. The approach used to reduce risk to an acceptable level should be proportionate to the significance of the risk. Risk reduction activities may be incorporated in protocol design and implementation, monitoring plans, agreements between parties defining roles and responsibilities, systematic safeguards to ensure adherence to standard operating procedures, and training in processes and procedures. Predefined quality tolerance limit should be established, taking into consideration the medical and statistical characteristics of the variables as well as the statistical design of the trial, to identify systematic issues that can impact subject safety or reliability of trial – ICHE6 (R2) Integrated Addendum to ICH E6(R1): Guideline for Good Clinical Practice 22 results. Detection of deviations from the predefined quality

tolerance limits should trigger an evaluation to determine if action is needed.

4.45.5 Risk Communication: The sponsor should document quality management activities. The sponsor should communicate quality management activities to those who are involved in or affected by such activities, to facilitate risk review and continual improvement during clinical trial execution.

4.45.6 Risk Review The sponsor should periodically review risk control measures to ascertain whether the implemented quality management activities remain effective and relevant, taking into account emerging knowledge and experience.

4.45.7 Risk Reporting The sponsor should describe the quality management approach implemented in the trial and summarize important deviations from the predefined quality tolerance limits and remedial actions taken in the clinical study report (ICH E3, Section 9.6 Data Quality Assurance).

4.46 Quality Assurance (QA): All those planned and systematic actions that are established to ensure that the trial is performed, and the data are generated, documented (recorded), and reported in compliance with GCP and the applicable regulatory requirement(s).

4.47 Quality Control (QC): The operational techniques and activities undertaken within the quality assurance system to verify that the requirements for quality of the trial-related activities have been fulfilled.

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

4.49 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.

4.50 Records and Reports: The investigator/institution should maintain adequate and accurate source documents and trial records that include all pertinent observations on each of the site's trial subjects. Source data should be attributable, legible, contemporaneous, original, accurate, and complete. Changes to source data should be traceable, should not obscure the original entry, and should be explained if necessary (e.g., via an audit trail).

4.51 Regulatory Authorities: Bodies having the power to regulate. In the ICH GCP guidance, the expression "Regulatory Authorities" includes the authorities that review submitted clinical data and those that conduct inspections. These bodies are sometimes referred to as competent authorities.

4.52 Virtual GCP inspection: the process of conducting inspections at a distance/virtually, supported by technology for communicating, sharing, reviewing, and developing documents and accessing systems, without the inspectors being physically present at the sites where the activities subject to an inspection have taken place / where the inspection would routinely be hosted".

4.53 Source Data: All information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial

necessary for the reconstruction an evaluation of the trial. Source data are contained in source documents (original records or certified copies).

4.54 **Source Document:** Original documents, data, and records (e.g., hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate copies, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories and at medico-technical departments involved in the clinical trial).

4.54 **Sponsor:** An individual, company, institution or organisation which takes responsibility for the initiation, management and/or financing of a trial.

4.55 **Standard Operating Procedure (SOP):** A detailed, written instruction for the management of clinical trial. They provide a framework enabling the efficient implementation and performance of all the functions and activities for a particular trial.

4.56 **Sub-investigator:** Any individual member of the clinical trial team designated and supervised by the investigator at a trial site to perform critical trial-related procedures and/or to make important trial-related decisions (e.g., associates, residents, research fellows). See also Investigator.

4.57 **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.

4.58 **Trial Master File (TMF):** Trial Master File (TMF) is the name of the collection of trial documents that GCP requires must be present before, during, and after the trial. The purpose of the collection of the essential documents is subsequently to be able to evaluate a clinical trial's implementation and the quality of data, and thus evaluate compliance with GCP guideline including applicable law. The TMF maybe electronic (eTMF) and must include "any documentation that facilitates reconstructing and evaluating the trial conduct, as part of the TMF" such as completed forms, checklists and reports, generated from following quality system procedures; assay method validation report for analysis of IMP or metabolite(s) in clinical samples; documentation to demonstrate validation of trial-specific builds of computer systems. Thus, it includes not just the core documents themselves, but any supporting document that shows the study quality system was followed.

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

4.60 **Unexpected Adverse Drug Reaction:** An adverse reaction, the nature or severity of which is not consistent with the applicable product information (e.g., Investigator's Brochure for an unapproved investigational product or package insert/summary of product characteristics for an approved product). (See the ICH Guidance for Clinical Safety Data Management: Definitions and Standards for Expedited Reporting.)

4.61 **Validation of Computerized Systems:** A process of establishing and documenting that the specified requirements of a computerized system can be consistently fulfilled from design until decommissioning of the system or transition to a new system. The approach to validation should be based on a risk assessment that takes into consideration the intended use of the system and the potential of the system to affect human subject protection and reliability of trial results.

