Medicines Control Authority of Zimbabwe

PHARMACOVIGILANCE AND CLINICAL TRIALS DIVISION

Clinical Trials Training Manual for Regulatory Centre of Excellence (RCORE) Training in Clinical Trials Regulatory oversight

This training manual is for capacity building in Regional Centres of Regulatory Excellence (RCOREs) and other training institutions and was adopted from the NEPAD RCORE Clinical Trial Training Manual, and in line with MCAZ Pharmacovigilance and Clinical Trials (PVCT) Division being awarded RCORE status in Clinical Trials Regulatory Oversight

Scope of the training: The Clinical trial training manual is structured based on current local and international clinical trials regulation requirements and International Conference on Harmonisation- Good Clinical Practice (ICH-GCP) guidelines. This also includes World Health Organisation (WHO), Ethics, Nuremberg Code and Declaration of Helsinki. The course is also conducted in collaboration with the MCAZ Pharmacovigilance and Clinical Trials Division, Medical Research Council of Zimbabwe (MRCZ), Clinical Pharmacology Department University of Zimbabwe Medical School and School of Pharmacy, University of Zimbabwe, experienced academic lecturers, senior regulatory officers and GCP inspectors.

Aim: The aim of the training manual is to give participant's the basic knowledge and skill to set up and run a clinical trials regulation department that competently evaluates clinical trial protocols, conduct GCP inspections, monitor ongoing clinical trials and run efficient Pharmacovigilance systems.

Objectives of the Clinical Trials Training manual.

The Clinical Trials regulatory oversight training manual is structured into the following training modules and objectives.

Module 1:– Medicinal product development, ICH-GCP and WHO Global Bench Marking Tool (GBT) Regulation Evaluation of National Regulatory System of Medicinal products-Clinical Trials Oversight (CT) indicators and fact sheets.

The objective of this module is to introduce participants to drug development and the importance of clinical trials. The principles of ICH- Good Clinical Practice are introduced here. The module also discusses the Ethics of Clinical trials in developing countries.

Module 2: Clinical Trial Protocol Evaluation:

The objective of this module is to give participants an overview of protocol development, the steps taken in preparing a protocol for a trial. With this background participants will then be introduced to protocol evaluation.

Module 3: GCP inspection and Report writing

The objective of the module is for participants will have a hands on experience of a GCP inspection and will also learn report writing and grade finding after an inspection

Module 4: Adverse Events and Safety Monitoring (Pharmacovigilance)

This module aims to provide a background and understanding on Pharmacovigilance, reporting systems, and management tools. This module will also look at reporting from clinical trial sites and management of reports.

The Clinical Trials Training program includes practical hands on training on how to evaluate a clinical trial protocol and how to conduct a GCP inspection. The same protocol used for the Protocol evaluation module will also be used for a practical GCP inspection training to be conducted in Harare, Zimbabwe. Further mentorship program/additional practical hands on training may be provided on request on attachment at the MCAZ Pharmacovigilance and Clinical Trials Division at the participants' cost.

Assessment / Course outcomes: A pre and post-test will be written for each module to determine participant's knowledge before and after training. Certificates will be issued to participants who will obtain a final mark score of 75% and above for each module. The points obtained from the course(s) may also be used for Institute of Continued Education (ICHE) points.

Who may attend the training: Regulatory officers, post graduate students including pharmaceutical industry and researchers who are interested in learning and gaining skills in Clinical trials Regulation oversight.

Cost of training: There is a subsidised training course fee for each module. Cost of accommodation/hotel, food and transport will however be borne by the participant. Sponsorship will be sourced from time to time if available.

Introduction

Introduction, Rationale and Scope

In line with the WHO Global Bench Marking Tool (GBT) for Evaluation of National Regulatory System of Medicinal products-Clinical Trials Oversight (CT) indicators and fact sheets, Revision VI version 1, November 2018, National Regulatory Authorities (NRAs) should have the legal mandate to authorize regulate and, if necessary, terminate clinical trials (CTs). The necessary requirements, guidelines, procedures and forms should be developed to be in line with country and region-specific guidelines as well as major international CT guidance including guidelines from the Declaration of Helsinki, the Nuremberg code, International Council on Harmonization, and World Health Organization Good Clinical Practices. CT oversight is aimed at protecting the safety and rights of humans participating in CTs, ensuring that trials are adequately designed to meet scientifically sound objectives, and preventing any potential fraud and falsification of data.

NRAs are responsible at two stages for the critical evaluation of the documentation supporting clinical studies: when CT's are being proposed for authorization and when the results are submitted in an application for marketing authorization. CT protocols should be reviewed and approved by Independent Ethics Committees before the trial commences. A CT review committee should review the protocols and should have the authority, when necessary, to require protocol revisions. The CT review committee should be composed of members who have the appropriate medical and scientific knowledge, experience and skills and who are free of conflicts of interest.

In order to ensure the quality and safety of investigational products, the investigational products should be manufactured in compliance with Good Manufacturing Practices for investigational medicinal products, and the supporting preclinical studies should be in compliance with Good Laboratory Practices. Additionally, the importation, storage, use, and/or destruction of investigational products should follow national requirements. Qualified and experienced inspectors should carry out on-site inspections of the CT sites to verify compliance with Good Clinical Practices, ethical principles and regulatory requirements, and to provide assurance of the quality and reliability of the data obtained. The oversight activities should be conducted with due concern for confidentiality.

The legal provisions should allow the NRA to recognize and/or rely on relevant CT decisions, reports and information from other NRAs or from designated regional and international bodies. In special circumstances (e.g., for public health interest), the legal provisions should allow the NRA to elect not to follow the routine CT procedures. Transparency in the entire oversight process is fundamental to ensuring the safety of patients and to ensuring that no product with unacceptable benefit to risk balance will be made available to the public.

Module 1: Medicinal Product development, ICH GCP, and WHO Global Bench Marking Tool (GBT) Regulation Evaluation of National Regulatory System of Medicinal products-Clinical Trials Oversight (CT) indicators and fact sheets.

Introduction to Medicinal product development

• In drug development clinical trials are often considered in four phases in addition to a pre-clinical stage. These phases are also used in vaccine development

Pre-clinical

A sponsor of a medicinal product trial first evaluates the drug's toxic and pharmacological effects through in vitro and in vivo laboratory animal testing. At the pre-clinical stage, the regulator will generally ask that sponsors:

- develop a pharmacological profile of the medicinal product
- determine the acute toxicity of the medicinal product in at least two species of animals

In animal testing, drug companies make considerable effort to use as few animals as possible and to ensure their humane and proper care.

Generally, two or more species are tested, usually one rodent, one non-rodent. The challenge is finding a relevant animal model that behaves in a similar way to a human.

Regulators are interested in the No Observed Effect Level (NOEL) and the No Observed Adverse Effect Level (NOAEL) of the medicinal product. Studies to establish a NOEL/NOAEL are generally conducted at the beginning of the toxicological test battery before the full range of short and long term health effects have been established. Short-term testing in animals takes from two weeks to three months.

Long-term testing in animals takes from a few weeks to several years. Some animal testing continues after human tests begin so long-term medicinal product use can be investigated to see whether it causes cancer or birth defects.

In addition, during the pre-clinical stage of medicinal product development, the formulation and manufacturing technique for the product are developed.

