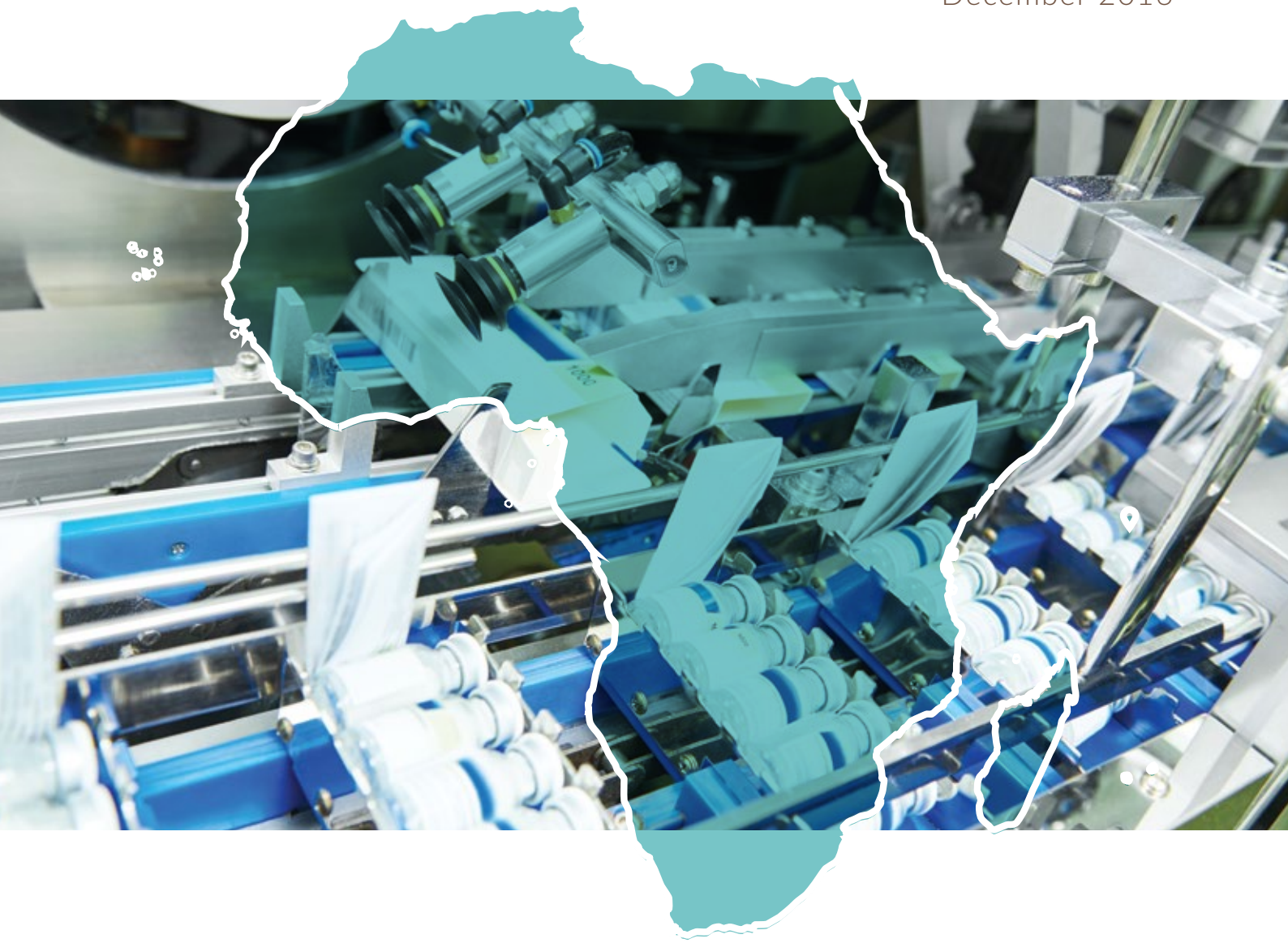
Clinical Trials Training Manual

for capacity building in Regional Centres of Regulatory Excellence (RCOREs) and other training institutions

December 2016



UNIVERSITY OF GHANA
School of Public Health

International AIDS Vaccine Initiative

FOOD AND DRUGS AUTHORITY FDA GHANA

NEPAD TRANSFORMING AFRICA

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FOREWORD

Effective clinical trials oversight and ethical clearance are key components of a fully functional national medical products regulatory system. To fulfil the aspirations of the African Medicines Regulatory Harmonization (AMRH) Programme to protect and safeguard public health African regulatory authorities and ethics committees should be fully functional, competent, and capable of ensuring that safe and efficacious medicines of highest quality are available for use in Africa in a timely and transparent manner, thus ultimately ensuring access.

This training manual seeks to fill knowledge gaps in clinical trials oversight and ethical clearance by National Regulatory Authorities and National Ethics Committees. As part of a functional and coordinated system both NRAs and NECs in countries have to work together to expedite clinical trials approval. Faster timelines have an effect to ensure timely access, safe, and efficacious medicines of assured quality.

Utilization of this manual will go a long way in efforts to strengthen ethics and regulatory capacity and competence for clinical trials ensuring oversight of product development in African countries by promoting the principles of harmonization, work-sharing, collaboration, joint activities and reliance.

It is my hope that the NEPAD designated Regional Centres of Regulatory Excellence (RCOREs) and other interested institutions in clinical trials capacity building and training such as academic institutions will find this manual useful in delivering their mandate. NRAs and NECs may also find this publication useful for reference in the discharge of their day to day activities.

This work has been made possible with the technical efforts of the Ghana Food and Drugs Authority (FDA) in collaboration with the School of Public Health, University of Ghana and with the support of the International AIDS Vaccines Initiative (IAVI) for whom we are immensely grateful. Many experts have also commented and made input on the content of the manual and for that we are also very grateful.

Dr. Ibrahim Assane Mayaki
CEO
NEPAD Planning and Coordinating Agency

PREFACE

This training manual has been developed for use by NEPAD designated RCOREs with clinical trials oversight and other interested institutions to deliver training programs for regulatory personnel across National Regulatory Agencies (NRAs) in Africa. It may also be used for the training of investigators who require training regarding regulation of trials within the sub-region.

The manual is structured to ensure that interactive training methods where theoretical inputs is integrated with practical sessions can be suitably delivered to participants. Practical sessions within the manual entails group exercises, where it is expected that participants will gain hands-on experience in the review of relevant documents. Case studies and case analysis appropriate for the African context is integrated with skill building activities and modules for both junior and senior practitioners.

This manual is therefore to be implemented in an interactive, practical and participatory approach.

Users of this manual will be exposed to an overview of the drug development process, the basis and relevance of regulatory and ethical oversight, requirements for optimum control of a clinical trial including documentation review and Good Clinical Practise inspections. The role of expert bodies in the regulation of clinical trials and the essence of timelines in the conduct of trials is also discussed.

The manual includes the following:

- Overall course plan and objectives
- Summaries of key information for respective modules
- Copies of forms and checklists for practical sessions
- Practical case studies based on actual submissions.
- A glossary of terms used in the materials
- Recommended reference and reading materials

Users of this manual are encouraged to fully get acquainted with every module and practical session presented.

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CHIEF EXECUTIVE OFFICER

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The Ghana Food and Drugs Authority wishes to thank the New Partnership for Africa's Development (NEPAD) Planning and Coordinating Agency and African Medicines Regulatory Harmonization (AMRH) Programme for its support following designation of the Authority as a Regional Centre of Regulatory Excellence (RCORE).

We also wish to thank Dr. Ibrahim A. Mayaki, the CEO of NEPAD Agency, Mr. Hudu Mogtari, the CEO of Ghana FDA, and also the Dean of our collaborating agency, the School of Public Health University of Ghana, Prof. Richard Adanu for exemplary leadership throughout the process. A special thank you also goes out to NEPAD Head of Industrialization, Science, Technology and Innovation (ISTI), Prof. Aggrey Ambali for providing exemplary leadership and guidance.

To each of the authors constituting the scientific team who worked tirelessly in the preparation of the different modules: Delese Mimi Darko, George Armah, Seth Owusu Agyei, Sarah Daniels, Eric Karikari Boateng, Patricia Akweongo, Yvonne Adu-Boahen, Nartekuor Nartey-Armooh, George Sabblah, Amma Frempomaa Asare, Richard Osei-Buabeng and supporting staff of the Ghana FDA Clinical Trials Department. Thank you for devoting your time and effort towards the development of this training manual.

Your combined knowledge and experience provided the perfect blend needed for this tool that will have a great impact in strengthening regulatory and ethics capacity of National Regulatory Authorities and National Ethics Committees in clinical trials oversight and ethical clearance.

We also extend our appreciation to our reviewers including Margareth Ndomondo-Sigonda, Paul Tanui, Hlazo Mkandawire (NEPAD Agency); Sunaina Hingorani, Frances Priddy, Bonnie Bender and Prince N. Bahati (IAVI); Dean Smith (Health Canada); and Medicines Control Authority of Zimbabwe (MCAZ). Other contributors that deserve special mention include Bob Lemon, Melissa Schroeter and other reviewers from Canada, Zimbabwe and Kenya, whose contributions were invaluable.

Finally, production of the manual would not have been possible without the timely funding support from the International AIDS Vaccine Initiative (IAVI) and we would specially like to thank Prince Bahati for his constant support, encouragement and guidance.

CONTENTS

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, analyzed 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, analyze, 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.

Independent Data-Monitoring Committee (IDMC) (Data and Safety Monitoring Board, 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 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.

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 medical 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 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.

INTRODUCTION

Welcome to the "Clinical Trial Regulatory Fellowship Training" course organised by the National Regulatory Authority (NRA) and its collaborators for the Program.

In 2005, when the World Health Organization (WHO started working with National (Drug) Regulatory Authorities in Africa to strengthen the regulatory oversight of clinical trials, few countries had a comprehensive regulatory system related to authorization and inspection of clinical trials. While some National Regulatory Authorities (NRAs) had a clear mandate in the regulation of Clinical Trials, they were yet to engage in activities in this particular area, meanwhile others were unsure of exactly what they were mandated to do.

Today 2016, the competencies of the various NRAs in African countries vary and this has led to regulatory systems that may be lacking in terms of clinical trial oversight. This is mainly due to the absence of applicable standardised training in clinical trials regulation. Consequently, trials may be conducted in unacceptable conditions compromising patient safety and data integrity, and therefore making any informed decisions addressing issues of public health a concern.

Aim of the Course

This course aims to equip African regulators and researchers with improved technical Globally accepted standards for the conduct and regulation of clinical trials will provide the appropriate platform for regulators and researchers across Africa to continually share their experiences over the years all with the aim of improving clinical trial conduct and will ultimately harmonize procedures for the regulation of clinical trials. This will aid and improve informed judgement in Public Health related issues as well as the development of new therapies/medicines to improve human health. In the long run the authenticity/credibility of data produced from trials conducted on the African continent will improve and the tendency for unnecessary exploitation of the vulnerable in Africa will decrease.

Training Methods

This Fellowship Program will use interactive training methods. Theoretical input will be integrated with practical sessions which will be in the form of Regulatory Attachment with the respective NRA. During group exercises participants will gain hands-on experience through activities such as Good Clinical Practise (GCP) inspections and reviewing relevant documents. Participants will provide feedback on all activities during feedback sessions and there will be an interactive discussion on all the topics on the final day of the fellowship course.

The main comprehensive course is 4 weeks; however this may be divided into 1-2 weekly courses depending on the applicant preferences.

A full Fellowship Program consists of 4 compulsory modules and an observation of a Technical Advisory Committee (TAC) Meeting. After the successful completion of the full program, participants will earn a Fellowship Certificate. However, it is possible to participate in single modules. Note that such participants will only receive a certificate of participation for the completed module(s) and will not observe a TAC meeting.

The Course and the Materials

Participant's manual

A copy of the participant's manual will be provided to each participant.

The manual includes the following:

- Overall course plan and objectives
- Summaries of key information from the lectures
- Copies of forms and checklists from the practical sessions
- The exercises which participants will do during the course
- A glossary of terms used in the materials
- Reading materials

Reference materials

The following materials will be given to participants on a memory stick.

1. The Declaration of Helsinki: World Medical Association (version 2013 and subsequent updates to date)
2. Handbook for Good Clinical Research Practice: Guidance for implementation. World Health Organization, Geneva (2005 version and subsequent updates to date)
3. Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines for Biomedical Research Involving Human Subjects 2002
4. Guideline for good clinical practice E6 (R1) - ICH harmonized tripartite guideline. International conference on harmonization of technical requirements for registration of pharmaceuticals for human use. July 2002
5. General considerations for clinical trials E8-IC H harmonized tripartite guideline. International conference on harmonization of technical requirements for registration of pharmaceuticals for human use. July 1997
6. Nuremberg Code 1947
7. Belmont report 1979
8. E2A-ICH harmonized tripartite guideline. International conference on harmonization of technical requirements for registration of pharmaceuticals for human use. October 1994.

Course Objectives

After completing the 4 week course participants will be able to

1. Understand the drug development process and the impact of research on the safety, quality and efficacy of medicines
2. Evaluate essential clinical trial documents such as the Protocol, Investigator's Brochure and the Informed Consent Form.
3. Understand the basics of GCP requirements in clinical trials and how they are implemented.
4. Understand the importance of the different laws, and guidelines, which govern the set up and conduct of clinical research with an emphasis on local requirements.
5. Demonstrate an understanding of the roles and responsibilities of different individuals and stakeholders in clinical research.
6. Identify essential documents to be kept by investigators and the purpose of maintaining a trial master file.
7. Understand the requirement for obtaining informed consent
8. Demonstrate an awareness of the correct safety reporting requirements for pre and post clinical trials in order to ensure patient safety.