4.62 **Vulnerable Subjects:** Individuals whose willingness to volunteer in a clinical trial may be unduly influenced by the expectation, whether justified or not, of benefits associated with participation, or of a retaliatory response from senior members of a hierarchy in case of refusal to participate. Examples are members of a group with a hierarchical structure, such as medical, pharmacy, dental, and nursing students, subordinate hospital and laboratory personnel, employees of the pharmaceutical industry, members of the armed forces, and persons kept in detention. Other vulnerable subjects include patients with incurable diseases, persons in nursing homes, unemployed or impoverished persons, patients in emergency situations, ethnic minority groups, homeless persons, nomads, refugees, minors, and those incapable of giving consent.

4.63 **Well-being (of the trial participants):** The physical and mental integrity of the participants participating in a clinical trial.

5.0 GUIDELINES

5.1 Good Clinical Practice Inspections

The Authority reserves the right to inspect and interrupt any trial for which authorization has been given, as and when necessary. In terms of section 16 (1) of MASCA Chapter 15:03 no person shall conduct a clinical trial of any medicine without the prior written authorization of the Authority, granted with the approval of the Secretary. Periodic Good Clinical Practice (GCP) Inspections of the trial sites shall be conducted to ensure that there is compliance with current Good Manufacturing Practice (cGMP), current Good Laboratory Practice (cGLP), approved protocol and participants' protection. The inspections may be carried out randomly, and/or for specific reasons, and shall be either announced or unannounced as part of risk minimisation to participants. A benefit-risk based approach is used by the Authority for the selection of ongoing studies to be inspected in line with MASCA chapter (15:03) section 23 mandate to monitor clinical trials from start to finish. All clinical trials will however be subjected to pre-trial GCP inspection for feasibility, site preparedness, and routine ongoing trial inspections for compliance with cGCP, cGMP and cGLP. For cause, inspections may be conducted if the Authority deems it necessary. Section 6.0 outlines for cause GCP inspections in detail.

An inspection would consist of a comparison of the procedures and practices of the principal investigator with the commitments set out in the protocol and reports submitted to The Authority by the investigator or the sponsor. Before an inspection, the principal investigator (or the co-investigator) shall be informed of the impending inspection either in writing, by phone or electronically. An unannounced inspection may however be conducted, if the MCAZ has reasonable cause to believe that the approved protocol is being violated. The **GCP inspection checklist (PVF 86)** used by MCAZ during inspections has been appended to this guideline. Joint inspections by MCAZ and other local clinical trial regulators such as the Medical Research Council of Zimbabwe (MRCZ) may be also conducted.

5.2 The GCP Inspection

Outlined below are details of the various phases of an inspection, including pre-inspection contact; the opening meeting and the actual inspection

5.2.1 Pre-Inspection Contact:

i. Appointments for inspection of an investigational site will be made by a telephone call and/or an e-mail.

ii. A written confirmation of the inspection date, time and program/or agenda (if applicable) will be forwarded to the site, the sponsor company or the Clinical Research Organization (CRO).
iii. The time span between initial contact and actual inspection shall be as short as possible. Any undue delay of the inspection on the part of the clinical investigator will be investigated.

5.2.2 Opening Meeting:

The purpose of this meeting is for the Inspector(s) to:

i. Explain the purpose of the inspection, i.e. routine or for -cause,
ii. Outline the scope of the inspection
iii. Obtain a brief review of the organization of the site being inspected.

5.2.3 The Inspection Purpose:

The overall purpose of the conduct of the inspection should be to establish whether the investigator has fulfilled his/her GCP responsibilities. This includes the following:

i. To ascertain whether the investigator is thoroughly familiar with the properties of the investigational product(s) as described in the investigator's brochure.
ii. To ensure that investigator has sufficient time to conduct and complete the clinical study,
iii. To ensure that the investigator has adequate staff and appropriate facilities (including laboratories) available for the duration of the study, and to ensure that other studies do not divert essential participants or facilities away from the study in hand.
iv. To establish whether the investigator has studied the protocol and whether the assisting personnel have been adequately informed of their responsibilities and they have been trained on the protocol and its procedures
v. To determine if The Authority's and Ethics Committee and other relevant approvals have been obtained with stipulated conditions adhered to.
vi. To determine in what manner the investigational products are handled and stored, and that investigational products are dispensed to study participants in accordance with the protocol and to ensure the products are of good quality.
vii. To ensure all records of trial medicines are up to date.
viii. To ensure that the confidentiality of all information about participants is respected (by all persons involved).
ix. To ensure that the investigator observes the following points particularly related to medical care: The Investigator is responsible for those participants who are under his/her care for the duration of the study and must ensure that

appropriate medical care is maintained during and after the study. Where appropriate, fully functional resuscitation equipment should be immediately available in case of emergency. Clinical, significant abnormal laboratory values or clinical observations must be followed up after completion of the study.