Early phase Trials

Phase I and II trials are also referred to as early phase trials. The interventions tested in early phase trials may be drugs or vaccines. Among the first tasks of early phase trials is to assess safety and define a suitable dose.

Early phase trials are generally 'exploratory' comparing the intervention with an alternative for a small number of people under tightly controlled conditions.

Early phase trials may include 'human pharmacology' studies, which describe pharmacokinetics or pharmacodynamics. Simply put, pharmacokinetics is what the body does to the medicinal product, while pharmacodynamics is what the medicinal product does to the body.

Pharmacokinetics investigates the course of a medicinal product through the body over a period of time, including processes of absorption, distribution, localisation in tissues, biotransformation, and excretion.

Pharmacodynamics investigates the mechanisms of drug action (e.g. how taking Paracetamol stops a headache.), and the relationship between medicinal product concentration and effect.

Before being licensed for use, any pharmaceutical product has to be tested in humans and shown to be efficacious. Thus, early phase trials may also be of the 'therapeutic exploratory' type, i.e. to estimate activity and dosage. Early phase trials may also start to make preliminary assessments of efficacy.

In the classification of trials by Phase I-IV, a product's first clinical trial is a Phase I trial. If successful it would then, in general, progress in turn through Phases II, III and IV.

Phase I

Phase I studies relate to the safety of the medicinal product under investigation usually in healthy volunteers. The aim is to assess major safety issues and understand how the drug is dealt with in the body.

Example of a Phase I trial

A Phase I Clinical Trial to Evaluate the Safety and Immunogenicity of a Multiple Strain Ebola DNA Plasmid Vaccine, VRC-EBODNA012-00-VP, in Adult Volunteers.

Phase II

Phase II studies usually involve a small (usually randomised) trial investigating the potential benefits of a medicinal product among patients with a particular disease. These trials are also used establish which therapies have the potential to be investigated in full-scale, phase III randomised trials while further assessing the safety of these therapies.

Example of a Phase II trial

Partnership for Research on Ebola Vaccines in Liberia (PREVAIL)

Objectives: To study the safety and efficacy of two Ebola vaccines

Late Phase: Phase III

Phase III trials are full-scale randomised controlled trials evaluating the benefits and safety of a medicinal product against a placebo or standard therapy in a substantial number of patients. This is the key stage in establishing the impact of a medicinal product and the majority of medicinal product trials you have come across in this course relate to this type of trial. They may also be called ‘pivotal’ trials.

Example of a Phase III trial

Artemisinin-Based Antimalarial Combinations and Clinical Response in Cameroon

To assess the efficacy of artesunate-amodiaquine, dihydroartemisinin-piperaquine, in comparison with artemether-lumefantrine during 42 days follow up period in 720 children with acute uncomplicated P. falciparum malaria, in two different endemic ecological areas - Savanna and equatorial forest regions of Cameroon.

Post Marketing Trials (Phase IV)

• Phase IV studies relate to the stage after a drug has been approved and involves the long-term monitoring of the safety of the drug. This phase has gained increasing importance as regulators and manufacturers realize that phases I-III trials cannot easily identify serious but rare adverse events. Hence more regulators are requesting post authorization safety studies as a condition for marketing approval.

Example of a Phase IV trial

Pharmacovigilance for ACTs in Africa (PVACT): A phase IV open label study assessing the safety and effectiveness of Artemisinin derivatives-based combination therapy (ACT) when used on a large scale and under “real life” conditions.

Ethics and Historical Perspective on Drug Development Regulations

History of Clinical Research Regulations

The Nuremberg Code 1947

The physicians involved in the Nazi experiments were tried for War Crimes in the 1945 Nuremberg trials. As a result of the trial The Nuremberg Code 1947 was passed. The code is set of principles for human experimentation. The very first statement in the code is: "The voluntary consent of the human subject is absolutely essential"

The Nuremberg Code was quickly accepted across the developed world as the definitive directive governing human experimentation.

World Medical Association

The World Medical Association (WMA) is an international organisation representing physicians. The WMA was founded on 17 September 1947, when physicians from 27 different countries met at the First General Assembly of the WMA in Paris.

The organisation was created to ensure the independence of physicians, and to work for the highest possible standards of ethical behaviour and care by physicians, at all times. This was particularly important to physicians after the Second World War, and therefore the WMA has always been an independent confederation of free professional associations.

In 1964 doctors at the World Medical Association sought to adapt the Nuremberg code thus The Declaration of Helsinki was born. This reiterated the Nuremberg Code's emphasis on voluntary and informed consent to research.

The Declaration of Helsinki

The declaration seeks to extend concern to vulnerable groups and offers special protections. There are ethical principles which provide guidance to physicians and other participants in medical research involving human subjects.

The document has been revised several times; in 1975, 1983, 1989, 1996, 2000, 2008 and 2013 with clarification in 2002 and 2004. However, in recent revisions it has become more aspirational, especially in terms of the duties researchers can discharge, such as providing long term access to interventions shown in the trial to be effective. The version currently embedded in ICH GCP is the 1996 version of the code.

Alternatives to the Declaration of Helsinki

To incorporate some of the ideas behind the Nuremberg Code and the Declaration of Helsinki into domestic US requirements, the Belmont Report was written in 1979. It outlines four main principles: respect for persons, beneficence, non-maleficence, and justice. It is more commonly referred to as the 'Common Rule,' which has legal status in the USA. This document is used particularly by ethics committees or Institutional Review Boards (IRBs), but is used more widely in the USA alongside the Declaration of Helsinki.

In 1982, CIOMS/WHO published the proposed international guidelines for biomedical research involving human participants. The International guidelines for biomedical research involving human subjects, revised in 1993, was endorsed by the WHO

Global Advisory Committee on Health Research and the Executive Committee of CIOMS. The most recent revision of the guidelines was published in 2002. The revised text consists of a description of general ethical principles and 21 guidelines with commentary. Contributors to the revision were particularly concerned with the application of ethical standards and the establishment of mechanisms for ethical review of human participants in resource-poor settings where local standards for scientific conduct may differ from those in western industrialized nations.

In 1991, CIOMS, in collaboration with WHO, prepared a separate document addressing public health and epidemiological research (International guidelines for ethical review of epidemiological studies).

In addition, two events are largely responsible for the introduction of drug safety regulation:

- In the US, in 1937, Elixir of Sulfanilamide, containing the poisonous solvent diethylene glycol, to transform a pill into a liquid for easier consumption by children killed 107 persons, many of whom were children.
- In Europe in 1961-1962, thalidomide, a sedative which was subsequently used as an anti-emetic in pregnancy, was found to have caused birth defects in thousands of babies.

Ethics in Clinical Research

Guidelines for ethical conduct in scientific research throughout the world are informed by the following ethical principles: respect for persons; beneficence/non-maleficence; and distributive justice (Beauchamp & Childress, 2001).

The principle of respect for persons emphasizes the importance of individual autonomy and, in the context of participation in scientific research, refers to the obligation of investigators to honour the wishes of a competent individual regarding their desire to participate in scientific research. A belief that individuals have the capacity to exercise free will—to act voluntarily and with self-determination — is an essential aspect of the ethical principle of respect for persons. Requirements for informed consent and confidentiality in the implementation of research are justified by the principle of respect for persons. The principle of respect for persons also suggests that researchers have an obligation to honour the concerns of communities involved in their studies.