Timetable

WEEK 1

Module 1 (Theory)

Time	Day 1	Day 2	Day 3	Day 4	Day 5
9.00am – 9.15am	Welcome	Re-cap of Previous day	Re-cap of Previous day	Re-cap of Previous day	Re-cap of Previous day
9.15am – 9.30am	Expectations & Objectives	Programme of the day	Programme of the day	Programme of the day	Programme of the day
9.30am – 10.30am	Programme of the Course	A Historical perspective on Drug Development Regulations	Clinical Trial Protocol Development- Designing/Building and Drafting the Protocol	Developing Clinical Trial Applications Before Trial Starts Essential Documents	Identifying Roles and Responsibilities in Clinical Trials What constitutes a clinical trial team Roles and Responsibilities
10.30am – 11.00am	Tea/coffee break				
11.00am – 12.30pm	Introduction to Drug Development	Defining Regulations	Clinical Trial Protocol Development – Reviewing the Protocol and case report forms/Defining Data/	Developing Clinical Trial Applications Methods of Data collection Data Processing and Management	Introduction to Technical Advisory Committee on Clinical Trials
12.30pm – 1.30pm	Lunch break				
1.30pm – 1.45pm	Questions and Discussions	Questions and Discussions	Questions and Discussions	Questions and Discussions	Questions and Discussions
1.45pm – 2.15pm	Introduction to Drug Development	Defining Regulations	Clinical Trial Protocol Development – Hands on Practical Sessions	Developing Clinical Trial Applications Recruitment and Randomisation	Assessment of Module 1 (Theory)

Time	Day 1	Day 2	Day 3	Day 4	Day 5
2.15pm – 2.30pm	Tea/coffee break				
2.30pm – 3.30pm	A Historical perspective on Drug Development Regulations	Clinical Trial Protocol Development – Overview/ Background/ Justification/Defining the Question and Intervention	IRB/IEC -Membership/ Composition/ Functions/Procedures and Roles.	Developing Clinical Trial Applications Follow-up of study participants	Overview of Regulatory attachment
3.30pm – 4.00pm	Evaluation of the Day	Evaluation of the Day	Evaluation of the Day	Evaluation of the Day	Evaluation of the Day

WEEK 2

Module 1 (Regulatory Attachment) and Module 2 (Theory)

Time	Day 1	Day 2	Day 3	Day 4	Day 5
9.00am – 9.15am	Welcome	Re-cap of Previous day	Re-cap of Previous day	Re-cap of Previous day	Re-cap of Previous day
9.15am – 9.30am	Expectations & Objectives	Programme of the day	Programme of the day	Programme of the day	Programme of the day
9.30am – 10.30am	Evaluation of Clinical Trial Application - NRA (Food and Drugs Authority) System	Evaluation of Clinical Trial Application – Protocol Evaluation	Evaluation of Clinical Trial Application – IB Evaluation	Trial Management What is a Project? What is Project management?	Trial Management Timelines Stakeholders Risks
10.30am – 11.00am	Tea/coffee break				
11.00am – 12.30pm	Evaluation of Clinical Trial Application – Guidelines and Forms	Evaluation of Clinical Trial Application - Protocol Evaluation	Evaluation of Clinical Trial Application - ICF Evaluation	Trial Management What is Program management What is a trial? What is a trial management?	Trial Management Trial Implementation
12.30pm – 1.30pm	Lunch break				

Time	Day 1	Day 2	Day 3	Day 4	Day 5
1.30pm – 1.45pm	Questions and Discussions	Questions and Discussions	Questions and Discussions	Questions and Discussions	Questions and Discussions
1.45pm – 2.15pm	Evaluation of Clinical Trial Application – SOPs	Evaluation of Clinical Trial Application - Protocol Evaluation	Evaluation of Clinical Trial Application - ICF Evaluation	Trial Management Scope and Quality Resources for Clinical Trials	Quality Assurance in Clinical Trials - SOPs/Equipment calibration/Tracking Essential Documents for Clinical Trials
2.15pm – 2.30pm	Tea/coffee break				
2.30pm – 3.30pm	Evaluation of Clinical Trial Application – Preliminary Assessment	Evaluation of Clinical Trial Application - IB Evaluation	Assessment of Module 1 (Regulatory Attachment)	Trial Management Budget	End of Study Process Close Out 1
3.30pm – 4.00pm	Evaluation of the Day	Evaluation of the Day	Evaluation of the Day	Evaluation of the Day	Evaluation of the Day

WEEK 3

Module 2 (Regulatory Attachment) and Module 3 (Theory + Regulatory Attachment)

Time	Day 1	Day 2	Day 3	Day 4	Day 5
9.00am – 9.15am	Welcome	Re-cap of Previous day	Re-cap of Previous day	Re-cap of Previous day	Re-cap of Previous day
9.15am – 9.30am	Expectations & Objectives	Programme of the day	Programme of the day	Programme of the day	Programme of the day
9.30am – 10.30am	End of Study Process Close Out 2 Analysis, Reporting and Dissemination of results	GCP Inspection Theory	Good Clinical Practice Inspection – Review of Inspection Document	Good Clinical Practice Inspection – Observer	Good Clinical Practice Inspection – Observer
10.30am – 11.00am	Tea/coffee break				
11.00am – 12.30pm	Managing Importation of Investigational Products	GCP Inspection Theory	Good Clinical Practice Inspection – Observer (Travel time to site)	Good Clinical Practice Inspection – Observer	Good Clinical Practice Inspection – Observer

Time	Day 1	Day 2	Day 3	Day 4	Day 5
12.30pm – 1.30pm	Evaluation of the Day				
1.30pm – 1.45pm	Questions and Discussions	Questions and Discussions	Questions and Discussions	Questions and Discussions	Questions and Discussions
1.45pm – 2.15pm	Managing Importation of Investigational Products	Good Clinical Practice Inspection – Guidelines and Forms, Site selection and Preparation	Good Clinical Practice Inspection – Observer	Good Clinical Practice Inspection – Observer	Good Clinical Practice Inspection – Report Writing
2.15pm – 2.30pm	Tea/coffee break				
2.30pm – 3.30pm	Assessment of Module 2 (Theory + Regulatory Attachment)	Good Clinical Practice Inspection – Review of Inspection documents	Good Clinical Practice Inspection – Observer	Good Clinical Practice Inspection – Observer	Assessment of Module 3 (Theory + Regulatory Attachment)
3.30pm – 4.00pm	Evaluation of the Day	Evaluation of the Day	Evaluation of the Day	Evaluation of the Day	Evaluation of the Day

WEEK 4

Module 4 (Theory + Regulatory Attachment) and TAC (Module 1 – 4: Regulatory Attachment)

Time	Day 1	Day 2	Day 3	Day 4	Day 5
9.00am – 9.15am	Welcome	Re-cap of Previous day	Re-cap of Previous day	Re-cap of Previous day	Re-cap of Previous day
9.15am – 9.30am	Expectations & Objectives	Programme of the day	Programme of the day	Programme of the day	Programme of the day
9.30am – 11.00am	Adverse event reporting	Pharmacovigilance in practice: Risk management & Signal detection	Reporting from Clinical Trials Sites – SAEs, Close-out and Final reports	Technical Advisory Committee Meeting – Observer	Course Assessment (Short test on practical session)
11.00am – 12.30pm	Adverse event reporting	Reporting from Clinical Trials Sites – Guidelines and Forms	Assessment of Module 4 (Theory + Regulatory Attachment)	Technical Advisory Committee Meeting – Observer	Discussions on short test
12.30pm – 1.30pm	Lunch break				

Time	Day 1	Day 2	Day 3	Day 4	Day 5
1.30pm – 2.30pm	Post Marketing Approval and Phase IV Monitoring Licensure Phase IV/Pilot Implementation	Reporting from Clinical Trials Sites – Notification of Study Commencement (Database)	Technical Advisory Committee Meeting – Presentation on TOR	Technical Advisory Committee Meeting – Observer	Participants' Evaluation of entire Fellowship course
2.30pm – 4.30pm	Reporting from Clinical Trial sites - IRB/FDA Obligations/ Interim Analysis/ DSMB	Reporting from Clinical Trials Sites – Progress and DSMB Reports	Technical Advisory Committee Meeting – Preparation	Discussions on Observed Technical Advisory Committee Meeting	
4.30pm – 5.00pm	Evaluation of the Day	Evaluation of the Day	Evaluation of the Day	Evaluation of the Day	Evaluation of the Day

THEORETICAL SESSION

Course content

The course will include the following topics:

Introduction to Drug Development introduces the principles of research and development that enables the evaluation of the safety and efficacy of new drugs prior to approval for human use. The role of industry sponsors, regulators, investigators and study participants in the conduct of clinical trials is described in the module.

Ethics and Historical Perspective on Drug Development Regulations reviews some of the historical events that have shaped current regulations and guidance for protecting human participants in clinical research are described in this module. It describes the significance of the Nuremberg Code, the Declaration of Helsinki, the Belmont Report and introduces ICH and CIOMS guidelines.

Defining Regulations (ICH, GCP) explains the purpose of the ICH and GCP guidelines and the basic requirements for compliance. It provides an understanding of the ICH and GCP guidelines and their impact on the Pharmaceutical Industry. Specific local requirements for the conduct of clinical trials are also emphasized.

Clinical Trial Protocol Development describes how a study Protocol is developed to ensure that procedures/measures outlined in the research study are carried out in a consistent and reproducible manner.

Institutional Review Board/Independent Ethics Committee describes the role of Institutional Review Boards and other Ethical Review Committees in safeguarding the rights, safety and well being of study participants by assuring the balance of risks and benefits of the research. Attention is drawn to vulnerable participants and how ethical studies can be conducted in a resource-limited environment. FDA'S requirements for IRB/IEC approvals required when submitting Clinical Trial Applications are discussed. Separate courses on other ethical aspects are offered e.g. setting up, administration and obtaining accreditation of an Ethics Committee/Institutional Review Board etc.

Monitoring of Clinical Trial Sites includes a number of reports that the NRA require to facilitate its monitoring activities for on-going clinical trials. Includes regulatory requirements, rationale, formats and timelines for submitting the reports

Quality Assurance in Clinical Trials is designed to provide participants with some basic information on how to ensure that study procedures are conducted in a standardized manner and all data that is collected or generated from the study can be guaranteed to be accurate and valid.

Essential Documents for Clinical Research describes those documents, which individually and collectively permit evaluation of the conduct of a trial and the quality of the data produced. The documents serve to demonstrate compliance of the investigator, sponsor, and monitor with the standards of Good Clinical Practice and with all applicable regulatory requirements.

Adverse Events discusses the Definitions, Reporting requirements, Responsibilities of the Investigator and the Sponsor and the role of the Data Safety Monitoring Board pertaining to Adverse Events and Serious Adverse Events.

GCP Inspections introduces the concept and basis for GCP inspections. The process required before, during and after the inspection is discussed. An overview of sanctions and penalties that may be imposed after an inspection is also outlined.

Protocol Evaluation and Developing Clinical Trial Applications describes in detail how Clinical Trial documents are processed by the competent authority and evaluated prior to authorization, during conduct and after trial. Specific protocol evaluation course and/or joint reviews are available on request with the clinical trial sponsor's consent.

Identifying Roles and Responsibilities in Clinical Research describes the crucial roles of the different stakeholders in Clinical Research and how they interact with each other.

Trial Management covers the trial management, including informed consent, participant recruitment and enrollment, monitoring visits and source document verification.

End of Study Process covers study closeout activities that confirm that the site investigator's study obligations have been met and post study obligations are understood.

Post Market Approval & Phase IV Safety Monitoring is designed to provide a good foundation in key aspects of Clinical Pre- and Post-Marketing Safety. It identifies the roles and responsibilities of marketing authorization holders and the FDA in the conduct of Pharmacovigilance.

MODULE I

LESSON I: Introduction to Drug 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 drugs 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 drug
- determine the acute toxicity of the drug 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 drug. 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 drug use can be investigated to see whether it causes cancer or birth defects.

In addition, during the pre-clinical stage of drug 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 drug, while pharmacodynamics is what the drug does to the body.

Pharmacokinetics investigates the course of a drug 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 drug 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 drug 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 drug 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 drug against a placebo or standard therapy in a substantial number of patients. This is the key stage in establishing the impact of a drug and the majority of drug 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.

LESSON II: 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 subjects. 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/nonmaleficence; 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 nonmaleficence concerns their obligation to do no harm. Taken together, the principles of beneficence and nonmaleficence 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.

Ethics and Clinical Research Practical session

Case study

Placebo-controlled study of Zidovudine (ZDV) to prevent perinatal transmission (vertical transmission, mother-to-child) of HIV (1997)

A number of clinical trials are planned, some under the aegis of the Joint United Nations Programme on HIV/AIDS (UNAIDS), WHO, Centers for Disease Control and Prevention (CDC) and National Institutes of Health (NIH), with the aim of reducing perinatal transmission (vertical transmission, mother-to-child) of HIV. These trials have been designed to determine whether relatively affordable and more feasible shorter courses of zidovudine given to pregnant women in developing countries (ZDV 5x daily for 4 weeks prior to giving birth) would reduce the risk of mother-to-child transmission. They will be conducted in countries where conventional local pregnancy care does not include antiretroviral treatment. The trial design, including a control group that would be provided with placebo, has already been approved by ethics committees in the countries in which the trials will be conducted.

Longer, more expensive and complex courses of zidovudine have already been shown to reduce mother-to-child transmission rates (by 66%) in a trial conducted in the US and France (1994). These earlier trials involved a total of about 17 weeks of therapy (ZDV administered orally 5x daily to HIV-infected pregnant women for 11 weeks prior to giving birth, then intravenous ZDV during labour, followed by oral treatment to newborns for a further 6 weeks). This regimen is now (1997) recommended as standard care in the US, but, because of its complexity and cost, it has not been implemented in most developing countries.

Questions

- What are the advantages and disadvantages of conducting these trials?
- Is a placebo-control group appropriate?
- What are the key ethical issues that this scenario raises?
- What course of action would you recommend?

LESSON III: 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 thbhiouo 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 Organizations
- International Organizations with an Interest in Pharmaceuticals

Refer to Appendix 3 for further details on these observers.

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)

LESSON IV: 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 is the study hypothesis?
- What is the clinical question being addressed
- How the clinical question should be addressed/ answered
- What tools should be used in addressing the question
- The Investigational product to be used
- How will the results be presented
- Safety issues

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

3. 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 in the 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
    - Objective/design/methodology
    - Process
    - Data requirements
    - Coding requirements
    - Data review requirements
    - Therapeutic considerations
    - Data Sources
    - Data collection methods
    - Statistical analysis requirements and strategies
    - Data integration and export
    - 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

4. Hands on Practical Sessions to review publicly available protocols

Participants shall be provided with sample protocol and relevant documents for review/evaluation.

LESSON V: Institutional Review Board/Independent Ethics Committee

Institutional Review Board/Independent Ethics Committee

- 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
    - IRB
    - ERC
  - Inform Consent Form
    - Identification of study
    - Identification of investigators
    - Identification of sponsor
    - Study procedures
    - Participant involvement
    - Benefits/Risks
    - Compensation
    - Confidentiality of data

LESSON VI: Developing Clinical Trial Applications

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

- Operational Tools
  - Forms
  - Guidelines
  - SOPs
  - Checklists
  - Templates

- General Information
  - Protocol identity
  - Investigator's details
  - Sponsor's details
  - Investigator/Sponsor agreement
  - Responsible persons
- 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 Plan
- Statistical methods
  - Sample size determination
  - Stopping rules
  - Data management
  - Population for analysis

LESSON VIII: Identifying Roles and Responsibilities in Clinical Trials

This section seeks to provide an overview of how the various roles and responsibilities based on design and conduct of the clinical trial is shared amongst the different individuals and organisations involved. In assigning responsibilities, one can appreciate which responsibilities are professional, moral or legal. One can articulate how these responsibilities relate to the various 'stakeholders'. It is very important that the individuals, committees and organisations involved in any clinical trial have clear responsibilities, so they can collaborate effectively and be held accountable if things go wrong.

- What constitutes a clinical trial team?
- Roles and Responsibilities

- **The Principal Investigator (PI/Co-PI):** assumes overall responsibility for the project at the site. The investigator should guarantee that the dignity, rights, safety and well-being of participants is given priority at all times and that the design, conduct, analysis and reporting of the trial results meets the set standards. In particular they are responsible for being adequately qualified and trained, being familiar with the intervention and up-to-date protocol, demonstrating there are adequate time and resources to complete the trial safely and successfully, ensuring all staff work by the same up-to-date protocol, conducting the project to the agreed protocol in accordance with legal and ethical requirements and guidance, seeking written voluntary consent from participants (or their legal representatives), informing participant's primary physician of her/his participation (with the participant's consent), recording any reasons the participant gives for withdrawing from the trial prematurely, checking that each participant is following the instructions properly, ensuring any randomization code is broken only in accordance with protocol, ensuring accuracy, completeness, legibility and timeliness of data reported to the sponsor especially any adverse events, making final results available to participants where appropriate.

  Other researchers (sub investigators, trial manager, lab manager, data manger etc) are responsible for the day-to-day running of the project and must follow the most-up-to-date protocol, report adverse reactions, protect data and report failures while discharging any professional duty of care they might have.