x. Serious adverse events (SAEs) are reported to the sponsor and to the MCAZ and institutional review board(s) within the stipulated time as specified in these guidelines

xi. The research pharmacy is operating according to the conditions set out by the MCAZ and the investigational and other study products are kept under their prescribed conditions and the records are up to date.

xii. Compliance with cGCP, cGMP and cGLP.

5.2.4 During an inspection, inspectors:

i. Should be given easy access to the trial sites and laboratories at all times, and Trial Master File (TMF).

ii. Should have easy access to all patient files and raw data utilized for and generated during the trial. All site data and documents including participant files must be available for verification.

iii. All observations and findings shall be verified in order to ensure the credibility of data and to assure that the conclusions that would be presented are derived correctly from the raw data.

5.3 Essential Documents for the Conduct of a Clinical Trial

5.3.1 Essential Documents are those documents which individually and collectively permit evaluation of the conduct of a trial and the quality of the data produced. These documents in addition to other functions not herein mentioned serve to demonstrate the compliance of the investigator, sponsor and monitor with the standards of Good Clinical Practice and with all applicable regulatory requirements.

5.3.2 The various documents are grouped in three sections according to the stage of the trial during which they will normally be generated:

i. Before the clinical phase of the trial commences,

ii. During the clinical conduct of the trial, and

iii. After completion or termination of the trial.

5.3.3 A description should be given of the purpose of each document, and whether it should be filed in either the investigator/institution or sponsor files, or both. It is acceptable to combine some of the documents, provided the individual elements are readily identifiable.

5.3.4 Trial master files should be established at the beginning of the trial, both at the investigator/institution's site and at the sponsor's office. A final close-out of a trial can only be done when the study monitor(s) has reviewed both

investigator/institution and sponsor files and confirmed that all necessary documents are in the appropriate files.

5.3.5 Any or all of the documents addressed in this guideline may be subject to, and should be available for, audit by the sponsor's auditor and inspection by the Authority.

5.4 Trial Procedures

5.4.1 This part identifies the nature of the information that shall be obtained during each inspection to determine if the clinical investigator is meeting his/her obligation. This outline provides only the minimal scope of the inspection and the inspector shall extend the inspection as the facts evolve. The inspection conducted shall be sufficient in scope to determine compliance with Good Clinical Practice. Additional documentation, scientific data, electronic records, and other detailed findings and/or exhibits may be requested for further evaluation after the inspection and would still be included in the inspection report subject to further clarification by the study team if required the inspection.

i. Verification of signed informed consent documents. Signatures shall be checked against evidence on patient files. It would be determined whether written informed consent was obtained for all participants prior to the entry into the study and whether this was recorded in the participants medical records. A copy of the information presented orally may also be obtained.
ii. Participant records shall be verified and complains register.
iii. The condition, organization, completeness, and legibility of the investigator's raw data files may need to be described.
iv. Necessary processes would be put in place to determine whether there is adequate documentation to assure that all inspected participants did exist and were available for the duration of their stated participation in the study.
v. The raw data in the clinical investigator's records would be compared with the completed case record forms.
vi. Whether the number and type of participants entered into the study were confined to the protocol limitations.
vii. Whether the inclusion and exclusion criteria as specified in the protocol were followed.
viii. Observations, information, and data condition of the participants at the time of entering into the trial.
ix. Observations and data on the condition of the participant throughout participation in the investigation, including results of lab tests, development of unrelated illness and other factors which might alter the effects of the test product.
x. Records of exposure of the participant to the test product.
xi. whether clinical laboratory testing (including ECGs, x-rays and other special investigations), as noted in the case reports, can be evaluated by the presence of completed laboratory reports in the source documents.

xii. The occurrence of adverse reactions would be determined and AE/SAE log, and protocol deviation log. The reporting of these events and/or deviations to the MCAZ and the Ethics Committee shall be documented.
xiii. All persons obtaining raw data or involved in the collection or analysis of such data would be identified.
xiv. Evidence of approval of protocol amendments and clarification memos, signature log, changes to the TMF, and auditors and monitors reports.