The principle of beneficence refers to the obligation of health-care providers and health researchers to act in a way that benefits the health and well-being of participants in scientific investigations; conversely, the principle of non-maleficence concerns their obligation to do no harm. Taken together, the principles of beneficence and non-maleficence emphasize the importance of maximizing benefits and minimizing potential harms. The principle of distributive justice is directly linked to issues of equality and fairness in determining who receives the benefits and who bears the burdens of biomedical and behavioural research. Certain populations—ethnic minorities, refugees and immigrants, for example— particularly those in

resource-poor environments, may be vulnerable to discrimination, coercion, or other injustices in the implementation of scientific investigations.

Recommendations for researchers and policy-makers concerned about ethical practices in multinational studies conducted in resource-poor settings are listed below.

- **Respect the cultural traditions of study populations and communities** Respect for cultural traditions builds a foundation of trust between researchers, study participants and the local community. Researchers should identify concerns that are culturally based and develop strategies for addressing them in a meaningful way. If possible, when protocol procedures require a transgression of local traditions and customs, investigators should consider developing alternatives methods for achieving successful results.
- **Strengthen capacity for developing collaborative partnerships** Collaborative partnerships must be strengthened between researchers in resource-rich and resource poor settings. Capacity building should be a priority. Investigators should make efforts to strengthen the local health infrastructure and to provide for the continuation of effective research interventions and programmes. Collaborative partnerships should be developed between researchers, funding agencies in public and private sectors, governmental institutions, and private industry to consider seriously methods for reducing health disparities that exist between resource-rich and resource-poor communities.
- **Strengthen education in research ethics for investigators:** In many settings, educational opportunities in research ethics are often inadequate or non-existent. Training in research ethics should be strengthened for investigators in both resource-poor and industrialized nations.
- **Strengthen capacity for independent ethical review of protocols** Ethical review of research protocols in resource-poor settings should be improved. Capacity building should include greater access to educational opportunities in research ethics for members of institutional review boards (IRBs) and ethical review committees (ERCs) in both resource-poor and resource-rich countries. Particular attention should be given to the need to be cognizant of cultural differences in reviewing protocols for collaborative research. Responsibilities of multiple IRBs involved in a single project must be clarified to avoid confusion.
- **Develop culturally meaningful approaches to informed consent** Researchers should develop culturally appropriate methods for obtaining informed consent. In some settings, sensitivity to local cultural context requires that investigators provide opportunities for individuals to seek advice or permission from a third person, such as a spouse or head of household. Researchers also may need to consult with local community leaders before implementing a study. In every situation, researchers should pay attention to ethical issues arising from the imbalance of power between researchers and participants. Researchers should be creative in designing strategies to ensure adequate comprehension of study goals, procedures, risks and benefits. This may require implementing

educational interventions before consent or developing methods for determining an individual's comprehension of the study objectives.

- **Apply appropriate standards of care and provisions for medical treatment** Researchers must consider appropriate standards of care in the design and implementation of an investigation and be ready to change the design if existing therapies become available in an area in which access to such therapies was previously denied to the study populations. Researchers should work collaboratively with funding institutions, governmental agencies, and pharmaceutical companies in developing strategies to provide effective therapies for participants during the course of a study and, if relevant, after a study has ended.
- **Provide ongoing feedback to the study participants and community** Prompt and continuous feedback reassures study participants and their community that their participation in a research project is critical. Researchers should develop plans to disseminate information about the study and its results in ways that are culturally and linguistically meaningful.
- **Develop plans for resolving conflicts surrounding research implementation** Researchers should carefully consider the potential for conflicts within the community that may occur during the course of the study or at its completion. This requires adequate knowledge about community dynamics and existing power structures before conducting a study. Often, conflicts may not or cannot be anticipated. When they happen, researchers should be flexible and creative in exploring all possible solutions.

Defining Regulations (ICH, GCP)

ICH

The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) is a collaborative project that brings together to make recommendations on ways to achieve greater harmonisation in the interpretation and application of technical guidelines and requirements for product registration in order to reduce the need to duplicate tests on human and animal subjects.

Structure of ICH

ICH is a joint initiative involving both regulators and industry as equal partners in the scientific and technical discussions of the testing procedures, which are required to ensure and assess the safety, quality and efficacy of medicines.

The focus of ICH has been on the technical requirements for medicinal products containing new drugs. The vast majority of those new drugs and medicines are developed in Western Europe, Japan and the United States of America and therefore, when ICH was established, it was agreed that its scope would be confined to registration in those three regions. However, their influence is much farther reaching.

ICH is comprised of Six Parties that are directly involved, as well as three Observers and the IFPMA.

The Six Parties are the founder members of ICH which represent the regulatory bodies and the research-based industry in the European Union, Japan and the USA. These parties include the European Union (EU), European Federation of Pharmaceutical Industries and Associations (EFPIA), Ministry of Health, Labour and Welfare in Japan (MHLW), Japan Pharmaceutical Manufacturers Association (JPMA), Food and Drug Administration (FDA) and Pharmaceutical Research and Manufacturers of America PhRMA.

The following important group of non-voting members acts as a link between the ICH and non-ICH countries and regions.

a. **Standing Observers**

- The International Federation of Pharmaceutical Manufacturers and Associations (IFPMA)
- The World Health Organization (WHO)

b. **Observers**

- Legislative or Administrative Authorities
- Regional Harmonization Initiatives (RHIs)
- International Pharmaceutical Industry

c. **Organizations**

- International Organizations with an Interest in Pharmaceuticals

The ICH policies are divided into different topics as outlined below.

- **Quality Topics**: Those relating to chemical and pharmaceutical Quality Assurance. Examples: Q1 Stability Testing, Q3 Impurity Testing
- **Safety Topics**: i.e., those relating to in vitro and in vivo pre-clinical studies. Examples: S1 Carcinogenicity Testing, S2 Genotoxicity Testing
- **Efficacy Topics**: i.e., those relating to clinical studies in human subjects.

Examples: E4 Dose Response Studies, Carcinogenicity Testing, E6 Good Clinical Practices. (Note Clinical Safety Data Management is also classified as an "Efficacy" topic - E2)

Good Clinical Practice

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

Compliance with this good practice provides assurance that the rights, safety and well-being of trial subjects are protected, and that the results of the clinical trials are credible and accurate.

ICH E6 (R2) and (R1) lays out the principles of GCP and can be traced back to 1996.

This document is called "Guideline for Good Clinical Practice" and is presented in full in the International Conference on Harmonisation ICH E6 document. ICH GCP provides the standard reference (ICH-GCP)

1. Clinical trials should be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, and that are consistent with GCP and the applicable regulatory requirement(s).
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.
3. The rights, safety, and well-being of the trial subjects are the most important considerations and should prevail over interests of science and society.
4. The available preclinical and clinical information on an investigational product should be adequate to support the proposed clinical trial.
5. Clinical trials should be scientifically sound, and described in a clear, detailed protocol.
6. A trial should be conducted in compliance with the protocol that has received prior institutional review board (IRB)/independent ethics committee (IEC) approval/favourable opinion.
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.
8. Each individual involved in conducting a trial should be qualified by education, training, and experience to perform his or her respective task(s).
9. Freely given informed consent should be obtained from every subject prior to clinical trial participation.
10. All clinical trial information should be recorded, handled, and stored in a way that allows its accurate reporting, interpretation and verification.
11. The confidentiality of records that could identify subjects should be protected, respecting the privacy and confidentiality rules in accordance with the applicable regulatory requirement(s).
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.