- **Sub Investigators (Sub-I)/Co-Investigators**
- **Study Coordinator (SC)/The Project Manager/trial manager**
- **Clinical Team Manager (PV and Drug Safety)**
- **Laboratory Team Manager**
- **Data Team Manager**
- **Contract Research Organization (CRO)/Monitor**
- **The Data Safety Monitoring Board (DSMB)**
- **The Sponsor:** The sponsor can be an individual, a healthcare organisation, a commercial company, a university, or a combination. The sponsor takes overall responsibility for confirming that proper arrangements to initiate, manage, monitor and finance the study are in place. The main responsibilities of the sponsor are for: Scientific design, Notification to regulatory authorities and confirmation of ethics approval, Financing arrangements and facilities, Manufacturing, handling and supplying any medicinal products and devices appropriately, Trial management, data handling and record keeping, Convening Trial Management Group (TMG), Trial Steering Committee (TSC), and Data Monitoring Committee (DMC), Designating appropriately qualified medical personnel who will be readily available if necessary, Arranging to compensate trial participants and investigators if necessary, Ensuring quality assurance and control, Reporting of the clinical trial.
- **Funder:** The funder of a clinical trial could be from the public sector, charities, industry or individual donors.

The funder could be the 'sponsor' who assumes liability for its management, or could be a completely different body. Before providing financial support, funders generally assess the scientific quality of the study and establish whether it provides value for money. This will usually involve independent peer-review. In addition, they must assess the quality of research environment and the experience and expertise of the Principal investigator, principal investigator(s) and other key researchers involved. They must also ensure that the research has a sponsor.

- **Employing institutions:** Employers of staff undertaking clinical trials have responsibility for ensuring that their staff are supported in, and held to account for, the professional conduct of research and that they understand and discharge their responsibilities. They should also deal with non-compliance or misconduct and learn from errors and complaints.

- **Statistical Department Trial Steering Committee:** The trial steering committee is usually established early in stages of a study design with the role of providing input and advice on the trial design, assisting with the development of the study protocol, monitoring and providing overall supervision for the trial. The TSC is to ensure that the study is planned according to acceptable scientific and ethical standards. These include ensuring that: all investigators conduct the trial in strict compliance with the protocol agreed to by the sponsor and, if required, by the regulatory authority(ies), and given approval/favourable opinion by the ethics committee, the Case Report Files (CRFs) are designed to capture the required data at all multi-centre trial sites, the responsibilities of coordinating investigator(s) and the other participating investigators are documented prior to the start of the trial, all investigators are given instructions on following the protocol, on complying with a uniform set of standards for the assessment of clinical and laboratory findings, and on completing the CRF, communication between investigators is facilitated.

- **Data Monitoring Committee (DMC):** This committee is also sometimes referred to as Independent Data monitoring Committee (IDMC) or Data Safety and Monitoring Board (DSMB). The DMC serves to assess the progress of a clinical trial including safety data and the critical efficacy end points at intervals defined in the study protocol, i.e. before the clinical trial gets underway. The DMC reviews confidential cumulative trial data, formulate a statistical assessment and make recommendations to the TSC after each review to continue, modify or stop trial. Another important function of the DMC is evaluating the risk/benefit ratio and recommend that a trial be stopped due to safety concerns, a strong efficacy profile in one arm of the trial, or the basis of futility.

- **Legal Department:** Usually key when it comes to all contract agreements, medical insurance cover for participants and health professionals. Involvement in various other contracts including supplies, items, equipment etc. is also important.

- **The Regulatory Authorities:** Organisations set up and giving responsibilities such as restricting access to investigational treatments, issuing license for 'suitable' research, monitoring and inspecting trial sites and issuing guidance among others.

Research ethics committees (RECs) or Institutional Review Board/Institutional or Independent Ethics Committee (IRB\IEC): Research ethics committees (RECs) are required to be independent of the research when formulating a judgement about how best to protect the rights and welfare of trial participants. Their independence ensures that any potential conflict of interests does not become an actual conflict. RECs are thus responsible for acting primarily in the interest of potential research participants and concerned communities. One of their principal duties is to ensure potential participants are given information about the trial which is complete and comprehensible. Without this information, potential participants cannot consent. In addition, there are limits to what a competent person can consent to and the REC is responsible for ensuring that

the trial interventions are themselves lawful and reasonable. For example, reproductive cloning is unlawful and consent would not provide an investigator with a defence against the charge of 'battery' in the event of doing research in this area.

Each committee usually comprises up to eighteen members to allow for a sufficiently broad range of experience and expertise, so that the scientific, clinical and methodological aspects of a trial can be reconciled with the welfare of research participants, and with broader ethical implications.

Trial participant: The responsibilities of participants are considered here. People do not have a specific responsibility to take part in trials merely to help others. However, as everyone benefits, either directly or indirectly, from the result of trials, it could be said that anyone using health and social care services should give serious consideration to becoming involved in research studies. Once having consented, trial participants legally reserve the right to withdraw at any time without necessarily giving any reason for withdrawing. However, we might argue that a participant should morally adhere to the trial protocol as instructed by the investigator unless there are problems, when he should seek advice. Sometimes, he or she may still wish to withdraw and, where possible, should give reasons for doing so. Some patients may be desperate to try a new intervention and there have been examples of participants sharing treatments in a placebo-controlled trial.

- People do not have a specific responsibility to take part in trials merely to help others. However, as everyone benefits, either directly or indirectly, from the result of trials, it could be said that anyone using health and social care services should give serious consideration to becoming involved in research studies.
- Once having consented, trial participants legally reserve the right to withdraw at any time without necessarily giving any reason for withdrawing. However, we might argue that a participant should morally adhere to the trial protocol as instructed by the investigator unless there are problems, when he should seek advice. Sometimes, he or she may still wish to withdraw and, where possible, should give reasons for doing so.
- Some patients may be desperate to try a new intervention and there have been examples of participants sharing treatments in a placebo-controlled trial.

LESSON IX: Observing a Technical Advisory Committee (TAC) Meetings

Objective

Participants, as observers, at the end of a TAC meeting shall be able to appreciate the mandate of the TAC which to provide the Authority with on-going and timely medical and scientific advice on current and emerging issues related to clinical trials through;

- Regularly review and advice 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 TAC by the Authority.
- Upon request Authority, the TAC 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 TAC 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 TAC may also recommend publication of case reports, their risk/benefit evaluations, recommendations and communications arising from the TAC meetings that are deemed appropriate for medical and

scientific journals with prior consent of the sponsor.

- The TAC 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 TAC 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 TAC meeting prior to which a non-disclosure and conflict-of-interest form shall be signed.

Observations and comments made shall be discussed with the Secretary of the Committee through the course facilitator.

MODULE I: REGULATORY ATTACHMENT

Evaluation of Clinical Trial Applications

Objectives

Participants shall be able to

i. Identify essential components of a CTA and the completeness of an application

ii. Evaluate the underlisted documents as per ICH GCP and applicable country specific regulatory requirements

   - Protocol
   - Investigator's Brochure
   - Informed Consent Form

iii. Identify lapses in a CTA

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 wholistic 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.

Review bodies must identify which information is considered critical and develop appropriate systems to ensure that such information is available when review is being done. Appendices 1a and 1h provide a summary of documents required for a complete CTA. Weights have been assigned to the various components to indicate the extent to which the document impacts on effective review of an Application.

Question

a. Do you consider the respective weights assigned to the documents required for a CTA appropriate?

b. Justify you answer to (a) above

c. Carefully peruse the sample of a Clinical Trial Application (CTA) submitted to National Regulatory Agency (NRA) and Ethics Review Committee (ERC) in parallel (Facilitators must ensure that all participants have duly signed and submitted the "Non-disclosure" form before supplying the CTA to be used for the session).

   i. Using the pre-assessment checklist (NRA) available in Appendix 1a, assess the completeness of the application and recommend whether it is adequate for regulatory review. Justify your recommendation.

   ii. Using the pre-assessment checklist (ERC) available in Appendix 1h, assess the completeness of the application and recommend whether it is adequate for ethical review. Justify your recommendation.

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 analyzing 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-center clinical trial, which requires collaboration in the research activities of many investigators and their staff at multiple institutions.

ICH requires that;

- Clinical trials should 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. Appendices 1b and 1i provide details about the content/format of a clinical trial protocol and a guide for the scientific and ethical review for national authorities and ethics bodies respectively.

Question

a. Study carefully the content/rationale for the requirements for sections (facilitator may specify sections of interest for discussion) of a clinical trial protocol to be submitted to the regulator using Appendix 1b (NRA) and Appendix 1i (ERC). Assess and comment on the adequacy of sections of protocol available in the CTA provided.

Assessment of Informed Consent Forms

It must be noted that during the ethical review of a clinical trial application, particular attention should be given to the provision of informed consent for all participants of a proposed clinical trial. As required by ICH, Informed consent is documented by means of a written, signed and dated informed consent form. The content of a standard Informed consent form and the rational for the provisions thereof are provided in Appendix 1f.

Question

a. **Considering the guide provided for reviewing ICF/Assent Form in Appendix 1j, comment on the suitability/adequacy of the ICF provided.**

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 underlisted 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. (Refer to Appendix 1c for an IPD Template).

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.

Investigator's Brochure

The Investigator's Brochure (IB) is a compilation of the clinical and nonclinical data on the investigational product(s) that are relevant to the study of the product(s) in human subjects. Its purpose is to provide the investigators and others involved in the trial with the information to facilitate their understanding of the rationale for, and their compliance with many key features of the protocol, such as the dose, dose frequency/interval, methods of administration, and safety monitoring procedures.

The IB also provides insight to support the clinical management of the study subjects during the course of the clinical trial. The information in an IB must be presented in a concise, simple, objective, balanced, and non promotional form that enables a clinician, or potential investigator, to understand it and make his/her own unbiased risk/benefit assessment of the appropriateness of the proposed trial. (Refer to Appendix 1d for an IB Template)

It should be prepared from all available information and evidence that supports the rationale for the proposed clinical trial and the safe use of the investigational product (IP) in the trial.

Summary of Product Characteristics (SmPC)

The SmPC sets out the position of a medicinal product as agreed during the course of the assessment process of a marketing authorisation application.

It forms the basis of information for healthcare professionals on how to use the medicinal product safely and effectively.

It provides specific advice on aspects concerned with the treatment or its side effects on the patient but does not give general advice on the treatment of particular medical conditions or general advice on administration procedures. (Refer to ***Appendix 1e*** for SmPC Template)

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.

Question

Appendices 1c, ***1d*** and ***1e*** are templates for an IPD, IB and SmPC respectively.

a. Review critically, the CTA provided and determine which of the above documents listed will enable you adequately assess the suitability of the IP for the proposed trial.

b. Justify your answer in a) above.

c. Compare and contrast the contents of an IPD and IB; identify the differences and similarities for discussion.

d. Using the relevant assessment guide

MODULE II

LESSON I: Trial Management

- The aim of this module is to understand what is meant by trial/project management and to develop knowledge of the skills which are required by project managers within the clinical trials environment. The objectives are to define what is meant by a project, what is meant by project management, success criteria for a clinical trial, explain why project management is important for ensuring success in clinical trials, and understand the skills required for successful management of a project.
- With ever-increasing demands on the research community to deliver results as quickly and efficiently as possible, project management is now seen as a key element of delivering clinical trials.
- The application of project management will vary between organisations involved with trials with some organisations taking a very formal approach to managing the project, whilst other organisations take a more relaxed approach to the process of managing the project.

1. Project/Trial Management

- What is meant by project management?
- It is the application of knowledge, skills, tools and techniques to project activities in order to meet stakeholder needs and expectations from a project. It can also be defined as the process of integrating everything that needs to be done as the project evolves through its life-cycle in order to meet the project objectives."
- How can it be applied within the clinical trials environment?
- To be able to understand how a project is managed in clinical trials, some basic terminologies such as below will have to be defined:
    - What is a project?
    - What is project management?
    - What defines a successful project?
    - What benefits we get by using project management in a clinical trials context?
- What detailed tools and techniques can be utilised to aid with the development of the project/trial and
- How the plans developed can be used as a means for controlling the project/trial.

2. Project Scope and Quality of a trial

- The scope of the clinical trial can be defined as:
    - What you want to achieve
    - Why you want to do it
    - When you need to have your objectives accomplished
    - The main steps that need to be carried out

The scope is normally recorded in a project statement, which is a short paragraph that defines what needs to be done, why it needs to be done and when it has to be finished. This provides the formal boundaries for the clinical trial

- Quality of a trial:

What Is Quality in clinical trials?

- It is the quality management processes of a clinical trial are all about making the trial fit for purpose and proving that this is the case to the standards set by ourselves, our project sponsors and any involved regulatory authorities.
- The easiest way to deliver a quality clinical trial is to ensure that the quality is planned in at the start. The key criteria that you need to define are those that the major stakeholders will use to accept the final deliverables, usually the final report and publications.
- Process required to ensure that the clinical trial project will satisfy the needs for which it was undertaken, by addressing both the management of the clinical trial and the product (or end result) of the clinical trial". The quality processes will be elaborated in during teaching.

3. Resources for clinical trials, Timelines and Budget

The aim of this session will be to define resources as they apply to projects in general and clinical trials management in particular. Resources needed throughout the trial will be investigated, identified and estimated in order to ensure that they are used consistently and effectively.

By the end of this Session one will be able to:

- define what constitutes a resource to the clinical trial manager
- determine which resources will be needed, and how to obtain them
- estimate how long each resource will be needed for
- manage resources effectively to ensure that a clinical trial is conducted without being constrained by resource issues
- ensure that the scope is executed effectively using the resources available to the clinical trial manager
- apply strategies for decision making about where extra resources should be applied
- understand why you need to take in the needs of team members in the resource allocation process

- **Timelines and budget:**

  This Session aims to introduce students to the concept and importance of timelines to scheduling, including how to create and test a work network, understand the critical path and use it to calculate path and float. You will also be introduced to how to create Gantt and milestone charts and use them effectively in your clinical trials project work.

  By the end of this Session students will be able to:

  - understand what is meant by a project timeline and how to use the work network diagram to establish the timeline for your clinical trial
  - appreciate the interrelationships between a work breakdown structure, a work network diagram, the critical path and a Gantt chart
  - define the purpose of work network diagrams, and explain how they are built
  - distinguish the different steps in the critical path method of project planning

The sponsor should define the clinical trial timeline, provide a financial declaration assuring the financial budgetary adequacy for the conduct of the clinical trial.

- **Budget**

  This introduces students to understanding and appreciating the importance of funding and budget generation leading to good budget management for a successful clinical trial.

  By the end of this Session participants will be able to:

  - identify the sources of finance for funding a clinical trial
  - identify the sources of clinical trial costs and understand their relative scale
  - generate a clinical trial budget
  - validate a clinical trial budget
  - understand the importance of contract types when third parties are involved
  - compare and contrast budgetary considerations in commercial and non-commercial trials

4. Stakeholders

This session aims at orienting participants in their understanding of the management of stakeholders and the project team in clinical trials.

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

- identify key stakeholders in clinical trials
- understand the interaction of stakeholders with the trial to gain insights into how to manage the stakeholders most effectively
- develop strategies to manage key stakeholders
- implement methods to aid managing the trials team
- define the roles that individuals take within project teams
- develop strategies to manage virtual teams

LESSON II: Trial Implementation

- The Informed Consent Process

  This topic discusses informed consent guidelines, the required and optional elements of informed consent, and the process for obtaining informed consent. The topic highlights some of the challenges associated with informed consent and the concept of vulnerable participants.

  - Purpose of Obtaining IC
  - Basic Elements of the IC
  - Consenting Process
  - Documentation requirement\Exceptions for IC
  - The role of the CRA in the IC process
  - Sample ICF

- Participant Recruitment and Enrolment

  This deals with the different options for participant recruitment, recruitment/retention incentives and regulatory guidelines governing this, and study compliance issues.

  - Recruitment/Enrolment Strategies
  - Screening/Enrolment Logs

- Monitoring Visits and Reporting

  This describes the different types of site visit, including pre, during and post-visit activities.

  - Types of Sites Visits
    - Pre-Study/Qualification/Selection Visit
    - Initiation Visit

- Interim/Routine Monitoring Visit
- Termination/Close-Out Visit

▫ Site Visit Activities

- Review ICF
- Review Investigator Site File (ISF)
- Meet with investigator and study coordinator
- Verify that specified trial functions are performed in accordance with protocol
- Verify enrollment of only eligible participants
- Conduct Drug Accountability

- Source Document Verification (SDV)

This describes some of the pivotal activities for both SC and CRA.