5.5 Trial Medication

5.5.1 The following are considered as important in an inspection with regard to clinical trial medicine:

i. Record keeping procedures for the investigational and comparator drugs. All invoices, import documents, importation and exportation approvals should be filed and easily retrievable when asked for.
ii. Dates and quantity of trial medication dispensed as well as the recipients must be available as well as corroboration by raw data notations.
iii. The blinding of medication, if appropriate, must be validated to ensure protection of the study from bias.
iv. The pharmacy and storage area will be inspected.
v. It would be determined whether the storage area has controlled access and whether it is securely locked.
vi. Access to the investigational product(s) and study medicines must be restricted to the investigator and the responsible pharmacist.
vii. Temperature logs shall be inspected for the storage area and for the fridge/freezer (if applicable)
viii. The premises and persons licences should be displayed and always up to date.

5.6 Laboratory

5.6.1 During an inspection the MCAZ will determine the systems and procedures that are followed within an organization that is conducting analysis of samples from clinical trials in compliance with the requirements of current Good Clinical Practice (cGCP).
5.6.2 Inspections of a laboratory being used to analyse samples from a clinical trial shall be in accordance with provisions outlined in the Good Clinical Laboratory Practice Guidelines published by WHO/TDR.

5.7 Data Management

5.7.1 If electronic data systems are involved in gathering data, storing data, or transmitting data to the sponsor, these would be identified, and their capabilities established. Data should be collected, processed, and stored in compliance with regulatory standards.

5.8 Grading of inspection findings

5.8.1 Inspection findings are graded as minor, major or critical and the description of each category is given below:

i. **Minor:** These are conditions, practices or processes that would not be expected to adversely affect the right, safety, or well-being of the subjects and/or the quality and integrity of data. Observations classified as minor, indicate the need for improvement of conditions, practices, and processes. Many minor observations might indicate a bad quality and the sum might be equal to a major finding with its consequences.

ii. **Major:** These are conditions, practices or processes that might adversely affect the rights, safety, or wellbeing of the subjects and/or the quality and integrity of data. Major observations are serious findings and are direct violations of GCP principles. Possible consequences may include data being rejected and/or legal action required. Observations classified as major, may include a pattern of deviations and/or numerous minor observations.

iii. **Critical:** These are conditions, practices or processes that adversely affect the rights, safety, or wellbeing of the subjects and/or the quality and integrity of data. Critical observations are considered to be totally unacceptable and possible consequences.

5.9 Exit Meeting / Inspection Report

5.9.1 At the post inspection meeting the inspectors shall discuss the findings of the inspection to the investigator, representative of the contract research organization and/or other key members of the study team. Further clarification(s) will be sought including any relevant exhibits thereof for further review and inclusion in the signed inspection report by the inspector after the inspection.

5.9.2 The matters discussed at this meeting shall be in line with the report written by the inspectors. Important matters include:

i. When significant violations of GCP are observed, reports shall contain sufficient narrative and accompanying documentation to support the findings.

ii. When it is apparent that the study has been conducted in substantial compliance with the guidelines, an abbreviated report reflecting such shall be compiled.

iii. If deficiencies were found during the inspection in any of the areas it needs to be explained and documentation attached as exhibits.
iv. Minor and/or major findings as well will be included in the inspection report. Several minor/ major findings may warrant classification as combined critical finding(s) in line with GCP requirements.

5.10 Responding to the Inspection Report

5.10.1 On receipt of the signed inspection report, the Principal Investigator (PI)/applicant is required to also submit a signed written response that addresses each finding made in the inspection report.

5.10.2 In rare cases, where there has been a misunderstanding or misinterpretation, the (robust) evidence and justification of why the PI does not accept the finding should be included in the response and in such cases it is advisable to discuss the issue and concerns with the Lead Inspector prior to the response being submitted.

5.10.3 Assess the risk and impact: Once the findings have been reviewed and accepted the next step is to assess the findings. Consider whether the findings are indicative of a systematic problem or a one off and understand the impact of the non-compliance and the risks it poses to participant safety and/or data integrity; this will be important in informing the proportionality of the corrective and preventative actions. If systematic issues are identified then the corrective and preventative actions should reflect how this will be managed across all affected trials

5.10.4 Undertake a root cause analysis: Determining the root causes of the finding will help in minimising the likelihood of recurrence.

5.10.5 Develop and document a Corrective and Preventive actions (CAPA) plan with deadlines to address the non-compliances: For each finding both corrective and preventative actions should be included unless there is justification as to why this is not appropriate. Corrective actions should consider whether the non-compliance can be fixed or at least the impact reduced. Preventative actions should address the findings of the root cause analyses. Timelines for corrective and preventative actions must be included in the responses and realistic in line with the amount of work to do and the available resources to do it.