13. Systems with procedures that assure the quality of every aspect of the trial should be implemented.

Institutional Review Board/Independent Ethics Committee

The following components are to be discussed.

- Membership Composition
- Functions and Operations
- Procedures and Records
- Role and Importance of the IRB/IEC in Clinical Trials
- Central vs Local IRBs

Ethics

- Proof of approval from authorized institutions e.g. IRB and ERC

Informed consent Form

- Identification of Study
- Identification of Investigators
- Identification of Sponsor
- Study Procedures
- Participant involvement
- Benefits/Risks
- Compensation
- Confidentiality of data

WHO Global Bench Marking Tool IGBT) requirements for evaluation of national Regulatory System of medicinal products-Clinical trials oversight (CT) indicators and fact sheets. Revision VI version 1, November 2018

Regulatory systems play a key role in assuring the quality, safety, and efficacy of medicinal products. Effective regulatory systems are an essential component of health systems and contribute to desired public health outcomes and innovation. The WHO- Global Benchmarking Tool (GBT) represents the primary means by which the WHO objectively evaluates regulatory systems, as mandated by WHA Resolution 67.20 on Regulatory System Strengthening for medicinal products. The tool and benchmarking methodology enables the WHO and regulatory authorities to:

- identifies strengths and areas for improvement;
- facilitate the formulation of an institutional development plan (IDP) to build upon strengths and address the identified gaps;
- prioritize IDP interventions; and
- monitor progress and achievements.

The GBT Revision VI replaces all tools previously used by WHO, representing the first truly 'global' tool for benchmarking regulatory systems. The GBT is designed to evaluate the overarching regulatory framework and the component regulatory functions (e.g. clinical trial oversight) through a series of sub-indicators that may also be grouped and examined according to nine cross-cutting categories or themes, for example, quality and risk management system. Fact sheets have been developed for each sub-indicator to guide the benchmarking team and ensure consistency in the evaluation, documentation and rating of the sub-indicator. The GBT also incorporates the concept of 'maturity level' or ML (adapted from ISO 9004), allowing WHO and regulatory authorities to assess the overall 'maturity' of the regulatory system on a scale of 1 (existence of some elements of regulatory system) to 4 (operating at advanced level of performance and continuous improvement). Revision VI of the GBT is comparable to Revision V while at the same time incorporating refinements intended to improve its usability.
WHO intends to use Revision VI of the GBT to evaluate and publicly designate WHO-listed authorities (WLAs) that have been objectively documented to perform at ML 3 or ML 4*. The proposed definition for WLAs and process by which this designation or 'listing' would occur will be the subject of a concept note that will be made available for public consultation

As part of the background reading material, please refer to the WHO -GBMT guidance documents REV. VI available on the WHO website https://www.who.int/medicines/regulation/benchmarking_tool/en/

The WHO GBT tool basically has 9 automated regulatory functions grading assessment tools that automatically assigns scores for each regulatory function 01 to 09 that will indicate the result of the WHO GBT performance maturity levels 1-4 depending on the answers given during the assessment. The WHO GBT regulatory functions include the following:

1. National regulatory system (RSs): indicators and fact sheets
2. Registration and marketing authorization (MA): indicators and fact sheets
3. Vigilance (VL): indicators and fact sheets
4. Market surveillance and control (MC): indicators and fact sheets
5. Licensing establishments (li): indicators and fact sheets
6. Regulatory inspection RI): indicators and fact sheets
7. Laboratory testing (LT): indicators and fact sheets
8. Clinical trials oversight (CT): indicators and fact sheets
9. NRA lot release (LOT): indicators and fact sheets

Module 2: Clinical Trial Protocol Evaluation

Clinical Trial Protocol Development

1. Overview/Background/Justification/Defining the Question and Intervention

This session will give the rationale for having a protocol and how it plays a role as the contract between the investigator and sponsor as well as the guiding document for the evaluation and monitoring of the study. The specifics to be discussed will include:

- What is known?
- What tools should be used in addressing the question
- What is the study hypothesis?
- The Investigational product to be used
- What is the clinical question being addressed
- How will the results be presented?
- How the clinical question should be addressed/answered
- Safety issues
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2. Designing/Building and Drafting the Protocol

This session will discuss the structure of the trial protocol, the format and the key components. Key Components include:

- Trial Summary and flow chart
- Procedure, treatment and follow up
- Investigational plan/study conduct/safety issues
- Outcome measures and Discontinuity
- Trial Design
- Sample size and statistical analysis plan
- Eligibility criteria and enrolment process
- Quality Assurance and Publication Policy
- Randomization
- Ethical considerations
- General information
- Protocol Identity

Reviewing the Protocol and case report forms/Defining Data

By the end of this session, the candidate will have been introduced to the systematic way of reviewing clinical trial protocols and the case report forms to help him/her understand the background, rationale, objectives, design, methodology, statistical considerations, organization of the clinical trial and the types of data being collected. The details to be discussed are:

Trial Protocol

- Data Sources
- Objective/design/methodology
- Data collection methods
- Process
- Statistical analysis requirements and strategies
- Data review requirements
- Therapeutic considerations
- Data requirements
- Data integration and export
- Coding requirements
- Administrative structure

Case Report Forms

- Review of case report form
- Understanding the CRF
- How are participants identified?
- Visits are uniquely identified
- Chronology of visits
- CRF collects all data?

Data

- What is data
- Types of data
- Regulatory requirements for data- validation
- Data management
- Data storage and retrieval

Developing Clinical Trial Applications

(Study Protocol, Inform Consent Form, Investigator's Brochure, DSMB)

Operational Tools

- Forms
- Guidelines
- SOPs
- Checklists
- Templates

General Information

- Protocol identity
- Investigator's details
- Sponsor's details
- Investigator/Sponsor agreement
- Responsible persons
- Exclusion Criteria
- Withdrawal criteria
- Effect of withdrawal procedures on objectives
- Treatment per participants
- Participant compliance
- Rescue medications

Background to Study

- Supporting data
- Investigational product details
- Evidence of safety/efficacy/effectiveness of IP/ placebo – GMP compliance
- Justifications
- Population
- IP/Placebo
- References
- Study Design

Trial objectives

- Endpoints
- Relationships between objectives & endpoints
- Bias control measures
- Study procedures
- Stopping rules
- Product accountability
- Source documents, CRFs

Participants

- Number
- Inclusion criteria
- Exclusion criteria
- Withdrawal criteria
- Effect of withdrawal procedures on objectives
- Treatment per participants
- Participant compliance
- Rescue medications (if any)

Assessing efficacy and safety

- Efficacy
  - Parameters
  - Method & timing of recording parameters
  - Analysis
- Safety
  - Parameters
  - Method & timing
  - Analysis

SAE Management

- Definition
- Reporting structure
- Reporting timelines
- Forms
- Responsibilities

Statistical methods

- Sample size determination
- Stopping rules
- Data management
- Population for analysis

Observing the Pharmacovigilance and Clinical Trials (PVCT) Committee Meeting

Participants, as observers, of the Pharmacovigilance and Clinical Trials PVCT Committee meeting shall be able to appreciate the mandate of the PVCT which is to provide the Authority with on-going and timely medical and scientific advice on current and emerging issues related to clinical trials through

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Regularly review and advise the Authority on the clinical trials system in Zimbabwe and make recommendations regarding its maintenance and improvement.