▫ Queries Resolution Process

▫ Drug Accountability Process

LESSON III: Quality Assurance in Clinical Trials

Tracking tools

- **Standard Operating Procedures (SOPs)** are detailed, written instructions to achieve uniformity of the performance of a specific function. They should be written in a standard format to establish methods of defined operations, addressed to those who will carry out these procedures, and fully describe the methods used to conduct the clinical trial.

  The standard format facilitates searches for information and eases updating or modifying. The format also standardizes cover information, review, signatures and amendment documentation with revision numbers and dates.

  The language of an SOP is clear, plain, not too sophisticated or jargon-filled and often takes the style of a series of short numbered or bulleted points which is preferable to a lengthy description.

  SOPs within a clinical trial, and under GCP, ensure the highest quality standards will be met in all aspects of trial conduct. SOPs should be drafted only after a review of the relevant literature, GCP, GMP or GLP and/or regulatory requirements. Various collaborators across the clinical trial should mutually discuss and review each other's SOPs, to learn from one another, and to prevent duplication of procedures.

  Once a SOP is finalized, it should be made available (either in hardcopy or electronically) to a wide distribution list of those associated with the procedures it describes, including supervisors. As part of the certification of competence to carry out a procedure, staff should know the current version and the location of the written SOPs and are expected to have read, and be familiar with, the SOPs and have agreed to follow them. There should be a regularly scheduled review of all SOPs to ensure that they continue to reflect the practices within the trial.

- Source documents and case reports forms
- Equipment calibration
- Clinical trial auditing

Essential Documents for Clinical Research

- Protocol
- ICF
- Curriculum Vitae
- Investigator Brochure
- CRF
- Source Documents
- Site Logs
- Laboratory Management Plans
- Project Management Plans
- Data Management Plans
- Data Entry Guidelines
- Data Validation Specifications
- Regulatory authorizations/approvals/notifications

LESSON IV: End of Study Process

The aim of this session is to examine the processes which are required in order to effectively manage the implementation phase of the project and to examine methods to resolve problems which might occur within a clinical trial.

At the end of this Session you will be able to:

- explain the factors which would influence the processes you would set up in order to effectively manage the implementation phase of a trial
- select appropriate progress reporting mechanisms
- design a change control process for a clinical trial
- determine whether the trial is behind schedule based upon progress information
- estimate the final cost of a trial based upon the project plan and progress information
- apply root cause analysis to problems which the trial encounters
- understand the options that the trial manager has in rectifying problems which occur on the trial
- explain what is required for effective close out of the trial

Hall marks in the close out therefore include:

- Study close-out plans
- Study close-out procedures
- Feedback to study participants and/or community

MODULE II – Regulatory Attachment

Investigational Product Importation

Objectives

Participants shall be able to

- Identify the appropriate documents required for various categories of investigational products
- Ensure products are imported through the approved channel
- Assess the consistency of product information in the required documents
- Ensure adequate accountability of investigation products

Procurement of Investigational Product for Clinical Trials

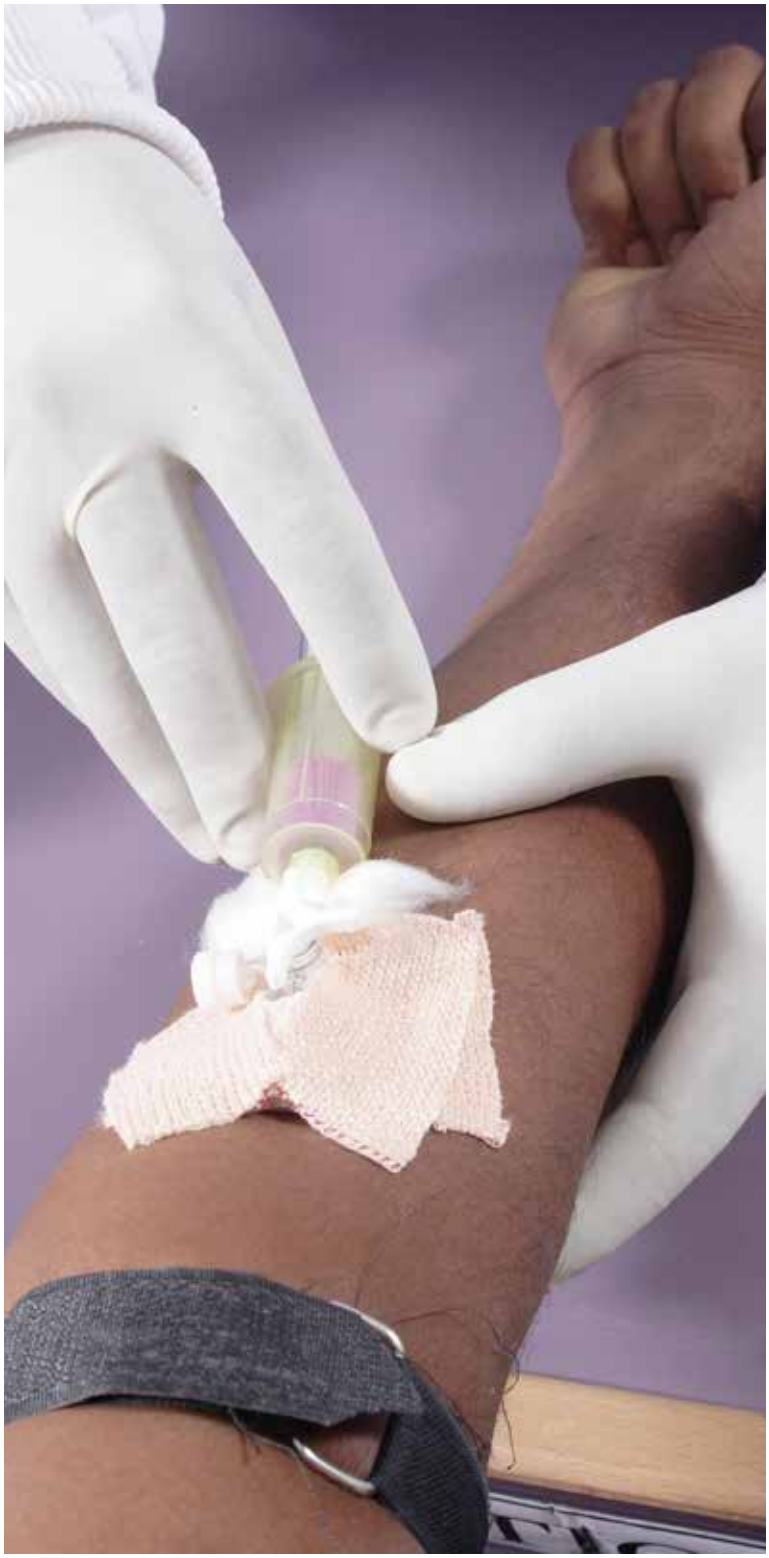
There will be a discussion on the national procedures available for the procurement of investigational products (including concomitant medications) to be used in a clinical trial. Emphasis will be on the differences between procurement from the local market and importation from other countries. Provision in Appendix 1g would be used as a general guide.

Question

Using a sample of a GC Net application form (permit) for importation of Investigational products to be used in a study, assess the consistency (with respect to product details and quantities) of information provide on the permit with information available in

a. CTA

b. Certificate of Analysis (CoA) and (batch release records where applicable)



MODULE III

GCP Inspections

Theory and Regulatory Attachment

Objectives

Participants shall be able to

i. Apply the necessary knowledge and skills required to ensure the application of ethical principles and good clinical practices
in biomedical research being conducted locally

ii. Ensure the appropriate application of international standards in the evaluation and monitoring of clinical trials.

iii. Prioritize clinical trial sites for GCP inspections

iv. Able to use the GCP checklist as a guide during inspections in order to harmonize/standardize procedures.

v. Grade GCP observations/findings made during inspections

vi. Assign responsibilities to these observations made with respect to the study team

vii. Make appropriate recommendations to the study team after GCP inspections

viii. Take the necessary regulatory actions against the site/study when necessary

Questions

I. Participants should familiarize themselves with the GCP inspection guide at Appendix 2a before the scheduled inspection. Any questions on it should be discussed with the facilitator.

   a. Using the guide as a checklist, each participant must note down his/her observations during the inspection.

   b. Using the grading provided at Appendix 2bi, grade the observations you have made with appropriate justifications. Appropriate references from the ICH (Appendix 2bii) and the relevant national guidelines should be provided for all observations made.

   c. Assign responsibilities to the observations made.

   d. Make a general recommendation on the site's compliance to GCP.

   e. What action should be taken based on your recommendation above?

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

   a. The phase of the clinical trial

b. The nature of the investigational product

c. The market authorization status of the investigational product

d. The population under study

e. The study design

f. Capacity of trial site

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

III. 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.

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 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.

Other Guidelines include those for National Regulatory Agencies

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 supplements, 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.

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.

MODULE IV

Adverse Events and Safety Monitoring (Pharmacovigilance)

LESSON I: Adverse Events

Objectives

At the end of this session, participants should be able to:

i. Know the components of adverse event reporting form (CIOMS 1 form) and the annual progress report form

ii. Understand the criteria for assessing seriousness criteria to adverse events received from clinical trial sites.

iii. Appreciate the important of phase IV studies and post approval safety monitoring

iv. Understand aggregate reporting (PSUR/PBRERs) and risk minimization activities

Adverse Events

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 AE/SAE form will need to be completed
- Verbal autopsies
    - A verbal autopsy (VA) is a method of gathering health information about a deceased individual to determine his or her cause of death. Health information and a description of events prior to death are acquired from conversations or interviews with a person or persons familiar with the deceased and analyzed by health professional or computer algorithms to assign a probable cause of death.
    - Verbal autopsy is used in settings where most deaths are undocumented
- Practical session
    - Analyzing SAE scenarios

LESSON II: Post Marketing Approval and Safety Monitoring

Post Marketing Approval & Phase IV Safety Monitoring

1. Public health impact of adverse drug reactions
2. Requirements to strengthening Pharmacovigilance:
    - Resources
    - Law
    - Science
3. Pharmacovigilance Regulation
    - Promote and protect public health by reducing burden of ADRs and optimizing the use of medicines:
        - Clear roles and responsibilities
        - Science based (move up hierarchy)
        - Risk based/proportionate
        - Increased proactivity/planning
        - Reduced duplication/redundancy
        - Integrate benefit and risk
        - Communication and transparency

4. Addresses almost all pharmacovigilance activities
    - Authorization requirements
    - Risk Management Plans
    - PSURs
    - Scientific Committees
    - Transparency and communication
    - Coordination of inspections
    - Audits
    - Effectiveness of risk minimization
    - ADR reporting
5. Post-authorization safety studies
    - Definition
    - General guidance and requirements
    - Good vigilance practice guidance
    - Clinical trial
    - Non-interventional study
6. Reporting of Pharmacovigilance data
    - Data relevant to the risk benefit balance
    - Reporting of ADRs:
    - Timelines for serious and non-serious ADRs

LESSON III: Reporting from Clinical Trial Sites

Objectives

Participants will be able to

i. 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)

ii. Appreciate the need to submit these reports

iii. Apply knowledge and skills acquired to assess these reports as per ICH GCP and applicable national regulatory requirements

iv. Identify issues/lapses with respect to submitted reports

v. Make the necessary recommendations to the trial team as well as take the necessary actions against the site/trial.

Preamble

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

"Oversight bodies MUST/MUST NOT NECESSARILY require reports from clinical trials throughout a trial's lifecycle"

Debators must address issues such us

a. Types or reports required/not required with respect to the respective stages in the lifecycle.

b. Justification for "a" above.

c. The mode/format/tools/alternatives for reporting.

d. Timelines for reporting

e. Persons responsible for reporting

f. Persons/authorities to whom respective reports/ alternatives should be addressed to.

g. Impact of listed reports/alternatives on data quality and participant safety

Hint: The facilitator must have access to the national reporting requirements, formats and timelines to guide discussions after the debate.

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

REFERENCES

1. Textbooks

Farrell B, Kenyon S, for the UKTMN Steering Group. UKTMN Guide to Efficient Trial Management. Third edition 2006. Section 2. http://www.tmn.ac.uk/files/Third_edition_TMG_Aug_2006.pdf

Smith PG, Morrow RH. Field Trials of Health Interventions in Developing Countries: a Toolbox. The World Health Organisation. Macmillan, 2nd edition 1996. Chapter 4 pp. 72-96

2. Key material in reader

World Medical Association. Declaration of Helsinki 2000 with clarifications http://www.wma.net/e/policy/b3.htm

EU Directive 2001/20/EC. http://www.wctn.org.uk/downloads/EU_Directive/Directive.pdf

3. Cited references

Council for International Organizations of Medical Sciences (CIOMS) 2002 International Ethical Guidelines for Biomedical Research Involving Human Subjects. http://www.cioms.ch/frame_guidelines_nov_2002.htm

Dangour AD, Clemens F, Elbourne D, Fasey N, Fletcher AE, Hardy P, Holder GE, Huppert FA, Knight R, Letley L, Richards M, Truesdale A, Vickers M and Uauy R (2006). A randomised controlled trial investigating the effect of n-3 long-chain polyunsaturated fatty acid supplementation on cognitive and retinal function in cognitively healthy older people: the Older People And n-3 Long-chain polyunsaturated fatty acids (OPAL) study protocol [ISRCTN72331636]. Nutrition Journal, 5:20.

Department of Health. Research Governance Framework 2001. European Directive 2001/20/EC http://www.wctn.org.uk/downloads/EU_Directive/Directive.pdf

International Conference on Harmonisation Tripartite Guidance for Good Clinical Practice 1996 http://www.ich.org

Lubsen J, Poole-Wilson PA, Pocock SJ, van Dalen FJ, Baumann J, Kirwan BA, et al (1998). Design and current status of ACTION: a coronary disease trial investigating outcome with nifedipine GITS. Gastro-intestinal therapeutic system. Eur Heart J;19(suppl I): 120-32.

Medical Research Council August 2004 Research Involving Human Participants in Developing Societies. http://www.mrc.ac.uk/Utilities/Documentrecord/index.htm?d=MRC002461

Poole-Wilson PA, Lubsen J, Kirwan BA, van Dalen FJ, Wagener G, Danchin N, et al. (2004) Effect of long-acting nifedipine on mortality and cardiovascular morbidity in patients with stable angina requiring treatment (ACTION trial): randomised controlled trial. Lancet 364: 849-57

4. Recommended reading for further study (optional)

Brunier, D.P. & Nahler, G. (eds.) International clinical trials: a guidebook and compendium of national drug laws. Denver, Colo.: Interpharm Press, 1999, 2v.