Principal Investigators are required to submit a signed response letter **within fourteen (14) days** of receipt of the signed GCP inspection report.

5.11 Inspection Closure

Once responses have been provided, evaluated by the inspection team and tabled at the Pharmacovigilance and Clinical Trials (PVCT) Meeting, a feedback letter will be provided to the Principal Investigator.

5.12 For cause inspections

A for-cause inspection may be the result of prior knowledge or suspicion of alleged violations of the Medicines and Allied Substances Control Act (MASCA) [Chapter 15:03]. A for-cause inspection may concentrate the data verification on specific areas of the study or may expand the data verification to cover multiple studies. This inspection may also result when a study is of singular importance to the approval of registration of a medicine, i.e. one of two adequate and well controlled studies. Inspections conducted 'for-cause' would have full reporting. Outlined below is a list of reasons for cause inspection may be conducted, however this list in not exhaustive:

5.12.1 SAE based GCP inspection
5.12.2 Pharmacy based GCP inspection
5.12.3 Failure to submit annual progress reports and final reports
5.12.4 Protocol deviation triggered inspection
5.12.5 Queries arising from amendments, clarification memos and also DSMB reports
5.12.6 GCP inspection based on trial master file amendments such as site relocations.
5.12.7 GCP inspection based on product defects of investigational products

5.13 Virtual GCP Inspections

During public health emergencies such as the COVID-19 pandemic, on-site inspections may not be possible due to multiple factors such as difficulties and restrictions related to travelling, restrictions to accessing facilities justified by health hazards and local authorities' recommendations/orders, as well as additional health risks for inspectors and inspectees. Virtual online inspections will follow the applicable procedures that already exist for coordinating, preparing, and conducting GCP inspections. The Authority takes into consideration the limitations imposed by using a remote process and recognises that such a remote process cannot completely replace on-site GCP inspections.

Due to the nature of virtual inspections, the PI will be required to email essential documents, TMF and relevant exhibits in advance for review by the inspectors before the virtual meeting. The preparation of a virtual inspection may be significantly more demanding compared to on-site inspections. As such, the Authority shall:

5.13.1 Contact the Principal Investigator within a reasonable time frame to assess whether the inspectee meets the technical requirements to provide remote access to electronic systems and maintain communication with and support to inspectors.

5.13.2 Provide an inspection plan, including the duration of the inspection and schedule expectations and requirements shall be discussed and agreed on prior to the inspection.

5.13.3 Ensure any recording (audio / video / screenshots) during the inspection process will be notified and agreed upfront between all involved parties.

5.13.4 The Authority will require the following documents before a virtual inspection is conducted: auditors and monitors reports, evidence of approval of protocol amendments, SAE logs, protocol deviation logs, pharmacy records and any other documents that may be deemed necessary by the Authority.

6.0 KEY RELEVANT DOCUMENTS

6.1 Medicines and Allied Substances Control Act (MASCA) [Chapter 15:03]
6.2 Statutory Instrument 150 of 1991
6.3 Import and Export Regulations for medicines SI57 of 2008
6.4 Clinical Trial Application Guidelines in Zimbabwe
6.5 ICH E6R (2) GCP guidelines
6.6 AVAREF Guideline for Joint and Assisted Reviews of Clinical Trial Applications for National Regulatory Authorities (NRAs) and Ethics Committees (EC)
6.7 International Ethical Guidelines for Biomedical Research Involving Human Subjects. Latest publication by Council for International Organizations of Medical Sciences (CIOMS)
6.8 UNAIDS- WHO HIV Biomedical Ethical Guidelines updated version 2020
6.9 Remote GCP inspections during the COVID-19 pandemic: EMA/INS/GCP/162006/2020

7.0 HISTORY

DOCUMENT HISTORY		
Revision Number	Date Approved	
N/A	N/A	N/A

APPENDICES

APPENDIX I: GCP INSPECTION CHECKLIST

PHARMACOVIGILANCE AND CLINICAL TRIALS DIVISION

PVF 86

GCP INSPECTION CHECKLIST

1.0 OBSERVATIONS

1.1 Observations are classified into the categories "**Critica**l", "**Major**", "**Other** (**Minor**)". The recommendations are listed at the end of the report.

1.2 An answer quoted **"C"** means **"critical"** deviation that can lead to the conclusion that the study is not of a satisfactory level of compliance with GCP/GLP.

1.2.1 Def (MHRA): **Critical finding**: patient safety implications or regulatory offence or casts doubt on validity of data.

1.3 An answer quoted **"M"** means **"major"** deviation. Several major deviations can lead to the conclusion that the study is not of a satisfactory level of compliance with the GCP/GLP.