Perform causality assessment of Adverse Event (AE) reports relating to clinical trials presented to the PVCT by the Authority. Upon request Authority, the PVCT will make recommendations to the Authority regarding actions the Authority may take to resolve issues or concerns related to the conduct of clinical trials. The PVCT will also recommend to the governing Authority, based on information made available to it by the by the Authority on the need halt or suspend a clinical trial.

The PVCT may also recommend publication of case reports, their risk/benefit evaluations, recommendations and communications arising from the PVCT meetings that are deemed appropriate for medical and scientific journals with prior consent of the sponsor.

The PVCT may recommend educational programs and topics for investigators aimed at enhancing reporting of AEs and improving compliance to Good Clinical Practice (GCP) as recommended by the ICH (International Conference on Harmonization) Guidelines and Helsinki Declaration.

Advise the Authority periodically on the MCAZ guidelines for clinical trials and GCP.

Advise the Authority on clinical end points in the review of protocols submitted to the Authority.

Evaluation of final reports of clinical trials that have been approved by the Authority. Such evaluation will be based on the information provided to the PVCT by the Authority. Evaluations should be relevant to the risk/benefit implications for the trial in question.

Advise the Authority on issues relating to GCP and Good Laboratory Practice (GLP) inspections conducted.

Note: Each participant shall be required to sit in a PVCT meeting prior to which a non-disclosure and conflict-of-interest form shall be signed

Evaluation of Clinical Trial Applications

Objectives

Participants shall be able to

1. Identify essential components of a CTA and the completeness of an application
2. Evaluate the under listed documents as per ICH GCP and applicable

country specific regulatory requirements
   2.1 Protocol
   2.2 Investigator's Brochure
   2.3 Informed Consent Form
3. Identify lapses in a CTA

Clinical Trial Application (CTA) Screening/Pre-Assessment

To facilitate effective and complete review of Clinical Trial Applications (CTAs), all CTAs should be screened for completeness before being processed for review. Availability of information required apart from permitting effective and holistic review also promotes optimal use of resources. If deficiencies are identified at screening, these should be duly communicated to the Applicant within the shortest possible time.

CT regulators (NRA) and ethics committees must develop and appropriate CT application system requirement. For example please refer to the MCAZ online CT application requirements. https://e-ctr.mcaz.co.zw

Assessment of a Clinical Trial Protocol

A protocol is "a document that describes the objective(s), design, methodology, statistical considerations and 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. Throughout the ICH GCP Guideline, the term protocol refers to protocol and protocol amendments". The protocol describes how to treat and evaluate the trial participants; it serves as a reference for monitoring and auditing trial conduct, and it conveys the plan for analysing the data when the study is complete.

Institutional Review Boards (IRBs) or Ethics Committees and regulatory authorities use the protocol as the basis for approving whether a trial can be initiated. A well-constructed protocol can ensure common understanding of the study objectives and procedures to be implemented, thereby improving quality and saving time and effort for those using it.

A protocol therefore is considered as the single-most important quality control tool for all aspects of a clinical trial; especially true in a multi-centre clinical trial, which requires collaboration in the research activities of many investigators and their staff at multiple institutions.

ICH requires that;

- Clinical trials be scientifically sound, and described in a clear, detailed protocol.
- A trial should be conducted in compliance with the protocol that has received prior institutional review board (IRB)/independent ethics committee (IEC) approval/favourable opinion.

Current best practice also requires regulatory review and approval for trial protocols before they are implemented.

Assessment of Informed Consent Forms

The content of Informed consent forms for a medical product CT in humans must comply with the current local and international ethics guidelines such as CIOMS ethics guidelines etc. that have their origins from the Declaration of Helsinki. This includes written voluntary consent and provision for signing and dating, including aspects of ascent for minors etc.

Assessment of Suitability of the Investigational Product

An investigational product is defined as "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 authorization when used or assembled (formulated or packaged) 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".

The investigational product is the pivot around which a clinical trial is conducted. It is therefore essential and critical for regulatory authorities to assess whether available nonclinical and clinical information on an investigational product is adequate to support the proposed clinical trial and is safe to be used in a proposed trial.

Information on the above is usually provided in the under listed documents;

- The Investigational product dossier (IPD)
- Investigator's brochure (IB) and
- The summary of product characteristics (SmPC).

These documents are comprehensive documents that summarize the body of information about an investigational product. They are critically important throughout the drug development process and must be updated with new information as it becomes available

Investigational Product Dossier (IPD)

The Investigational Product Dossier (IPD) is one of several pieces of Investigational Medicinal Product (IMP) related data required whenever the performance of a clinical trial is intended.

The IPD is one of the core documents that compose the CTA.

The IPD gives information on;

- the quality of the IP including reference products and placebos to be used in the clinical trial,
- data from non-clinical studies
- data from previous clinical trials
- its clinical use

The IPD uses the information above to evaluate the benefits and risks associated with the administration of an IP during the conduct of the clinical trial.

The Quality section of the IPD, describes all aspects of the Chemistry, Manufacturing and Control (CMC) of the product under investigation thus ensuring safety and establishing the scientific relevance of the IP along with already completed non-clinical and clinical studies. The nature of the information and the level of detail to be provided in an IPD vary depending on the product type (New Chemical Entity, Biologics, Cell and Gene Therapy Products) and the stage of clinical development. If information required is not available, it must be justified in the CTA.

An Applicant may cross-refer to the IB for the pre-clinical and clinical parts of the IPD.

Requirements for submission of information on the IP

The requirements for information on the investigational products differ from country to country.

Generally, however, it is required that for non-marketed IPs, an IPD must be submitted with an IB for review. In some cases, an IB may be submitted with supporting documents outlining the chemistry, manufacturing and control (CMC) of the IP.

If an IP already has marketing authorization in the respective country, the information in SmPC is considered as adequate for the assessment of the IP. In this instance, the IPD and IB may not be required as it is envisaged that, information provided in the IB has been reviewed as part of the marketing authorization application. An IPD may also be waived depending on the phase of the clinical trial and knowledge accrued on the IP at the time of submission of the application e.g. late clinical development stage i.e. phase 3 and post phase 3 studies. In such cases submission of only IB will suffice. However, if a marketed product is being studied for a new use (i.e., a new indication), an IB specific to that new use should be prepared

Other Guidelines include those for National Regulatory Agencies for clinical trials in Zimbabwe:

The Medicines Control Authority of Zimbabwe (MCAZ)

The MCAZ is responsible for protecting public and animal health by ensuring that accessible medicines and allied substances and medical devices are safe, effective and of good quality through enforcement of adherence to standards by manufacturers and distributors. Its mandate of MCAZ is to protect public health ensuring that medicines and medical devices on the market are safe, effective and of good quality. The Medicines Control Authority of Zimbabwe (MCAZ) Pharmacovigilance and Clinical Trials (PVCT) was

awarded Regulatory Centres of Excellence (RCORE) status in Clinical Trials Regulation oversight, in collaboration with the Medical Research Council of Zimbabwe (MRCZ).

Visit http://www.mcaz.co.zw for more details.