Dresser, R. When science offers salvation: patient advocacy and research ethics. Oxford; New York: Oxford University Press, 2001.

http://www.liv.ac.uk/%7Esrlclark/ethics.html#ethics (Database of resources in ethics of clinical trials)

Nuffield Council on Bioethics. The ethics of research related to healthcare in developing countries: Nuffield Council on Bioethics. March 2005. http://www.nuffieldbioethics.org/

Shapiro K, Benatar SR. HIV prevention research and global inequality: steps towards improved standards of care J Med Ethics. 2005;31(1):39-47

Smith, T. Ethics in medical research : a handbook of good practice New York ; Cambridge, UK: Cambridge University Press, 1998

APPENDICES

APPENDIX 1a

PRE-ASSESSMENT FORM FOR CLINICAL TRIALS APPLICATION

Name of trial _____

Phase _____

Principal Investigator (PI) _____

Contact/Tel no _____

Applicant's Name _____

Sponsor's Name _____

CHECKLIST

Requirements	Guide	Comment
Covering Letter		
Fees/Proof of payment	*This is set will be country specific*	
Clinical Trial Application Form	*A blank is provided as an addendum to this document*	
Trial Protocol	*In the format provided by the ICH Guide E6(RI)*	
Investigational Product Information:		
Investigators Brochure/SmPC	*In the format provided by the ICH Guide E6(RI)*	
Report Summaries of prior clinical trials with the IP		
Participant Information Leaflet (PIL) and Informed Consent Form (ICF)	*This should conform to the information provided in the CTA, Protocol and IB.*	

Requirements	Guide	Comment
Any publications referenced from the PIL should be checked for accuracy of conclusions.		
Parental-guardian ICFs and assents may be required.		
Certificate of GMP manufacture of the trial medicines	*This is not always available for investigational products. Sufficient information should be provided that will satisfy the reviewer/s that the material as manufactured has a defined quality, and is safe, stable and consistent.*	
Package Insert/s for other trial medicines	*These may not be registered in the country and translations into language/s acceptable to the reviewers and the NRA may be required. The use of unregistered comparator or concomitant medicines may require additional justification.*	
Certificate of GMP manufacture of the placebo/comparator - if appropriate	*Sufficient information should be provided that will satisfy the reviewer/s that the material as manufactured is safe, and consistent with defined quality.*	
Evidence of accreditation of the designated Laboratories	*Laboratories to be used for assay of clinical samples must provide evidence of Accreditation with a recognized control authority - to conduct the specified tests. This applies both to the laboratories conducting safety/ screening tests as well as those conducting specialized end-point assays.*	
In the absence of an accreditation authority, evidence of GLP compliance and of validation of the assay methods should be provided		
Insurance Certificate specific for the trial	*It should be current, valid for the full duration of the trial (or there must be a written commitment for renewal for the duration of the trial) and follow-up period.*	

Requirements	Guide	Comment
The certificate should contain a reference to the trial Protocol number and the countries to which cover is extended.		
The insurance cover should be provided from a company which is ABPI compliant.		
Signed and completed Declarations by Investigators	*It is expected that Investigators will be qualified, experienced and have specific GCP training.*	
The Principal Investigators should have acted as sub-investigators in at least one prior clinical study.		
The investigator must have read the Protocol and Investigators Brochure, and must confirm that the information provided in the CTA is a true reflection of these.		
The investigator must commit to comply with the Protocol.		
The investigator must have no conflicts of interest, and no history of GCP non-compliance malpractice (or at least should have been absolved of wrong-doing)		
Ethics Committee/s approval of the Protocol	*It is usual that the application will be submitted to the NRA and IEC at the same time.*	
Thus approval will not usually be available during the submission. The applicant should provide a copy of the application letter to the IEC.		
The NRA should receive the IEC approval timeously for inclusion in the deliberations leading to the final approval.		
Any condition, amendment or additional information required by the IEC should be communicated to the NRA.		

Requirements	Guide	Comment
Full, legible copies of key, peer-reviewed published articles		
supporting the application	*These are often difficult to obtain in certain countries.*	
It is important that these are available to confirm assertions, and conclusions drawn in the CTA, Protocol, IB, or PIL.		
Other appended documents	*May include Power-of-Attorney agreement, contracts, material transfer agreement*	
Financial declaration	*Commitment by Sponsor and Investigator that there would be adequate funding for the study*	
Final Declaration		

Remarks: _____

Name/signature of receiving officer: _____

Date: _____

APPENDIX 1b

CTIMP PROTOCOL GUIDANCE AND TEMPLATE

FULL/LONG TITLE OF THE TRIAL	
SHORT STUDY TITLE/ACRONYM	
RESEARCH REFERENCE NUMBERS	
TRIAL REGISTRY NUMBER AND DATE	
PROTOCOL VERSION NUMBER AND DATE	
OTHER RESEARCH REFERENCE NUMBERS	
SPONSOR/CO-SPONSORS/JOINT-SPONSORS	

FULL/LONG TITLE OF THE TRIAL

Aim: To identify the Trial to enable retrieval from literature or internet searches. It should be immediately evident what the study is investigating and on whom to allow rapid judgment of relevance.

For intervention or exposure studies a structured title should contain:

- Information on participants
- Intervention (exposure)
- Comparison groups
- Outcomes
- Phase
- Study design

SHORT STUDY TITLE/ACRONYM

Aim: To provide a summary of the long title. It is usually the title used on information sheets and consent forms for research participants or others giving consent or assent on their behalf.

The short title should be:

- Sufficiently detailed to make clear to participants what the research is about in simple English
- If acronyms are used the full title should explain them.

APPENDIX 1b

PROTOCOL VERSION NUMBER AND DATE

Aim: To track changes to the document for trial conduct, review, and oversight so it is clear which is the most recent document.

Version control:

- All draft versions should be numbered 0.1, 0.2 etc.
- The final version for submission should be numbered 1.0
- The changes made relative to the previous protocol version should be listed after submission

RESEARCH REFERENCE NUMBERS

PACTR Number: All clinical trials to be conducted in Africa must be registered with the Pan African Clinical Trial Registry.

ISRCTN Number/ Clinical trials.gov Number: Accepted registers include:

- EU Clinical Trials Register: This is a register of studies in the European Union Countries (https://www.clinicaltrialsregister.eu).
- International Standard Randomised Controlled Trials Number (ISRCTN) Register. This register accepts registration of randomised controlled trials and any other research study designed to assess the efficacy of health interventions in the human population.
- ClinicalTrials.gov. This is a register of studies in the United States and around the world.

SPONSORS Number: Generated by the Sponsor. Enter if applicable

FUNDERS Number: Generated by the funder. Enter if applicable

APPENDIX 1b

SIGNATURE PAGE

The undersigned confirm that the following protocol has been agreed and accepted and that the Principal Investigator agrees to conduct the trial in compliance with the approved protocol and will adhere to the principles outlined in the National Regulatory Agency's laws on Clinical Trials and any subsequent amendments of the clinical trial regulations, GCP guidelines, the Sponsor's SOPs, and other regulatory requirements as amended.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the Sponsor

I also confirm that I will make the findings of the study publically available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the study will be given; and that any discrepancies from the study as planned in this protocol will be explained.

For and on behalf of the Study Sponsor:

Signature:_____ Date: __/__/__

Name (please print):_____

Position:_____

Principal Investigator:

Signature:_____ Date: __/__/__

Name (please print):_____

Statistician:

Signature:_____ Date: __/__/__

Name (please print):_____

Position:_____

APPENDIX 1b

KEY TRIAL CONTACTS

Insert full details of the key trial contacts including the following

Principal Investigator	Full contact details including phone, email and fax numbers
Trial Co-ordinator	Full contact details including phone, email and fax numbers
Sponsor	Full contact details including phone, email and fax numbers The sponsor can be defined as the individual, company, institution, or organisation assuming overall responsibility for the initiation and management of the trial, and is not necessarily the main funder. Sponsorship responsibilities may be shared by joint- or co-sponsors
Joint-sponsor(s)/co-sponsor(s)	Full contact details including phone, email and fax numbers of ALL organisations assuming sponsorship responsibilities as a joint- or co-sponsor/s (If applicable)
Funder(s)	Names and contact details of ALL organisations providing funding and/or support in kind for this trial
Clinical Trials Unit	Full contact details including phone, email and fax numbers (If applicable)
Key Protocol Contributors	Full contact details including phone, email and fax numbers (If applicable)
Statistician	Full contact details including phone, email and fax numbers
Trials pharmacist	Full contact details including phone, email and fax numbers
Committees	Full contact details including phone, email and fax numbers

APPENDIX 1b

TRIAL SUMMARY

It may be useful to include a brief synopsis of the trial for quick reference. Complete information and, if required, add additional rows.

Trial Title		
Internal ref. no. (or short title)		
Clinical Phase		
Trial Design		
Trial Participants		
Planned Sample Size		
Treatment duration		
Follow up duration		
Planned Trial Period		
	Objectives	Outcome Measures
Primary		
Secondary		
Investigational Medicinal Product(s)		
Formulation, Dose, Route of Administration		

APPENDIX 1b

FUNDING AND SUPPORT IN KIND

FUNDER(S) (Names and contact details of ALL organisations providing funding and/or support in kind for this trial)	**FINANCIAL AND NON FINANCIALSUPPORT GIVEN**

APPENDIX 1b

ROLE OF STUDY SPONSOR AND FUNDER

Aim: To clarify the potential influence of sponsor and funders over the trial

The sponsor can be defined as the company, institution, or organisation assuming overall responsibility for the initiation and management of the trial, and is not necessarily the main funder. Identification of the trial sponsor provides transparency and accountability.

The protocol should explicitly outline the roles and responsibilities of the sponsor(s) and any funder(s) in trial design, conduct, data analysis and interpretation, manuscript writing, and dissemination of results. It is also important to state whether the sponsor(s) or funder(s) controls the final decision regarding any of these aspects of the trial.

NB in a CTIMP the sponsor has legal responsibilities that cannot be delegated.

APPENDIX 1b

ROLES AND RESPONSIBILITIES OF TRIAL MANAGEMENT COMMITEES/GROUPS & INDIVIDUALS

Trial Management Committees

Aim: To outline the various committees or groups involved in trial coordination and conduct.

There are three main trial management groups which may be involved in the set up and management of a clinical trial, depending on the trial size, design and number of sites. For each committee/group the protocol should state their roles and responsibilities and degree of independence from Sponsor and Investigators. If not included in the document the protocol should state where the information on the committee/group can be found.

- Trial Steering Committee

  The TSC must have a majority independent representation, including the

  Chair, meet regularly and send reports to the sponsor. Lay members or patient representatives are desirable

- Data Monitoring (and ethics) Committee

  Independence is a key characteristic of a Data Monitoring Committee where the committee members are completely uninvolved in the running of the trial and who cannot be unfairly influenced (either directly or indirectly) by people, or institutions, involved in the trial.

- Trial Management Group

  The Trial Management Group should meet regularly to ensure all practical details of the trial are progressing well and working well and everyone within the trial understands them.

APPENDIX 1b

PROTOCOL CONTRIBUTORS

Aim: To describe all the contributors to the protocol

The protocol should:

- Explicitly outline the roles and responsibilities of the sponsor and any funders in study design, conduct, data analysis and interpretation, manuscript writing, and dissemination of results.
- It is also important to state whether the sponsor or funder controls the final decision regarding any of these aspects of the trial.
- Describe in what aspects of the protocol design have patients, service users, and/or their carers, or members of the public been involved.

KEY WORDS: Insert relevant key words to describe the study; no more than 6 phrases

APPENDIX 1b

LIST OF CONTENTS

APPENDIX 1b

LIST OF ABBREVIATIONS

Define all unusual or 'technical' terms related to the trial. Add or delete as appropriate to your trial. Maintain alphabetical order for ease of reference.

AE	Adverse Event
AR	Adverse Reaction
CA	Competent Authority
CRF	Case Report Form
CRO	Contract Research Organisation
CTA	Clinical Trial Authorisation
CTIMP	Clinical Trial of Investigational Medicinal Product
DMC	Data Monitoring Committee
DSUR	Development Safety Update Report
EU	European Union
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
IB	Investigator Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonisation of technical requirements for registration of pharmaceuticals for human use.
IDMC	Independent Data Monitoring Committee
IMP	Investigational Medicinal Product
IMPD	Investigational Medicinal Product Dossier
ISF	Investigator Site File
ISRCTN	International Standard Randomised Controlled Trials Number
MA	Marketing Authorisation

MHRA	Medicines and Healthcare products Regulatory Agency
MS	Member State
NHS R&D	National Health Service Research & Development
NIMP	Non-Investigational Medicinal Product
PACTR	Pan African Clinical Trials Registry
PI	Principal Investigator
PIC	Participant Identification Centre
PIS	Participant Information Sheet
QA	Quality Assurance
QC	Quality Control
QP	Qualified Person
RCT	Randomised Control Trial
REC	Research Ethics Committee
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SDV	Source Data Verification
SOP	Standard Operating Procedure
SmPC	Summary of Product Characteristics
SSI	Site Specific Information
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMG	Trial Management Group
TMF	Trial Master File
TSC	Trial Steering Committee

APPENDIX 1b

TRIAL FLOW CHART

Aim: To give readers a schematic overview of the trial

A flow diagram should be included.

Careful consideration must be given by the protocol authors to ensure that the protocol is sensibly structured and ordered to allow users of the document to follow the patient and trial pathway accurately and with ease. Flow diagrams are helpful tools to guide users of the protocol through the patient and trial pathway, for instance a participant pathway detailing intended fit of the screening and recruitment process with usual practice may be helpful for complex intervention trials and a schedule of events in table format is also recommended. The schedule of events can be included where most appropriate in the protocol.

Key information to convey includes the timing of each visit, starting from initial eligibility screening through to study close-out; time periods during which trial interventions will be administered; and the procedures and assessments performed at each visit (with reference to specific data collection forms, if relevant)

APPENDIX 1b

STUDY PROTOCOL

Insert title, consistent with the title on the front page

1. BACKGROUND

Aim: To place the trial in the context of available evidence.

The background should be supported by appropriate references to the published literature on the disease or condition, its treatment and the use of the study drug for the indication and contain:-

- an up-to-date systematic review of relevant studies, new research should build on formal review of prior evidence
- a brief description of the proposed study
- a description of the population to be studied
- the investigational product(s) and their mechanism of action
- relevant data from preclinical/non-clinical studies
- relevant data from previous clinical trials such as efficacy, safety, tolerability, pharmacokinetics & pharmacodynamics
- if no data is available, include a statement that there is no available clinical research data to date on the investigational product

It should be written so it is easy to read and understand by someone with a basic sense of the topic who may not necessarily be an expert in the area. Some explanation of terms and concepts is likely to be beneficial.

2. RATIONALE

Aim: To explain why the research questions being asked are important and why closely related questions are not being covered.

This should include:

- A clear explanation of the research question/hypothesis and the justification of the trial i.e. why the question is worth asking and, through consultation with public and patient groups, why this is worthwhile to patients. Replication to check the validity of previous research is justified, but unnecessary duplication is unethical.
- The currently available treatment(s) and their limitations, why you think the IMP(s) might be an improvement on those treatments, why the treatment difference is clinically important to patients and if it is realistic. (The treatment difference is often referred to as the minimum clinically important difference or the difference we should not want to miss. A drug which reduces everyone's systolic blood pressure by 2 mm of mercury may be genuinely effective,

but the effect would not form the basis of a routine intervention)

- This justification is particularly important if the trial proposes to use the IMP:
  - in children or in adults unable to consent for themselves
  - in higher doses
  - for longer duration
  - in a subject population that might handle it differently (e.g. hepatic or renally impaired patients, children, elderly or immunocompromised individuals)
  - it is being used in combination with another medicinal product
  - the indication/medical condition compromises the subject's tolerance
  - in healthy volunteers

The rationale for the use of a placebo in the trial if one is being used

Justification for the choice of route of administration, dosage, dosage regimen, and treatment period(s)

It should also include an explanation and justification as to the choice of control interventions/comparators especially if it involves withholding or delaying standard of care

2.1 Assessment and management of risk

Aim: To describe a risk/benefit analysis plus risk management if the IMP(s) is to be used outside its licence.

The following should be described:

- The known and potential risks and benefits to human subjects
- How high the risk is compared to normal standard practice
- How the risk will be minimised/managed

Consider the starting dose, dose increments, administration of doses, and the resources required by site(s); particularly in terms of facilities and staff, procedures, type of patients, staff training required.