1.3.1 Def (MHRA): **Major finding**: non-compliance with regulations that could have impact.

1.4 **Other** deviations need to be addressed in order to sustain the confidence in the work of the organization.

1.4.1 Def (MHRA): **Other (Minor) non-compliance**: Lots of minor compliance may add up to a major non-compliance.

1.5 Each time the **"NO"** box is ticked, the corresponding deviation will appear in the inspection report.

1.6 NC/NA means: not checked or not applicable.

A FACILITY INSPECTION	**Critical Deviation**	**Major Deviation**	**Other Deviation**	**NA**
A1 Trial Master File				
A.1 Reception Area				
A1.1 Is this area of an adequate size and accessible for participants? **Field site:** **Trial site:**				
A1.2 What trial population will be included in the study" e.g. babies, disabled participants.				
A1.3 Is the receptionist, who has the first contact with a potential participant, trained to encounter a potential participant. **Field site:**				

Trial site:				
A1.4 Is the receptionist the capturer of data for participant data base? **Field site:** **Trial site:**				

A1.5 Is she/he trained in basic knowledge in vaccine trials? **Field site** **Trial site**				
A.2 Consulting Area				
A2.1 Is the consulting area where the PI evaluates the participants during visits adequate in size? **Field site** **Trial site**				
A2.2 Are there lock-up cupboards for confidential documents? **Field site:** **Trial site:**				
A2.3 Is the trial specific equipment available in the consulting room? **Field site** **Trial site**				
A2.4 If not, is the area where procedures are performed Adequate and easily accessible? **Field site** **Trial site**				
A2.5 Does the PI recruit, manage and maintain the trial visits? To add to inspection training that this could not be applicable in the case of field sites. **Field site** **Trial site**				
A2.6 Does a delegated team member plan and organize visits according to visits schedule at field trials?				

A.3 Procedure Room				
A3.1 Is all equipment e.g. Baumanometer, scale, lung function machine (asthma, COPD) as per protocol available calibrated and validated?				
A3.2 Are SOPs on how to use equipment available? QA				
A3.3 Is the blood sampling area kept according to infection control procedures?				
A3.4 Is there a specific area where participants could be evaluated for reactogenicity as per protocol?				

A3.5 Is waste handling according to applicable guidelines, e.g. from the RA or site or government?				
A3.6 Is the emergency trolley available in the procedure area? As per the requirements for vaccines e.g. anaphylactic shock.				
A3.6.1 Is the trolley locked and are the keys available and controlled?				
A3.6.2. Is the emergency trolley frequently checked and documentation as proof available?				
A.3.6.3. Are expiry dates clearly checked and controlled?				
A.3.6.4. Are oxygen and accessories available, checked and signed.				
A.3.6.5. Are PI and sub-investigators ALS trained?				
A.3.6.6. Is clinical staff CPR trained?				
A.4 Pharmacy (Investigational Product Storage Area)				
A4.1 Is the pharmacy access controlled, temperature and humidity controlled?				
A4.2 Are vaccines stored as per required temperature and humidity?				
A4.3 Is the preparation of investigational product management done according to the approved protocol by suitable qualified staff?				
A4.4 In case of vaccines, are a single spillage SOP available and the study team trained to handle such an incidence.				
A4.5 Are electronic or hand written temperature logs available?				
A4.6 Is the SOP on how to handle electricity or temperature failure in the pharmacy available.				
A4.7 Are the different studies investigational products in separate lock-up cupboards and clearly identified?				
A4.8 Are vaccines transported and handled as per cold chain requirements?				
A4.9 Is IP and Participant selection followed as per randomization procedure.				

A.5 Archive				
A5.1 Is there an archive at the site?				
A5.2 Is the archive access controlled?				

A5.3 Is a person designated to control the handling of documents and are records of handlers maintained?				
A5.4 Is there an agreement between Sponsor and Trial Site/CRO on the archiving of documentation?				
A5.6 Is the archive storage area fireproof and pest controlled?				
A.6 Clinical Laboratory				
A.6.1 Is the clinical laboratory at the trial site?				
A6.2 If not, are procedures in handling biological samples clearly documented?(If clinical laboratory is nearby arrange for GLP inspection)				
A6.3 Are all equipment and testing procedures used in the laboratory validated? QA				
A6.4 Is the laboratory accredited for the tests to be performed? QA				
A6.5 Was the use and frequency of quality control adequate? (QA)				
A6.6 Does the laboratory participate in any external proficiency testing? (QA)				
A.7 Waste disposal				
A7.1 Is the disposal of biological specimens and sharps appropriate?				
A7.2 Are there separate disposal containers for different waste.				
A7.3 Is a three colour coding system used as per international coding? **A7.3.2** Black for non-infectious waste **A7.3.1** Red for infectious and blood waste. **A7.3.3**Yellow containers for sharps.				
A7.4 Is a sharps holder or needle incinerator available at the point of clinical procedure?				
A7.5 Is there a contract with a waste disposal removal company?				
B. QUALITY ASSURANCE SYSTEM				
B.1 Is a quality assurance system established?				
B.2 Are there SOPs for all critical procedures?				