The Medical Research Council of Zimbabwe (MRCZ)

This is the National Ethics Committee (NEC) established in 1974 in terms of the Research Act of 1959 and Government Notice Number 225 of 1974 in order to provide health researchers and institutions which/in which health research is conducted, with independent ethical advice on research conducted by those researchers or by/within those institutions. The MRCZ is established and supported by the Government of Zimbabwe through the Ministry of Health and Child Welfare.

Visit http://www.mrcz.org.zw for more details.

The Research Council of Zimbabwe (RCZ) was established in 1986 to promote, direct, supervise and coordinate research. One of the major functions of RCZ is advising Government on issues of research for sustainable development. RCZ also provides an exceptional forum for interaction and discussion for the mutual benefit of Government, academia and industrialists.

Visit: http://www.rcz.ac.zw/ for more details

The National Biotechnology Authority is established in terms of the National Biotechnology Act of 2006. Its functions are to support and manage biotechnology research, development and application in Zimbabwe.

Some Examples of National Regulatory Agencies

The Food and Drug Administration in the USA

The US Food and Drug Administration is the largest of the world's drug regulatory agencies. It has a wide range of responsibilities for drugs, biologicals, medical devices, cosmetics and radiological products. The FDA consists of administrative, scientific and regulatory staff organised under the Office of the Commissioner.

Visit http://www.fda.gov/for more details

The European Medicines Agency in the EU

The European Commission represents the 27 members of the EU. The Commission is working, through harmonisation of technical requirements and procedures, to achieve a single market in pharmaceuticals which would allow free movement of products throughout the EU. The European Medicines Agency

(EMA) was established by the Commission. Technical and scientific support is provided by the Committee for Medicinal Products for Human Use (CHMP) of the EMA.

Visit http://www.ema.europa.eu for more details.

Each Member State has its own agency. For example, in the UK, the Medicines and Healthcare products Regulatory Agency is legally required to oversee domestic regulation.

Visit http://www.mhra.gov.uk for more details.

The Ministry of Health, Labour and Welfare in Japan

The Ministry of Health, Labour and Welfare has responsibilities for approval and administration of drugs, medical devices and cosmetics in Japan. Technical and scientific support are provided by the Pharmaceuticals and Medical Devices Agency (PMDA) (which was established in April 2004 as a new administrative agency for scientific review for drug approval), and by the National Institute of Health Sciences (NIHS) and other experts from academia.

Visit http://www.mhlw.go.jp/english/index.html for more details.

The Food and Drugs Authority, Ghana

It is the National Regulatory Authority, established in August 1997 to regulate food, drugs, food supplement, herbal and homeopathic medicines, veterinary medicines, cosmetics, medical devices, household chemical substances, tobacco and tobacco products. The FDA is also mandated to have regulatory oversight of clinical trials in Ghana. The FDA, Ghana, was awarded Regulatory Centres of Excellence (RCORE) status in Clinical Trials Regulation oversight, in collaboration with the University Of Ghana School Of Public Health.

The FDA was also awarded RCORE in Medicines Registration. Visit http://www.fdaghana.gov.gh for more details.

Module 3: GCP Inspection and report Writing.

Objectives

Participants shall be able to:

- Apply the necessary knowledge and skills required to ensure the application of ethical principles and good clinical practices in biomedical research being conducted locally
- Ensure the appropriate application of international standards in the evaluation and monitoring of clinical trials.
- Prioritize clinical trial sites for GCP inspections
- Able to use the GCP checklist as a guide during inspections in order to harmonize/standardize procedures.
- Grade GCP observations/findings made during inspections
- Assign responsibilities to these observations made with respect to the study team
- Make appropriate recommendations to the study team after GCP inspections
- Take the necessary regulatory actions against the site/study when necessary

Participants should familiarize themselves with the GCP inspection guide before the scheduled inspection. Any questions on it should be discussed with the facilitator.

- Using the guide as a checklist, each participant must note down his/her observations during the inspection.
- Using the grading provided in the GCP inspection guide grade the observations/ inspection findings you have made with appropriate justifications in line with ICH E6 (R2). Appropriate references from the ICH E6 (R2) and the relevant national guidelines should be provided for all observations made.
- Assign responsibilities to the observations made.
- Make a general recommendation on the site's compliance to GCP.
- What action should be taken based on your recommendation above?

Below are a number of risk factors that may influence decisions to conduct an inspection at a clinical trial site,

- The phase of the clinical trial
- The nature of the investigational product
- The market authorization status of the investigational product
- The population under study
- The study design
- Capacity of trial site

- Previous experience of the regulator with sponsor/principal investigator with respect to compliance to GCP requirements.

Develop a risk assessment scale/algorithm for the above and explain how the scale you have developed will influence how you will prioritize GCP inspections for your institution.

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

Clinical trials, conducted within the European Union, must comply with the requirements of the 'Clinical Trial Directive' and GCP Directive 2005/28/EC. According to Directive 2001/83/EC all clinical trials included in marketing authorisation applications in the European Union, irrespective of their geographical location, are required to be conducted in accordance with the GCP and ethical principles equivalent to those of Directive 2001/20/ EC.

Any clinical trial included in the application could be subject to inspection. Compliance by an applicant or marketing-authorisation holder (MAH) with GCP and the other provisions of a marketing authorisation for medicinal products for administration to humans will be assessed by the EU/EEA Inspectorates when the Committee for Medicinal Products for Human Use (CHMP) considers it necessary. The CHMP may request inspections in EU/ EEA and also in third countries (i.e. countries outside the EU/EEA).

The inspections are usually requested during the initial review of a marketing authorization application (MAA), but could be raised post-authorization (e.g. inspection of studies conducted or completed as part of the condition of a marketing authorization, a new indication, a new pharmaceutical form or because of concerns arising from the studies previously submitted).

Different types of GCP inspections may be requested by the CHMP. The scope of these inspections may vary according to the objectives and the focus of the inspections. These inspections may be routine or may be triggered by issues arising during the validation of the pivotal clinical trials submitted to the European Medicines Agency (herein after 'the Agency') or during the assessment of the dossier by the assessors or by other information such as previous inspection experience.

A routine inspection is an inspection carried out as a routine surveillance of GCP compliance in the absence of specific trigger elements.

A triggered inspection is an inspection requested because there is a concern due to either the actual issues observed or the potential impact of deviations from GCP on the conduct of the study as a whole or at a particular site. In general, the CHMP request for a GCP inspection is focused on the most important trials involved in the application.

The objectives of a GCP inspection requested by the CHMP are:

- To determine whether the trial was conducted in accordance with applicable regulatory requirements which include local regulations and ethical standards, and the CPMP/ICH/135/95 Note for Guidance on GCP (ICH-GCP), Directive 2001/83/EC as amended and Directive 2001/20/EC
- To provide answers to questions arising from the assessment process;
- To determine whether the data submitted in the dossier are credible and accurate.

The findings or failures to comply with GCP are presented formally to the representatives of the inspected entity and the sponsor/applicant of the trial in the inspection report (IR). Any response from the inspected entity and the sponsor is considered and the process is completed with the issuing of the IR and its addenda to the Agency. If the outcome of the inspection is negative (GCP non-compliance and/or invalid data), the CHMP can take any necessary regulatory action, which may involve the refusal to authorize the product or the indication submitted, etc.
The grading of each finding is entered as classified in the IR. The findings are classified by the GCP Inspectors as “critical”, “major” and “minor”

Critical: 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 totally unacceptable. Possible consequences: rejection of data and/or legal action required. Observations classified as critical may include a pattern of deviations classified as major, bad quality of the data and/or absence of source documents. Manipulation and intentional misrepresentation of data belong to this group.