This trial is categorised as: (delete as appropriate)

- Type A = No higher than the risk of standard medical care
- Type B = Somewhat higher than the risk of standard medical care
- Type C = Markedly higher than the risk of standard medical care

See Appendix 1

3. OBJECTIVES AND OUTCOME MEASURES/ENDPOINTS

Aim: To define the primary research question, to address a specific hypothesis and to clearly define the secondary objectives

The objectives are generally phrased using neutral wording (e.g., "to compare the effect of intervention A versus intervention B on outcome X") rather than in terms of a particular direction of effect.

3.1 Primary objective

Aim: To define the primary research question, to address a specific hypothesis

The protocol should define:

- The hypothesis which should be stated in quantifiable terms; e.g. "the experimental treatment will result in 12 months of additional survival compared to the control treatment"
- The null and the alternative hypotheses
- For multi-arm trials, the objectives should clarify the way in which all the intervention groups will be compared (e.g., A versus B; A versus C)

A useful guide to use in the development of a specific research question are the PICOT criteria:

P Population (patients) - What specific patient population are you interested in?

I Intervention (for intervention studies only) - What is your investigational intervention?

C Comparison group - What is the main alternative to compare with the intervention?

O Outcome of interest - What do you intend to accomplish, measure, improve or affect?

T Time - What is the appropriate follow-up time to assess outcome

3.2 Secondary objectives

Aim: To clearly define the secondary objectives

The protocol should describe the secondary objectives which:

- May or may not be hypothesis-driven
- May include secondary outcomes
- May include more general non-experimental objectives (e.g., to develop a registry, to collect natural history data)

3.3 Outcome measures/endpoints

Aim: To define primary and secondary endpoints/outcomes for the trial which usually appear in the objectives and sample size calculation.

An ideal endpoint/outcome is valid, reproducible, relevant to the target population, and responsive to changes in the health condition being studied.

The protocol should define:

- The endpoint/outcome of main interest (primary outcome)
- The remaining endpoints/outcomes (secondary outcomes)
- Whether the endpoint/outcome reflect efficacy (beneficial effect) or harm (adverse effect)
- The rationale for the choice of trial endpoint/outcome
- For each endpoint/outcome, the trial protocol should define four components:
    - the specific measurement variable, which corresponds to the data collected directly from trial participants (e.g. allcause mortality);
    - the participant-level analysis metric, which corresponds to the format of the outcome data that will be used from each trial participant for analysis (e.g., change from baseline, final value, time to event);
    - the method of aggregation, which refers to the summary measure format for each study group (e.g., mean, proportion with score > 2);
    - the specific measurement time point of interest for analysis

3.4 Primary endpoint/outcome

Aim: To identify a single response variable (primary endpoint/outcome) to answer the primary research question.

The primary endpoint/outcome should be a clear, unarguable, quantitative measure of effect that will be the focus of the primary analysis and will drive the choice of sample size. Less is more e.g. "The primary endpoint/outcome is 28 day survival." It may be pertinent to list the time point at which endpoint/outcome will be measured if it is possible to be measured more than once during the trial. The protocol should describe any rules, references or programmes for calculation of derived values and describe what form it will take for analysis (e.g. continuous, categorical, ordinal)

Since there is only one choice of sample size, which may be based on the statistical power for the single primary analysis, there can only be one primary endpoint/outcome. The exception to this is in a study that is comparing a new diagnostic or measurement technique to an existing standard. In which case, it is acceptable to have two co-primary endpoints: the old and the new technique.

3.5 Secondary endpoints/outcomes

Aim: To identify a series of well-established endpoints of clinical importance that in theory could be the primary endpoint in another trial

This should be a sequence of concise statements referring to observations that say nothing about the trial objectives or analysis. There can be any number of secondary measures, although they should all be relevant to the declared aims of the study

3.6 Exploratory endpoints/outcomes

AIM: To identify any other endpoints/outcomes which are not well established

Objectives	Outcome Measures	Time point(s) of evaluation of this outcome measure (if applicable)
Primary Objective Example: To compare the effect of treatment A versus treatment B on the levels of protein X in the blood	Describe the outcome measures and how/when they will be measured during the trial. Outcome measures should reflect the objectives. It is important that only one outcome measure is selected as it will be used to decide the overall results or 'successes of the trial. The primary outcome measure should be measurable, clinically relevant to participants and widely accepted by the scientific and medical community. Assessments of outcome measures should be described in detail in section 7 Example: Concentration of protein X in blood samples from participants on each treatment	Example: Blood sampling at day 0 and day 28 post-treatment
Secondary Objectives Example: To assess the safety of treatment A in <insert condition/ population>	As above	

Objectives	Outcome Measures	Time point(s) of evaluation of this outcome measure (if applicable)
Tertiary Objectives Please add if applicable, otherwise delete this row	As Above	

4. TRIAL DESIGN

Aim: To describe the ideal design for the research question and what the trial is designed to show.

The framework of a trial refers to its overall objective to test:

- The superiority (treatment is superior to placebo or comparator treatment)
- Non-inferiority ('not worse than' the comparator treatment)
- Equivalence (treatment is similar to the comparator treatment) of one intervention with another
- In the case of exploratory pilot trials, to gather preliminary information on the intervention (e.g. harm, pharmacokinetics, etc.) and the feasibility of conducting a full-scale trial

Common designs include:

- Parallel group design: each group of participants receives only one of the study treatments.
- Cross-over design: each of the participants is given all the study treatments in successive periods. The order in which the participants receive each treatment is determined at random.
- Factorial design: two or more treatments are evaluated separately and in combination against a control. For instance, in a factorial design to assess the effect of drug A and drug B for the treatment of pain, participants would receive drug A only, drug B only, a combination of drug A and B, or placebo.
- Cluster randomised controlled trials: the treatment is randomised to groups of participants (e.g. families) rather than individual participants.
- Groups sequential: outcomes are assessed in a group and sequential manner
- Multiple-armed design: study with more than two arms. For example, a three-armed study comparing a treatment with inactive control/placebo, and an alternative active treatment

There is increasing interest in adaptive designs for clinical trials, defined as the use of accumulating data to decide how to modify aspects of a trial as it continues, without undermining the validity and integrity of the trial. Examples of potential adaptations include stopping the trial early, modifying the allocation ratio, re-estimating the sample size, and changing the eligibility criteria. The most valid adaptive designs are those in which the opportunity to make adaptations is based on pre-specified decision rules that are fully documented in the protocol.

5. STUDY SETTING

Aim: To describe where the study will be run and any site specific requirements

The protocol should include:

- If it is a multicentre or single centre study
- If there are any site specific requirements to run the study
- Whether there are different 'types' of site (e.g. recruiting, treating, continuing care, etc.) and what the specific requirements are for each
- Where a list of the participating sites can be found
- If applicable, eligibility criteria for trial centres and individuals who will perform the interventions (e.g., surgeons, psychotherapists)
- Consideration of the participant population and where they are found. What are the usual care pathways? Are patients with the condition of interest found in primary or secondary care? If using secondary care sites, will primary care Participant Identification Centres (PICs) be needed to recruit participants, or are patients found in secondary care?

6. ELIGIBILITY CRITERIA

Aim: To define the trial population

This section should set out precise definitions of which participants are eligible for the trial, defining both inclusion and exclusion criteria. Inclusion criteria should define the population the trial is aiming to include and indicate the generalizability of the trial findings. Exclusion criteria should exclude sub-groups of the population due to, for example, safety and other clinical risks or burden to the participant.

The eligibility criteria should be clear so they can be applied consistently through the trial and definitions for the timelines and flexibility of each eligibility criterion must be carefully considered to ensure that arbitrary or un-workable definitions are not used. Such definitions can affect eligibility due to the fact that eligibility waivers are usually not permitted by Regulatory Authorities. The choice of criteria can affect recruitment and attrition to the trial as well as it generalizability.

6.1 Inclusion criteria

- Subjects capable of giving informed consent, or if appropriate, subjects having an acceptable individual capable of giving consent on the subject's behalf (e.g. parent or guardian of a child under 16 years of age)
- Gender
- Gender
- Age
- Clinical parameters, compliance with EACH parameter for each subject will need to be clearly documented

6.2 Exclusion criteria

Females of childbearing potential and males must be willing to use a highly effective (acceptable effective contraceptive measures are only acceptable for IMP's with unlikely human teratogenicity/fetotoxicity in early pregnancy) method of contraception (hormonal or barrier method of birth control; abstinence) Contraceptive methods that can achieve a failure rate of less than 1% per year when used consistently and correctly are considered as highly effective birth control methods. **Such methods include:**

- Combined (estrogen and progesterone containing) hormonal contraception associated with inhibition of ovulation:
    - oral
    - intravaginal
    - transdermal
- Progestogen-only hormonal contraception associated with inhibition of ovulation
    - oral
    - injectable
    - implantable
- Intrauterine device (IUD)
- Intrauterine hormone-releasing system (IUS)
- Bilateral tubal occlusion
- Vasectomised partner
- Sexual abstinence

Note - In order to specify the duration of the risk mitigation measures after discontinuation of treatment with the IMP, the risk assessment should include an estimation of the end of relevant systemic exposure (the time point where the IMP, including any active or major metabolites, has decreased to a concentration that is no longer considered relevant for human teratogenicity/fetotoxicity).

- If the SmPCs of the IMPs state that the IMPs are not teratogenic you might be able to state that this is NA for your trial].
- Note - A combination of male condom with either cap, diaphragm or sponge with spermicide (double barrier methods) are also considered acceptable, but not highly effective, birth control methods.
- Females of childbearing potential must have a negative pregnancy test within 7 days prior to treatment initiation). [If the SmPCs of the IMPs state that the IMPs are not teratogenic you might be able to state that this is NA for your trial]. NOTE: Subjects are considered not of child bearing potential if they are surgically sterile (i.e. they have undergone a hysterectomy, bilateral tubal ligation, or bilateral oophorectomy) or they are postmenopausal.

- WOCBP should only be included after a confirmed menstrual period and a negative highly sensitive urine or serum pregnancy test, except for IMPs where an absence of risk of human teratogenicity/fetotoxicity in early pregnancy can be justified by human pregnancy data.
- Note - For advanced therapy medicinal products (ATMP) embryofetal risk assessment and the need for contraception and pregnancy testing recommendations should be considered on a case-by-case basis.
- Females must not be breastfeeding.
- Males - For genotoxic IMPs, the male subject should use condom during treatment and until the end of relevant systemic exposure in the male subject, plus a further 90-day period. For a non-pregnant WOCBP partner, contraception recommendations should also be considered.
- Consider contraindications to trial treatment (e.g. as listed in SmPc), incompatible concurrent treatments, recent involvement in other research.
- Allergies to excipients of IMP and placebo
- Significant medical history of a particular illness/disease. It is important to detail specifically how long you consider the history needs to be eg. evidence of very early childhood asthma with no recurrence in adulthood is potentially not very significant in a patient aged 50.

7. TRIAL PROCEDURES

Add schedule of procedures as an appendix, if appropriate

Aim: To provide a clear and concise timeline of the trial visits, enrolment process, interventions, and assessments performed on participants

The protocol should describe what the procedures/assessments are at each visit and where they will be undertaken i.e. hospital/GP surgeries/at home and if not at the trial site the timelines for notification of these results to the trial team, especially if they are outside of the range etc.

7.1 Recruitment

Aim: To describe how patients are identified and recruited

This section should give details of the participant eligibility screening process for the project including information to be collected regarding participants who are screened and for participants who are not randomised/registered where data is being collated for Consolidated Standards of Reporting Trials (CONSORT) or other similar reasons for reporting the generalisability of the results. If a decision is made to not collect this information, the justification for this should be documented.

Anonymised information on participants who are not randomised/registered for CONSORT reporting should include:

- age,
- gender,

- ethnicity (if applicable),
- whether the patient is registered or not registered,
- the reason not eligible for trial participation, or if they are eligible but declined

7.1.1 Patient identification

The following should be described in the protocol:-

- Who will identify participants
- What resources will be used
- Will identification involve reviewing or screening the identifiable personal information of patients, service users or any other person (if so will this be undertaken by members of the normal clinical team or will Section 251 – http://www.hra.nhs.uk/about-the-hra/our-committees/section-251/what-is-section-251/- be applied for?)
- Will any participants be recruited through PICs
- Will any participants be recruited by publicity; posters, leaflets, adverts or websites
- Details of the sources of identifiable personal information that will be used to identify potential participant. Normally only a member of the patient's existing clinical care team should have access to patient records without explicit consent in order to identify potential participants, check whether they meet the inclusion criteria or make the initial approach to patients. If the research proposes to use someone outside the clinical team to identify suitable participants or as first contact with the participant, the reason for this should be explained
- The arrangements for referral if the participants are to be identified by a separate research team
- If patient or disease registers are used to identify potential participants a brief description of the consent and confidentiality arrangements of the register should be included
- Certain studies, such as cluster trials, incorporate a separate screening process relevant to that trial design – in such cases it may be appropriate to collect more detailed information regarding screened participants.
- It should be clear who will confirm eligibility. **NB** in a CTIMP this must be confirmed by a medical practitioner.

7.1.2 Screening

Aim: To list any screening requirements such as laboratory or diagnostic testing necessary to meet any noted inclusion or exclusion criteria such as:-

- ECG
- Laboratory tests
- Biopsies and samples
- Scans

Any assessments and or procedures performed as part of routine care which will be used to screen patients for eligibility will require defined timelines (e.g. x-rays within the last 6 months). Specify the maximum duration allowed between screening and recruitment (if applicable).

Screen failures i.e. patients who do not meet eligibility criteria at time of screening may be eligible for rescreening subject to acceptable parameters. If this is the case then the process needs to be clearly laid out.

If eligibility screening involves procedures that emit ionising radiation it is vital that the exposure is categorised correctly. The following guidance should be followed:

Ionising radiation exposures are considered to be 'research exposures' where the exposure is required as a specified part of, and for the purpose of, the research. **For example:**

- Diagnostic procedures undertaken prospectively to confirm the eligibility of potential participants for the study or to provide (qualitative or quantitative) data regarding disease status at baseline; or
- Radiotherapy as part of a treatment strategy to which patients are assigned prospectively by the protocol, either as part of an experimental or control arm, and which will be evaluated by the study; or
- Diagnostic procedures scheduled at formal time-points within the trial protocol to assess disease status or response to treatment; or
- Diagnostic imaging or image-guided procedures undertaken prospectively whilst the patient is enrolled in the study

Exposures which meet any of these criteria are considered to be research exposures even where they would otherwise be part of normal clinical care for patients treated outside the research setting, and whether or not research participation will result in 'additional' exposure over and above routine care.

The protocol should also detail all intended payments to participants e.g. reasonable travel expenses for any visits additional to normal care.

7.2 Consent

The Principal Investigator (PI) retains overall responsibility for the informed consent of participants at their site and must ensure that any person delegated responsibility to participate in the informed consent process is duly authorised, trained and competent to participate according to the ethically approved protocol, principles of Good Clinical Practice (GCP) and Declaration of Helsinki. If delegation of consent is acceptable then details should be provided.

Informed consent must be obtained prior to the participant undergoing procedures that are specifically for the purposes of the trial and are out-with standard routine care at the participating site (including the collection of identifiable participant data unless the trial has prior approval from the Confidentiality Advisory Group (CAG) and the Research Ethics Committee (REC))

The right of a participant to refuse participation without giving reasons must be respected.

The participant must remain free to withdraw at any time from the trial without giving reasons and without prejudicing his/her further treatment and must be provided with a contact point where he/she may obtain further information about

the trial. Where a participant is required to re-consent or new information is required to be provided to a participant it is the responsibility of the PI to ensure this is done in a timely manner.

The PI takes responsibility for ensuring that all vulnerable subjects are protected and participate voluntarily in an environment free from coercion or undue influence

Where the participant population is likely to include a significant proportion of participants who cannot read or write, require translators or have cognitive impairment, appropriate alternative methods for supporting the informed consent process should be employed. This may include allowing a witness to sign on a participant's behalf (in the case of problems with reading or writing), or allowing someone to date the form on behalf of the participant, or providing Participant Information Sheets in other languages or in a format easily understood by the participant population (in the case of minors or cognitive impairment).