B.3 Is the adherence to the SOPs ensured?				
B.4 Is there an internal self-assessment of the quality assurance system?				
B.5 Are training records for staff on SOPs available?				
B.6 Are superseded SOPs available in a history file on request.				
B.7 Are revision periods of SOPs adhered to as required?				
B.8 Is a contract of delegated responsibilities (clearly identified and listed) between sponsor/CRO and PI available?				
B.9 Ask for an Organogram of the Trial Site/CRO and note the following points: **9.1**. Number and categories of people employed. **9.2**. Description of the qualifications, training and experience of the personnel. **9.3** Work load of study team. **9.4** Number of concurrent clinical studies performed on site and identification of participants to avoid confusion and mix-ups of IP's administration.				
B.10 Ask for a description of the quality assurance system set up at the trial site.				
B.11 Check the existence, availability, accessibility and validity of the operating procedures; ask for a list of the Standard Operating Procedures used for the trial.				
B.12 Are quality control procedures applied to each stage of data handling to ensure that all data is reliable and has been processed correctly?				
B.13 Is the sponsor responsible for the monitoring of the trial?				
B.14 Did the monitor adhere to the monitoring plan as per protocol to ensure that the investigator obligations were fulfilled?				
B.15 Was AE, SAE handled according to SOPs and regulatory requirements?				
B.16 Is a signed monitoring visit log up to date?				

APPENDIX II: DOCUMENTATION

Essential Documents are those documents that individually and collectively permit evaluation of the conduct of a trial and the quality of the data produced. These documents serve to demonstrate the compliance of the investigator, sponsor and monitor with the standards of GCP and all applicable regulatory requirements. (ICH GCP section 8.1) WHO reference?

TO CHECK the availability of the following documents:

(During the planning stage the following documents should be generated **before** the conduct of the trial.

C. DOCUMENTS	**Critical Deviation**	**Major Deviation**	**Other Deviation**	**NA**
C.1 Before the conduct of the trial				
C.1.1 General				
C.1.1.1 Is an approved, signed and final version of the Protocol (including amendments) available?				
C.1.1.2 Does the protocol describe the type of information which must be reported between; sponsor/EC/investigator and the NRA/sponsor				
C.1.1.3 Is the final version of the Investigator's Brochure Available?				
C.1.1.4 Is the Information Leaflet, information regarding the trial in lay terms available?				
C.1.1.5 Is the Informed Consent Form (translation) and applicable procedure available?				
C.1.1.6 Is a sample of the case report forms (CRF) as per protocol requirements available?				
C.1.1.7 Is any other written information (e.g. advertisements) available?				
C.1.1.8 Is IEC approval of advertisement for participant recruitment available?				
C.1.1.9 Are financial aspects of the trial as predefined in an agreement between the Investigator and the sponsor available?				

C.1.1.10 Is the Guaranteed indemnity/insurance document/statement available?				
C.1.1.11 Is the insurance valid for the duration of the trial?				
C.1.1.12 Are the signed agreements between involved parties e.g. Investigator/CRO, investigator/ Sponsor available?				
C.1.1.13 Are the source documents and CRF verification procedure (SOP) available? (QC)				
C.1.1.14 Is clear documentation of transfer of responsibilities available?				
C.1.1.15 All approval documentation must be available:				
C1.1.15.1 Independent Ethics Committee approval (Clearly stated which dated version of protocol and informed consent is approved).				
C1.1.15.2 Regulatory approval. (Clearly stated which dated version of protocol and informed consent is approved).				
C1.1.15.3 Verify the importation dates of unregistered vaccines versus NRA approval dates.				
C.1.1.16 List of Ethics Committee members and their disciplines.				
C.1.1.17 The IEC should have documented policies and procedures as a basis for its work. (WHO GCP 3.2)				
C.1.1.18 Minutes of meeting where relevant documentation were reviewed and approved				
C.1.1.19 List of members voted for approval (conflict of interest)				
C.1.1.20 Latest signed and dated CVs of investigators and study team members.				
C.1.1.21 Proof of valid GCP training of all study team members.				