Major: Conditions, practices or processes that might adversely affect the rights, safety or well-being 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: data may be rejected and/or legal action required. Observations classified as major, may include a pattern of deviations and/or numerous minor observations.

Minor: 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. Possible consequences: 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

Module 4: Adverse Events and Safety Monitoring (Pharmacovigilance)

Adverse Events

Objectives

- At the end of this session, participants should be able to:
- Know the components of adverse event reporting form (CIOMS 1 form) and the annual progress report form
- Understand the criteria for assessing seriousness criteria to adverse events received from clinical trial sites.
- Appreciate the important of phase IV studies and post approval safety monitoring
- Understand aggregate reporting (PSUR/PBRERs) and risk minimization activities

Definitions of Adverse Events, Adverse Drug Reactions and Serious Adverse Events (SAE)

Adverse Event (AE) Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An adverse event (AE) can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

Serious Adverse Event (SAE) or Serious Adverse Drug Reaction (Serious ADR) 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.

Unlisted (Unexpected) Adverse Event An adverse event is considered unlisted if the nature or intensity is not consistent with the applicable product reference safety information. For a study drug, the expectedness of an adverse event will be determined by whether or not it is listed in the Investigator's Brochure.

SUSAR Suspected Unexpected Serious Adverse Reaction

The Importance of reporting Adverse Events

The purpose of expedited reporting is to make regulators, investigators ethics committees aware of new important information on serious reactions. It is required for all unexpected adverse events.

The investigator has certain responsibilities for immediate reporting (within 24 hours) of all serious adverse effects (SAEs) to the sponsor followed by detailed written reports. The sponsor should keep all records of SAEs and notify competent regulatory authorities and where appropriate the ethics committee that approved the trial.

There are specific requirements for reporting suspected unexpected serious adverse (drug) reactions (SUSARs) for clinical trials of an investigational medicinal product (CTIMPs).

All SUSARs must be reported to the regulator within specific timelines:

Fatal or life-threatening SUSARs: The regulator must be notified of the initial report, irrespective of the amount of information, as soon as possible, but no later than seven calendar days after first knowledge by the research team that the case qualifies as a SUSAR. Additional information, if required, must be obtained by the research team urgently and as complete a report as possible must follow within eight additional calendar days

All other SUSARs

A complete report needs to be filed as soon as possible but no later than the minimum criteria for reporting as applicable regulatory guidelines in each respective NRA.

Process of reporting Adverse Events

It is the responsibility of the investigator to collect all AEs (both serious and non-serious). The computer algorithms to assign a probable cause

Verbal autopsies

A verbal autopsy (VA) is a method of gathering deaths are undocumented health information about a deceased individual to determine his/her cause of death. Health information and a description of events prior to death are acquired from conversations or inter-views with a person or persons familiar with the deceased and analysed by health professionals or computer algorithms to assign a probable cause of death. Verbal autopsy is use in settings where deaths are undocumented.

AE/SAE form will need to be completed in the case of death.

Post Marketing Approval & Phase IV Safety Monitoring

1. Public health impact of adverse drug reactions
2. Requirements to strengthening Pharmacovigilance:
    - 2.1 Resources
    - 2.2 Law
    - 2.3 Science
3. Pharmacovigilance Regulation

▫ Promote and protect public health by reducing burden of ADRs and optimizing the use of medicines:

- 3.1 Clear roles and responsibilities
- 3.2 Science based (move up hierarchy)
- 3.3 Risk based/proportionate
- 3.4 Increased proactivity/planning
- 3.5 Reduced duplication/redundancy
- 3.6 Integrate benefit and risk
- 3.7 Communication and transparency

4. Addresses almost all Pharmacovigilance activities
    - 4.1 Authorization requirements
    - 4.2 Risk Management Plans
    - 4.3 PSURs
    - 4.4 Scientific Committees
    - 4.5 Transparency and communication
    - 4.6 Coordination of inspections
    - 4.7 Audits
    - 4.8 Effectiveness of risk minimization

4.9 ADR reporting

5. Post-authorization safety studies

`5.1 Definition

5.2 General guidance and requirements

5.3 Good vigilance practice guidance

5.4 Clinical trial

5.5 Non-interventional study

6. Reporting of Pharmacovigilance data

6.1 Data relevant to the risk benefit balance

6.2 Reporting of ADRs:

6.3 Timelines for serious and non-serious ADRs

Reporting from Clinical Trial Sites

Objectives

Participants will be able to

- Identify the different types of reports expected to be submitted from trial sites (AE/SAE reports, trial progress reports, DSMB reports, trial close-out reports, final trial report)
- Appreciate the need to submit these reports
- Apply knowledge and skills acquired to assess these reports as per ICH GCP and applicable national regulatory requirements.
- Identify issues/lapses with respect to submitted reports
- Make the necessary recommendations to the trial team as well as take the necessary actions against the site/trial.

This session will be in the form of debate with participants being put into groups to debate the motion:

Debaters must address issues such us

- Types or reports required/not required with respect to the respective stages in the lifecycle.
- Justification for “a” above.
- The mode/format/tools/alternatives for reporting.
- Timelines for reporting
- Impact of listed reports/alternatives on data quality and participant safety
- . Persons responsible for reporting

Hint: The facilitator must have access to the national ref. Persons/authorities to whom respective reports/ porting requirements, formats and timelines to guide discussions after the debate.-

Risks Management and Signal Detection

The aim of this Session is to introduce how project risks can be identified and managed during a clinical trial.

By the end of the Session you will be able to:

- understand the concept of risk in general and as applicable
- develop a methodology to evaluate (quantify) the risk applicable to clinical trials
- describe the control (management) of risk

- list the sources of risk in clinical trials including:
- develop a system for documenting risk
    - development of a process to identify risks
    - describing the techniques used to systematically identify risks
- describe the types of responses to risks
- review the risk element associated with contracts ▫
- recognise risk management as key to success

GLOSSARY

Adverse Drug Reaction (ADR) In the pre-approval clinical experience with a new medicinal product or its new usages, particularly as the therapeutic dose(s) may not be established: all noxious and unintended responses to a medicinal product related to any dose should be considered adverse drug reactions. The phrase responses to a medicinal product means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility, i.e. the relationship cannot be ruled out. Regarding marketed medicinal products: a response to a drug which is noxious and unintended and which occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of diseases or for modification of physiological function (see the ICH Guideline for Clinical Safety Data Management: Definitions and Standards for Expedited Reporting).

Adverse Event (AE) Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An adverse event (AE) can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

Amendment (to the protocol) See Protocol Amendment.

Applicable Regulatory Requirement(s) Any law(s) and regulation(s) addressing the conduct of clinical trials of investigational products.

Approval (in relation to Institutional Review Boards) The affirmative decision of the IRB that the clinical trial has been reviewed and may be conducted at the institution site within the constraints set forth by the IRB, the institution, Good Clinical Practice (GCP), and the applicable regulatory requirements.

Audit 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 regulatory requirement(s).

Audit Certificate A declaration of confirmation by the auditor that an audit has taken place.

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

Audit Trail Documentation that allows reconstruction of the course of events.

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).

Case Report Form (CRF) A printed, optical, or electronic document designed to record all of the protocol required information to be reported to the sponsor on each trial subject.