The protocol should specify what arrangements the Sponsor considers to be appropriate at site(s) to support the consent process for these participants. For example, if verbal translation is needed, should this be via a hospital interpreter or a personal interpreter; are telephone translation services acceptable; if translated written material is to be provided to participants, are these to be provided by the sponsor, or translated locally, and what arrangements are in place to confirm the accuracy of the translation, e.g. back translation; if age appropriate information for minors is to be provided, what age ranges is this divided into; if parent/guardian consent for a minor to participate is being sought, what are the acceptable relationships of the guardian to the minor?

Note that for studies involving sites in Wales, to comply with the Welsh Language Act 1993, the Participant Information Sheets and Consent forms must be translated into Welsh or provided bilingually where this is requested by a participant at a research site.

The protocol should fully describe the process which typically involves:

- Discussion between the potential participant or his/her legally acceptable representative and an individual knowledgeable about the research about the nature and objectives of the trial and possible risks associated with their participation
- The presentation of written material (e.g., information leaflet and consent document which must be approved by the REC and be in compliance with GCP, local regulatory requirements and legal requirements
- The opportunity for potential participants to ask questions
- Assessment of capacity. For consent to be ethical and valid in law, participants must be capable of giving consent for themselves. A capable person will:
    - Understand the purpose and nature of the research
    - Understand what the research involves, its benefits (or lack of benefits), risks and burdens
    - Understand the alternatives to taking part
    - Be able to retain the information long enough to make an effective decision.
    - Be able to make a free choice

- Be capable of making this particular decision at the time it needs to be made (though their capacity may fluctuate, and they may be capable of making some decisions but not others depending on their complexity)
- Where participants are capable of consenting for themselves but are particularly susceptible to coercion, it is important to explain how their interests will be protected

General good practice in research (and the basis of legal frameworks relating to both CTIMPs and non-CTIMPs) require that persons incapable of giving legal consent should be given special protection.

A person is assumed to have the mental capacity to make a decision unless it is shown to be absent. Mental capacity is considered to be lacking if, in a specific circumstance, a person is unable to make a decision for him or herself because of impairment or a disturbance in the functioning of their mind or brain. In practice for participants with mental incapacity this means that they should not be included in clinical trials if the same results can be obtained using persons capable of giving consent and should only be included where there are grounds for expecting that their taking part will be of direct benefit to that participant, thereby outweighing the risks. The Mental Capacity Act 2005 does not apply to CTIMPs.

The Clinical Trial Regulations define a child as a person under the age of 16 years of age. The legal framework and ethical considerations for involving young people (between the ages of 16 and 17) in research are set out in the Department of Health Reference Guide to Consent for Examination or Treatment (2009) and should be referred to for any trial including young people (between the ages of 16 and 17). In practice for young people and children this means that only medicinal products which are likely to be of significant value for young people and children are fully studied and the protection of participating children is fully considered.

For further details on the ethical considerations of including persons with mental incapacity or minors in research see the guidance notes available on the HRA website.

http://www.hra.nhs.uk/resources/before-you-apply/consent-and-participation/consent-and-participant-information/

Where the trial allows the inclusion of subjects who lack the capacity to consent for themselves (for example, in cases where the research is related to the disease/illness causing mental incapacity) the full procedure for consent by a legal representative must be included in the protocol, along with appropriate information sheets and consent forms.

The issue of entry of incapacitated adults into CTIMPs is covered by The Medicines for Human Use (Clinical Trials) Regulations and the required procedures to be included in the trial protocol are detailed within these regulations. For studies involving Scottish research sites these Regulations supersede the Adults with Incapacity (Scotland) Act 2000 where any conflict arises. The specific schedules of the Regulations must be read and adhered to by the protocol authors.

Where a participant is able to consent for a CTIMP but later becomes incapacitated, the management of these participants must also be stipulated in the protocol; in all such cases the original consent given endures the loss of capacity, providing that the trial has not significantly altered (there may be clinical justification under such circumstances for cessation of any further clinical intervention while data collection for follow-up purposes continues).

7.2.1 Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable

Aim: To describe the consenting procedure for ancillary studies (if applicable)

The protocol should state:

- If data and/or biological specimens for ancillary studies will be acquired and stored during the trial.
- If the data and/or biological specimens will be used for a specified subset of studies or for submission to ethically approved research tissue banks for future specified or unspecified research
- What options participants will be given in respect to their participation in ancillary research including:
    - Whether participation in the ancillary research is required for participation in trial or if participants may opt out but still participate in the main study
    - Consent for the use of their data and specimens in specified protocols
    - Consent for use in future research unrelated to the clinical condition under study
    - Consent for submission to an unrelated bio-bank
    - Consent to be contacted by trial investigators for further informational and consent-related purposes
- Whether their withdrawal from the ancillary research is possible and what will happen to material provided up to that point:
    - For example if the data and/or specimens will be coded and identifiable
    - What withdrawal means in this context
    - What information derived from the specimen related research will be provided to them, if any

7.3 The randomisation scheme

Aim: To provide a full description of the process of how treatments will be allocated between subjects in enough detail to theoretically enable a full reproduction of the process.

The protocol should describe:

- The method of randomisation e.g.:
    - Simple randomisation based solely on a single, constant allocation ratio is known as simple randomisation. Simple randomisation with a 1:1 allocation ratio is analogous to a coin toss. No other method of allocation surpasses the bias prevention and unpredictability of simple randomisation
    - Restricted randomisation which includes any randomised approach that is not simple randomisation including:-
        - Blocked randomisation
        - Biased coin and urn randomisation
        - Stratified randomisation

If an unequal treatment allocation will be used and a justification for its use

If the allocation ratio will adaptively evolve over the course of the trial and a short overview statement to that effect with a reference to the full description in the “Interim Analysis” section

If minimisation is going to be used. Minimisation assures similar distribution of selected participant factors between study groups. The first participant is truly randomly allocated; for each subsequent participant, the treatment allocation that minimises the imbalance on the selected factors between groups at that time is selected. That allocation may then be used, or a choice may be made at random with a heavy weighting in favour of the intervention that would minimise imbalance (for example, with a probability of 0.8).

Full details of a restricted randomisation scheme (including minimisation) should not be included in the trial protocol as knowledge of these details might undermine randomisation by facilitating deciphering of the allocation sequence. Instead, this specific information should be provided in a separate document with restricted access.

7.3.1 Method of implementing the allocation sequence

Aim: To describe how the allocation sequence will be run in the trial.

Successful randomisation in practice depends on two interrelated aspects:

1. Generation of an unpredictable allocation sequence and
2. Concealment of that sequence until assignment irreversibly occurs.

Protocols should describe:

- The system to use be used e.g. a web based randomisation/treatment allocation system
- Who will access this at each site
- How the allocation will be documented e.g. will the system provide an immediate allocation with a confirmatory email
- Who else will be provided with a copy of the treatment allocation or randomisation number etc.
- How will randomisation codes be accessed out-of-hours or in an emergency

7.4 Blinding

Aim: To describe the blinding process to avoid bias in detail. If blinding is not to be used then justification should be provided.

The protocol should explicitly describe:

- Who will be blinded to intervention groups including:
    - Trial participants
    - Care providers
    - Outcome assessors

A full description is essential and ambiguous terminology such as “single blind” or “double blind” should not be used.

- The comparability of blinded interventions e.g. similarities in appearance, use of specific flavours to mask a distinctive taste
- The timing of final unblinding of all trial participants (e.g., after the creation of a locked analysis data set)
- Any strategies to reduce the potential for unblinding such as pretrial testing of blinding procedures.
- When blinding of trial participants and care providers is not possible because of obvious differences between the interventions, blinding of the outcome assessors can often still be implemented. It may also be possible to blind participants or trial personnel to the study hypothesis in terms of which intervention is considered active.

7.5 Unblinding

Aim: To provide a clear description of the conditions and procedures for unblinding.

The study code should only be broken for valid medical or safety reasons e.g. in the case of a severe adverse event where it is necessary for the investigator or treating health care professional to know which treatment the patient is receiving before the participant can be treated. Subject always to clinical need, where possible, members of the research team should remain blinded.

The following information should be inserted into the protocol:

- The code breaks for the trial are held [please add relevant department] and are the responsibility of [please add personnel]
- In the event a code is required to be unblinded a formal request for unblinding will be made by the Investigator/ treating health care professional
- If the person requiring the unblinding is a member of the Investigating team then a request to the holder of the code break envelope/list, or their delegate will be made and the unblinded information obtained
- If the person requiring the unblinding is not the CI/PI then that health care professional will notify the Investigating team that an unblinding is required for a trial subject and an assessment to unblind should be made in consultation with the clinical and research teams
- On receipt of the treatment allocation details the CI/PI or treating health care professional will continue to deal with the participant's medical emergency as appropriate
- The CI/PI documents the breaking of the code and the reasons for doing so on the CRF/data collection tool, in the site file and medical notes. It will also be documented at the end of the study in any final study report and/or statistical report
- The CI/Investigating team will notify the Sponsor in writing as soon as possible following the code break detailing the necessity of the code break
- The CI/PI will also notify the relevant authorities. The written information will be disseminated to the Data Safety Monitoring Committee for review in accordance with the DMC Charter

- As investigator is responsible for the medical care of the individual trial subject (Declaration of Helsinki 3§ and ICH 4.3) the coding system in blinded trials should include a mechanism that permits rapid unblinding (ICH GCP 5.13.4). The investigator cannot be required to discuss unblinding if he or she feels that emergent unblinding is necessary.

7.6 Baseline data

Aim: To clearly describe the baseline data that needs to be collected. **NB** only data that forms part of the predefined data set essential for analysis should be collected.

The following should be considered:

- The relevance of each baseline variable. Do not include a variable solely on the grounds that it is always recorded, if there is genuinely no interest in the variable
- Do any of the procedures need to be undertaken in a certain order
- Are explanations needed? E.g. if 3 measurements are to be taken and averaged that should be explained
- For particularly complex procedures or those that differ from routine standard practice, these should be detailed in full. E.g. if a 6 lead ECG is normal routine practice but the trial requires a 12 lead EGC this will need to be made clear to avoid potential errors
- If there are any translational aspects of the trial for example the collection of blood or tissue samples, this should be detailed in the relevant sections of the protocol (e.g., assessments section, analysis section, storage of samples section etc)
- If specialist, non-standardised assessments are required, care should be taken to detail exactly what needs to happen during the assessment
- It is an offence under the data protection act to process data that is irrelevant or excessive for the purpose for which it was collected. CRFs must therefore collect only the information directly relevant to the objectives and outcome measures detailed in the protocol. Collecting additional data not so specified is not permissible.

7.7 Trial assessments

Aim: To clearly describe the trial assessments.

The protocol should describe:

- All study procedures and assessments, including those that are part of routine care
- The timing of the assessments should be detailed and broken down into visit numbers as appropriate
- The detail of any run-in or washout periods
- The time points for assessment data e.g. The following are to be recorded each month for the first 12 months and every three months afterwards:

- History and clinical examination
- Assessment of the toxicity of the previous course
- Weight
- Full blood count
- Biochemical series
- Chest X-ray
- Etc.

- How compliance will be checked if home dosing
- When diary cards should be checked
- Assessment data required at the end of trial visit
- The methods and timing for assessing, recording and analysing efficacy parameters e.g.:
  - The values/scores that will determine success or failure and how they will be assessed if appropriate
  - Survival e.g.: These will be measured from the date of randomisation and will be reported for all deaths due to all causes. The cause of death is to be recorded in all instances
  - Quality of life assessments if required

7.8 Long term follow-up assessments

Aim: To clearly describe the long term follow-up assessments

If patients will be monitored after the active treatment phase has closed the protocol should describe:

- The frequency of follow-up visits
- Duration of follow-up period
- Assessments to be carried out
- How the follow up due to the research differs from standard of care
- Retention strategies
- How patients will be identified as 'lost to follow-up'
- Measures taken to obtain the information if visits or data collection time-points are missed.
- Which outcome data will be recorded from protocol non-adherers

Trial investigators should seek a balance between achieving a sufficiently long follow-up for a clinically relevant outcome measurement, and a sufficiently short follow-up to prevent missing data and avoid the associated complexities in both the study analysis and interpretation.

7.9 Qualitative assessments – Nested studies

Aim: To describe any qualitative research that forms part of the trial

This section should detail any qualitative component to the trial and provide a rationale for the timing and tools for assessment, for example measuring the acceptability of the intervention or measuring reasons for non-adherence to study medication. This section should also detail instructions for the timing and administration of measures and whether the nested qualitative component is optional or not. Timing should include the window around the time point for which each questionnaire/focus group/interview should be completed, details regarding chasing of questionnaires and how participants with missing baseline measures will be followed-up. **NB** Any data that contribute to the outcome/endpoints of the study should ideally be included in the case report form with a signature of the reviewer.

7.10 Withdrawal criteria

Aim: To give a full description of the withdrawal criteria

It is always within the remit of the physician responsible for a patient to withdraw a patient from a trial for appropriate medical reasons, be they individual adverse events or new information gained about a treatment.

The protocol should therefore:

- Describe under what circumstances and how subjects will be withdrawn from the trial/investigational product treatment – including whether the patient would continue to be part of the trial if IMP was withdrawn for specific reasons.
- Give details of documentation to be completed on subject withdrawal (including recording reasons for withdrawal and any follow-up information collected with timing)
- Whether and how subjects are to be replaced
- The follow up of subjects that have withdrawn from the treatment/trial
- State under what circumstances the trial might be prematurely stopped.

NB Remember the safety profile of the IMP(s) and the objective(s) of the trial. It may be necessary to give the circumstances under which treatment may be resumed.

7.11 Storage and analysis of samples

Aim: To describe the procedure for dealing with biological samples

The protocol should describe the procedure for dealing with biological samples:

- The criteria for the collection, analysis, storage and destruction of biological samples
- The arrangements for sample collection
    - Sample type(s) e.g. whole blood, plasma, serum, saliva, urine, stool, fresh tissue biopsy, paraffin tissue block
    - Volume of sample(s) to be collected

- Types of tubes, containers, swabs to be used for sample collection, and whether these will be provided by the sponsor or must be sourced locally by site(s)
- Sample processing arrangements e.g. centrifugation (how soon after collection should samples be spun, how long for, at what speed, at what temperature)

- The arrangements for sample analysis
  - Whether samples will be tested/analysed locally or sent to a central facility
  - How soon after collection should the samples be analysed or shipped
  - If the samples are to be shipped, include details of the arrangements for this (e.g. on dry ice), indicate whether the sponsor or the site(s) will be responsible for arranging the courier to transport the samples
  - What will happen to the samples after they have been analysed; will they be stored or destroyed (see below)
- The storage arrangements for samples
  - How soon after collection should the samples be put under storage conditions
  - how long will the samples be stored for, and what will be done with the samples after this time (e.g. destruction)
  - Where samples will be stored; locally at site(s) or sent to a central storage facility (and shipping arrangements if the latter)
  - Whether any samples will be held in long-term storage for future unspecified use, or held in an ethically approved tissue bank (in which case consent and Human Tissue Act need to be considered and addressed)
  - What conditions should the samples be stored under (if samples are to be stored in specialist fridges or freezers e.g. a -80°C freezer, then it is beneficial to specify that samples will be stored at -80°C +/- 10°C (or the tolerance to which you specify), rather than to state -80°C. This will avoid numerous notifications of temperature deviations, when not really required)
- The destruction arrangements for samples
  - When the samples will be destroyed; after analysis, after a set storage period?
  - How the samples should be destroyed
  - How destruction should be recorded
  - That for any specialist sample handling, processing and or shipment, a lab manual will be available and to refer to the manual

The following statement sets out the responsibilities of the trial site in regard to samples and can be included in the protocol if appropriate.