C.1.1.22 Pre-trial GCP site assessment report (only at the Sponsor site.				
C.1.1.23 List of DSMB members (National or international)				
C.1.1.24 Verify the availability of the Local Safety Monitor's CV.				
C.1.1.25 Trial initiation visit, agenda and study team attendance list.				
C.1.1.26 Verify the availability of the Serious Adverse Event reporting forms and reporting procedures/timelines (including supporting SOPs).				
C.1.2 SOP (QC)				
C.1.2.1 Are training records for staff on SOPs available?				
C.1.2.2 Are study team trained on the protocol?				
C.1.2.3 Are study team trained on protocol specific procedures.				

C.1.3 Laboratory				
C.1.3.1 Normal values/ranges for medical/laboratory technician procedures as supplied by the laboratory.				
C.1.3.2 Is the laboratory accredited? (QC)				
C.1.3.3 Quality Control or quality assessment of laboratory by the sponsor.				
C.1.3.4 Validation methods where applicable (QC)				
C.1.4 Investigational Product				
C.1.4.1 Sample labels of IP (Only at Sponsor)				
C.1.4.2 Are IP labelled according to GMP and regulatory requirements?				
C.1.4.3 Were the IP labelled for clinical trials use only?				
C.1.4.4 All shipping records of IPs (dates, batch numbers).				

C.1.4.5 Were the records of delivery, receipt of the IP available?				
C.1.4.6 Is there a procedure for the importation and batch release?				
C.1.4.7 Proof that conditions as stated in the protocol have been maintained during shipment and storage of products.				
C.1.4.8 CoA of IPs (Check stability, batch number, expiry dates)				
C.1.4.9 Were IP accountability records e.g. quantities ordered and received available?				
C.1.4.10 Decoding procedures for blinded trials.				
C.1.4.11 Is there a randomization procedure referring to the master list according to sponsor instructions?				
C.1.4.12 Instructions for handling of investigational product and trial related materials.				
C.1.4.13 Proof that the correct diluent has been packed according to the correct storage condition and shipped with the vaccine?				
C.1.4.14 Were retention samples available?				

(In addition to having on file the aforementioned documents the following documentation should be added to the files **during** the conduct of the trial).

C.2 Documentation added during the trial				
C.2.1 Updates of Investigator's Brochure e.g. ADRs				
C.2.2 Any approved amendments to Protocol Informed consent				
C.2.3 IEC and regulatory approval of any new investigators, and their CVs .				
C.2.4 Proof of valid GCP training .				

C.2.5 Updates of normal values/ranges for medical/laboratory/technical procedures as supplied by the laboratory/contract laboratory.				
C.2.6 Vaccine accountability documentation and correct use of the product according to the protocol and IP management.				
C.2.7 Shipment documentation of any new batches of IPs including CoA, batch release and temperature control.				
C.2.8 Communication other than monitoring visits Letters Meeting minutes and agendas notes of telephone calls				
C.2.9 Signed Informed Consents				
C.2.10 Source documents e.g. X-ray, serology print out, diary cards.				
C.2.11 Signed and dated CRFs.				
C.2.12 SAE reporting to sponsor.				
C.2.13 Reporting of any serious unexpected ADR and relevant information to NRA and IEC where required.				
C.2.14 Progress reports to IEC.				
C.2.15 Participant screening log.				
C.2.16 Participant identification code list.				
C.2.17 Participant enrolment log.				
C.2.18 Study team signature sheet with delegated functions by PI.				
C.2.19 Retained biological samples (records, storage conditions).				
C.2.20 All deviations e.g. inclusive criteria (waiver) recorded.				
C.2.21 All deviation e.g. inclusive/exclusive criteria (waiver) recorded.				

(Documentation after completion or termination of the trial).

C.3 Documentation after the trial				
C.3.1 IP accountability at site (final reconciliation)				
C.3.2 Documentation on disposal of IPs .				
C.3.3 Complete participant identification code list.				
C.3.4 Audit certificate (if applicable), i.e. carried out.				
C.3.5 Final trial close-out monitoring report.				
C.3.6 Final report by investigator to IEC and regulatory authority (refer to ICH GCP section 4.13).				
C.3.7 Clinical study report (refer to ICH GCP section 5.22)				
C.3.8 Treatment allocation and decoding documentation that have occurred available.				
C.3.9 Is a follow up plan available (post trial period) for participants with adverse events related to the IP as per protocol?				

D. INFORMED CONSENT PROCESS

D.1 Was the informed consent form version used the same as the one approved by the IEC/IRB.				
D.2 Was a written SOP used to solicit informed consent?				
D.3 Were all the participants given a copy of a signed informed consent form?				
D.4 Did all the participants sign the consent form prior to any study related procedure?				