Clinical Trial/Study 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.

Clinical Trial/Study Report A written description of a trial/ study of any therapeutic, prophylactic, or diagnostic agent conducted in human subjects, in which the clinical and statistical description, presentations, and analyses are fully integrated into a single report (see the ICH Guideline for Structure and Content of Clinical Study Reports).

Comparator (Product) An investigational or marketed product (i.e., active control), or placebo, used as a reference in a clinical trial.

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

Confidentiality Prevention of disclosure, to other than authorized individuals, of a sponsor's proprietary information or of a subject's identity.

Contract A written, dated, and signed agreement between two or more involved parties that sets out any arrangements on delegation and distribution of tasks and obligations and, if appropriate, on financial matters. The protocol may serve as the basis of a contract.

Coordinating Committee A committee that a sponsor may organize to coordinate the conduct of a multicentre trial.

Coordinating Investigator An investigator assigned the responsibility for the coordination of investigators at different centres participating in a multicentre trial.

Contract Research Organization (CRO) A person or an organization (commercial, academic, or other) contracted by the sponsor to perform one or more of a sponsor's trial-related duties and functions.

Direct Access Permission to examine, analyse, verify, and reproduce any records and reports that are important to evaluation of a clinical trial. Any party (e.g., domestic and foreign regulatory authorities, sponsor's monitors and auditors) with direct access should take all reasonable precautions within the constraints of the applicable regulatory requirement(s) to maintain the confidentiality of subjects' identities and sponsor's proprietary information.

Documentation All records, in any form (including, but not limited to, written, electronic,

magnetic, and optical records, and scans, x-rays, and electrocardiograms) that describe or record the methods, conduct, and/ or results of a trial, the factors affecting a trial, and the actions taken.

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

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

Data and Safety Monitoring Board (DSMB)) (Independent Data Monitoring Committee, Monitoring Committee, Data Monitoring Committee) An independent data-monitoring committee that may be established by the sponsor to assess at intervals the progress of a clinical trial, the safety data, and the critical efficacy endpoints, and to recommend to the sponsor whether to continue, modify, or stop a trial.

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 subject or the subject's legally acceptable representative cannot read, and who reads the informed consent form and any other written information supplied to the subject.

Independent Ethics Committee (IEC) An independent body (a review board or a committee, institutional, regional, national, or supranational), constituted of medical professionals and non-medical members, whose responsibility it is to ensure the protection of the rights, safety and well-being of human subjects involved in a trial and to provide public assurance of that protection, by, among other things, reviewing and approving/providing favourable opinion on, the trial protocol, the suitability of the investigator(s), facilities, and the methods and material to be used in obtaining and documenting informed consent of the trial subjects. The legal status, composition, function, operations and regulatory requirements pertaining to Independent Ethics Committees may differ among countries, but should allow the Independent Ethics Committee to act in agreement with GCP as described in this guideline.

Informed Consent A process by which a subject 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. Informed consent is documented by means of a written, signed and dated informed consent form.

Inspection The act by a regulatory authority(ies) of conducting an official review of documents, facilities, records, and any other resources that are deemed by the authority(ies) to be related to the clinical trial and that may be located at the site of the trial, at the sponsor's and/or contract research organization's (CRO's) facilities, or at other

establishments deemed appropriate by the regulatory authority(ies).

Institution (medical) any public or private entity or agency or medical or dental facility where clinical trials are conducted.

Institutional Review Board (IRB) An independent body constituted of medical, scientific, and non-scientific members, whose responsibility is to ensure the protection of the rights, safety and well-being of human subjects involved in a trial by, among other things, reviewing, approving, and providing continuing review of trial protocol and amendments and of the methods and material to be used in obtaining and documenting informed consent of the trial subjects.

Interim Clinical Trial/Study Report A report of intermediate results and their evaluation based on analyses performed during the course of a trial.

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 authorization when used or assembled (formulated or packaged) 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.

Investigator A person responsible for the conduct of the clinical trial at a trial site. If a trial is conducted by a team of individuals at a trial site, the investigator is the responsible leader of the team and may be called the principal investigator. See also Sub-investigator.

Investigator/Institution An expression meaning "the investigator and/or institution, where required by the applicable regulatory requirements".

Investigator's Brochure A compilation of the clinical and Preclinical data on the investigational product(s) which is relevant to the study of the investigational product(s) in human subjects.

Legally Acceptable Representative (LAR) An individual or juridical or other body authorized under applicable law to consent, on behalf of a prospective subject, to the subject's participation in the clinical trial.

Medicinal Product: A substance or combination of substances that is intended to treat, prevent or diagnose a disease, or to restore, correct or modify physiological functions by exerting a pharmacological, immunological or metabolic action.

Monitoring The act of overseeing the progress of a clinical trial, and of ensuring that it is conducted, recorded, and reported in accordance with the protocol, Standard Operating Procedures (SOPs), Good Clinical Practice (GCP), and the applicable regulatory requirement(s).

Monitoring Report A written report from the monitor to the sponsor after each site visit and/or other trial-related communication according to the sponsor's SOPs.

Multicentre Trial A clinical trial conducted according to a single protocol but at more than one site, and therefore, carried out by more than one investigator.

Preclinical Study Biomedical studies not performed on human subjects.

National Regulatory Authority (NRA) The national competent authority responsible for authorizing and monitoring a clinical trial taking place in its country. Some of these Agencies are responsible for the regulation and control of medicinal products such as medicines, vaccines, blood products and medical devices.

Opinion (in relation to Independent Ethics Committee): The judgement and/or the advice provided by an Independent Ethics Committee (IEC).

Original Medical Record See Source Documents.

Post authorization safety study (PASS): Any study relating to an authorised medicinal product conducted with the aim of identifying, characterising or quantifying a safety hazard, confirming the safety profile of the medicinal product, or of measuring the effectiveness of risk management measures.

A post-authorisation safety study may be an interventional clinical trial or may follow an observational, non-interventional study design.

Protocol A document that describes the objective(s), design, methodology, statistical considerations, and 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. Throughout the ICH GCP Guideline the term protocol refers to protocol and protocol amendments.

Protocol Amendment A written description of a change(s) to or formal clarification of a protocol.

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 Good Clinical Practice (GCP) and the applicable regulatory requirement(s).

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.

Randomization 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.

Regulatory Authorities Bodies having the power to regulate. In the ICH GCP guideline 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.

Serious Adverse Event (SAE) or Serious Adverse Drug Reaction (Serious ADR) 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.

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 and evaluation of the trial. Source data are contained in source documents (original records or certified copies).

Source Documents 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).

Sponsor An individual, company, institution, or organization which takes responsibility for the initiation, management, and/or financing of a clinical trial.

Sponsor-Investigator An individual who both initiates and conducts, alone or with others, a clinical trial, and under whose immediate direction the investigational product is administered to, dispensed to, or used by a subject. The term does not include any person other than an individual (e.g., it does not include a corporation or an agency). The obligations of a sponsor-investigator include both those of a sponsor and those of an investigator.

Standard Operating Procedures (SOPs) Detailed, written instructions to achieve uniformity of the performance of a specific function.

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.

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

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.

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

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).

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, and patients in emergency situations, ethnic minority groups, homeless persons, nomads, refugees, minors, and those incapable of giving consent.

Well-being (of the trial subjects) the physical and mental integrity of the subjects participating in a clinical trial.