"It is the responsibility of the trial site to ensure that samples are appropriately labelled in accordance with the trial procedures to comply with the 1998 Data Protection Act. Biological samples collected from participants as part of this trial will be transported, stored, accessed and processed in accordance with national legislation relating to the use and storage of human tissue for research purposes and such activities shall at least meet the requirements as set out in the

2004 Human Tissue Act and the 2006 Human Tissue (Scotland) Act."

7.12 End of trial

For trials requiring MHRA approval the end of the trial should be defined in the protocol. The sponsor must notify the MHRA and main REC of the end of a clinical trial within 90 days of its completion. It is usually the date of the last visit/ data item of the last patient undergoing the trial.

8. TRIAL MEDICATION

Aim: To provide a full description of the investigational drug(s) to be used plus any medical device, food supplement, radiation, surgery, behavioural interventions, etc. that forms part of the trial

According to the definition of the EU clinical trial directive 2001/20/EC, an investigational medicinal product is a pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical trial, including products already with a marketing authorisation, but used or assembled (formulated or packaged) in a way different from the authorised form, or when used for an unauthorised indication, or when used to gain further information about the authorised form. Information about the comparator product/placebo should also be given in this section.

8.1 Name and description of investigational medicinal product(s)

Aim: To give a full description on the IMP

The protocol should specify:

- If the trial uses a licensed drug, the generic name only, unless a specific brand must be used, for example as per an IMP supply agreement (e.g. if IMP is to be supplied free of charge by the manufacturer)
- If only the generic name is used then a statement that any brand of the IMP can be used should be included
- A description of the IMP proportional to the development status of the IMP (e.g. for marketed products reference to the authorized medicinal product with at least details of strength dosage form and Product Licence holder should be given, for new or modified products a full although concise description should be given
- For CTIMPs using chemotherapy treatment the National Cancer Research Network (NCRN) Chemotherapy and Pharmacy Advisory Service (CPAS) Guidance should be referred to in drafting this section of the protocol

8.2 Legal status of the drug

Aim: To define the legal status of the drug

The protocol should include details of whether this drug is licensed for use in the UK or other countries and its indication. If the IMP is unlicensed or ring-fenced commercially supplied IMP then the following statement can be used:

'The trial is being carried out under a Clinical Trial Authorisation (CTA). The drug is therefore only to be used by the named investigators, for the patients specified in this protocol, and within the trial.'

8.3 Summary of Product Characteristics (SmPC)

The protocol should detail if a Summary of Product Characteristics (SmPC) or Investigator Brochure (IB) or simplified SmPC is going to be used, what version and how updated versions will be incorporated into the trial

8.4 Drug storage and supply

Aim: To describe the procedures for the shipment, receipt, distribution, return and destruction of the investigational medicinal products including placebo.

The protocol should include:

- Details of supply including whether it is free of charge from the IMP manufacturer or normal hospital stock
- If the IMPs to be used in the trial are being provided or manufactured by a company specifically for use in the trial and if they are details of the arrangement
- Any special supply processes, e.g. a triggered release process or central supply to all sites from a 3rd party
- How the drug should be stored
- Who will supply e.g. which pharmacy and how e.g. 'upon receipt of a suitably signed trial specific prescription'
- If the drug is to be supplied to the trial team for re-constitution outside of the pharmacy department
- Any storage instructions once dispensed from pharmacy e.g. stored in a fridge at ##°C and used within 24 hours depending on the requirements of the product
- Details of accountability and destruction/return
- Arrangements for post-trial access to IMP

For multicentre trials where supply details may vary between sites, this section should cover only aspects applicable to all sites.

8.5 Preparation and labelling of Investigational Medicinal Product

Aim: To give a precise and complete description of the preparation and labelling of the IMP

- The protocol should include:
- The form of the drug(s) including placebos if used in the trial
- Details on how the drug is to be prepared
- Technical modalities if applicable (e.g. if the product is to be given in a syringe and is a powder and needs to be re-constituted, this should be described here)
    - Details on packaging & labelling

Preparation and labelling of the investigational medicinal products should be completed in accordance with the relevant GMP guidelines.

8.6 Dosage schedules

Aim: To give a precise and complete description of the dosage schedules

The dosing schedule for each drug should include:-

- Description and justification of route of administration; oral, intravenous etc.
- Frequency of administration
- Timing of each dose
- If the drug is to be infused, it is important to detail how long the infusions will take – for example 5mg/kg (to a maximum of 250mg) infused over 8 hours
- Maximum dosage allowed each time the drug is given
- Methods for individualised doses (if applicable)
- Maximum duration of treatment of a subject. The total amount of time the patient will be receiving the IMP. This is not necessarily the length of patient participation in the trial
- Remember to take particular care over changes to doses as infants and children grow

8.7 Dosage modifications

Aim: To give details here on required dose modifications (if applicable)

The protocol should detail:

- If the dose should be modified for example in the case of certain adverse events (specify the exact dose modifications and events)
- The stopping rules
- Whether the dosage will be modified in accordance with the patients results (e.g. lab results – and what the results should be) and whether this will be completed under controlled hospital conditions or whether the patient will be required to adjust their own dosages following medical guidance at home
- Whether the dose can be modified due to patient request
- Procedures in the event of toxicity reactions (if applicable) e.g. if it is possible to reduce the dosage of IMP or if any rescue medication may need to be administered

8.8 Known drug reactions and interaction with other therapies

Aim: To identify any known drug reactions or interaction with other therapies

The protocol should:

- Cross-reference this with the section on safety reporting if applicable

- Also cross reference this with the SmPC and/or IB
- List any prohibited concomitant medications or therapies in this section

8.9 Concomitant medication

Aim: To provide a full description of concomitant medication

The protocol should:

- Specify medication(s)/treatment(s) permitted and not permitted before and/or during the trial and their time restrictions
- Consider possible interactions or effects that could confound the results and conclusions. Do not confuse these with Non-Investigational Medicinal Products (NIMPs)

8.10 Trial restrictions

Aim: To provide a full description of trial restrictions

The protocol should specify:

- Any contraindications whilst on the active phase of the trial including dietary requirements/restrictions
- Whether contraception needs to be used and the duration for use. The list of approved contraception for the trial should be fairly extensive. For example: Women of childbearing potential are required to use adequate contraception for the duration of the trial and for ## after the completion of the trial. This includes:
  - Intrauterine Device (IUD)
  - Hormonal based contraception (pill, contraceptive injection etc.)
  - Double Barrier contraception (condom and occlusive cap e.g. diaphragm or cervical cap with spermicide)
  - True abstinence
- Also list any requirements for male participants

8.11 Assessment of compliance

Aim: To describe how compliance will be assessed

Define procedures for:

- Monitoring (e.g. watching subject swallow pills and checking their mouth afterwards, getting patients to complete a diary card, package returns)
- Deciding the percentage of IMP compliance acceptable for patient to continue on the trial
- Recording of subject compliance information (what will be recorded, when and where)
- How non-compliance to the protocol study procedures will be documented by the investigator and reported to the Sponsor

- Deciding when persistent non-compliance will lead the patient to be withdrawn from the study e.g. percentage of non-compliance acceptable for patient to continue on the trial is <80% non-compliance equates to patient withdrawal (this includes compliance with IMP and study procedures e.g. visit window, refusal of study specific assessments)
- Following-up non-compliant subjects
- Improving compliance- ideally these should be strategies that can be easily implemented in clinical practice so that the level of compliance in the real world setting is comparable to that observed in the trial

8.12 Name and description of each Non-Investigational Medicinal Product (NIMP)

Aim: To give a full description of each NIMP

The protocol should include some details about the NIMPs which are any products supplied to the trial participants according the protocol but are NOT under investigation.

They could be:

- Challenge agents
- Rescue or escape medication
- Any other product which is not under investigation that will be used in the trial, including any background medication(s) administered to all subjects

Include details of the dosage, treatment duration and administration; if it is going to be provided by the sponsor and other details of storage and supply as appropriate.

A similar system to that required for IMPs needs to be implemented if the NIMPs are unlicensed (e.g. might come from another EU country or a country outside EEA)

In all other cases host sites are responsible to maintain a system which allows adequate reconstruction of NIMP movements. There should be a procedure to record which patients received which NIMPs during the trial and an evaluation of the compliance.

9. PHARMACOVIGILANCE

9.1 Definitions

Term	Definition
Adverse Event (AE)	Any untoward medical occurrence in a participant to whom a medicinal product has been administered, including occurrences which are not necessarily caused by or related to that product.
Adverse Reaction (AR)	An untoward and unintended response in a participant to an investigational medicinal product which is related to any dose administered to that participant. The phrase "response to an investigational medicinal product" means that a causal relationship between a trial medication and an AE is at least a reasonable possibility, i.e. the relationship cannot be ruled out. All cases judged by either the reporting medically qualified professional or the Sponsor as having a reasonable suspected causal relationship to the trial medication qualify as adverse reactions.
Serious Adverse Event (SAE)	A serious adverse event is any untoward medical occurrence that: • results in death • is life-threatening • requires inpatient hospitalization or prolongation of existing hospitalization • results in persistent or significant disability/incapacity • consists of a congenital anomaly or birth defect Other 'important medical events' may also be considered serious if they jeopardise the participant or require an intervention to prevent one of the above consequences. NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.
Serious Adverse Reaction (SAR)	An adverse event that is both serious and, in the opinion of the reporting Investigator, believed with reasonable probability to be due to one of the trial treatments, based on the information provided.

Term	Definition
Suspected Unexpected Serious Adverse Reaction (SUSAR)	A serious adverse reaction, the nature and severity of which is not consistent with the information about the medicinal product in question set out: • in the case of a product with a marketing authorisation, in the summary of product characteristics (SmPC) for that product • in the case of any other investigational medicinal product, in the investigator's brochure (IB) relating to the trial in question

NB: to avoid confusion or misunderstanding of the difference between the terms "serious" and "severe", the following note of clarification is provided: "Severe" is often used to describe intensity of a specific event, which may be of relatively minor medical significance. "Seriousness" is the regulatory definition supplied above.

9.2 Operational definitions for (S)AEs

Aim: to provide operational definitions for (S)AEs

This section of the protocol must describe the following for (S)AEs and for (Serious) Adverse Reactions ((S)ARs):

a. What will be reported to the Sponsor and using which CRF

b. Whether (S)AEs and (S)ARs will be evaluated for duration and intensity according to standard references such as the National Cancer Institute Common Terminology Criteria for Adverse Events V4.0 (NCI-CTCAE)

The identification of (S)AEs and (S)ARs that require reporting to the Sponsor will differ for individual trials and will be influenced by:

1. The nature of the intervention, for example:
    - CTIMP trial with well known safety profile; using licensed drug in licensed indication: in such trials it may be considered appropriate that certain AEs and ARs are not required to be reported if they will not improve the knowledge regarding the safety profile of the drug and are not required for the trial analysis.
    - CTIMP trial with less well known safety profile; using unlicensed drug or licensed drug outside of the licensed indication and where little class evidence is available. In such trials it would be considered appropriate that all ARs are required to be reported with consideration given to whether all or certain AEs will be reported.
    - For blinded CTIMPs with high morbidity or mortality, where efficacy endpoints could also be SUSARs, the integrity of the trial may be compromised if the blind is systematically broken and under these or similar circumstances such SUSARs/SARs would be treated as disease related and not subject to systematic unblinding.
2. The endpoints or design of the trial, for example:
    - Where efficacy endpoints could also be (S)AEs or (S)ARs the integrity of the trial may be compromised by having

such events reported through the safety monitoring/pharmacovigilance process. In such cases, the protocol can specify that deterioration of the existing condition or known side-effects recorded as primary or secondary end-points are not reported as (S)AEs or (S)ARs but are recorded separately. For example, the protocol can specify that deterioration of the existing condition or known side-effects recorded as primary or secondary endpoints are not reported as adverse events.

- Other exceptions may include hospitalisation for:
  - Routine treatment or monitoring of the studied indication not associated with any deterioration in condition.
  - Treatment which was elective or pre-planned, for a pre-existing condition not associated with any deterioration in condition, e.g. pre-planned hip replacement operation which does not lead to further complications.
  - Any admission to hospital or other institution for general care where there was no deterioration in condition.
  - Treatment on an emergency, outpatient basis for an event not fulfilling any of the definitions of serious as given above and not resulting in hospital admission.

In all cases AEs and/or laboratory abnormalities that are critical to the safety evaluation of the participant must be reported to the Sponsor; these may be volunteered by the participant, discovered by the investigator questioning or detected through physical examination, laboratory test or other investigation. Where certain AEs are not required to be reported to the Sponsor, these should still be recorded in the participant's medical records. Clear guidance in the protocol should state where this is the case.

Expected SAEs for the disease and trial drug/intervention should be listed in the protocol and it should be stated that these would not be considered to be SUSARs unless the severity of the event was considered to be unexpected. Where SAEs are listed but happen rarely then an explanation of the likely risk of an event may be considered of value.

When determining the expected nature of SAEs, appropriate Reference Safety Information (RSI) must be used, for instance an IB for the IMP must be used where the IMP is unlicensed (i.e. it does not have a marketing authorisation). Where the IMP being used is licensed, but is being used outside of its licensed indication, an IB should be used where available and should be supplied from the collaborating pharmaceutical company. Otherwise it is acceptable to use the latest SmPC. Where a generic IMP is to be used one comprehensive SmPC should be chosen at time of request for a CTA for use in the trial for the purposes of pharmacovigilance monitoring only; for any other information regarding a generic IMP, the site should be instructed to refer to the relevant manufacturer's SmPC and ensure that a copy of this is saved in the Investigator Site File.

The IMP reference documentation that is used for pharmacovigilance purposes is used to assess the causality and expectedness of events and will be checked by the Sponsor for changes on the anniversary of the CTA. A statement should be included in the protocol describing which document is approved for use within the trial for pharmacovigilance monitoring (it is best not to include the IB/SmPC as an appendix to the protocol, as a protocol amendment would be required if the IB/SmPC is updated).

Routinely breaking the blind in double blind trials could compromise the integrity of the trial. For this reason the protocol should state that breaking the blind will only take place where information about the participant's trial treatment is clearly necessary for the appropriate medical management of the participant. In all cases the Investigator would be expected to evaluate the causality and expectedness of SAEs as though the participant was receiving the active medication.

9.3 Recording and reporting of SAEs AND SUSARs

Aim: To describe the recording and reporting of SAEs AND SUSARs

The period of time over which AEs, ARs, SAEs, SARs and SUSARs must be recorded and reported must be clearly stated in the protocol. **The point where recording/reporting usually starts is:**

- For AEs/SAEs – consent
- For ARs/SARs and SUSARs – 1st IMP dose

The point where recording/reporting ends is based on the regulatory requirements, intervention and the trial design and the following should be considered in making this decision:

- The active monitoring period for (S)ARs should be defined based on the amount of information available regarding how long the IMP remains active in the participant, how long it may remain active/inactive in the participant and potentially be transferable to a foetus, how long it takes for (S)ARs to peak (e.g. is there an expected cumulative effect of dosing and when is this likely to occur), known late effects (e.g. secondary malignancies that will require active monitoring). It is not acceptable to simply state that SAEs will be actively monitored for 30 days post last treatment without justification.
- Following the active monitoring period (when the participant has finished treatment and the active monitoring period has ended) investigators are still required to report any SARs or SUSARs that they become aware of.
- Safety reporting periods for SAEs and SARs must be equal across all arms of a randomised trial to prevent any bias in reporting.

Where a participant withdraws consent for further processing of data, this does not preclude the reporting of SARs and SUSARs which are required to continue being reported according to the protocol for regulatory purposes. The PIS should include a section explaining this to the participant.

In all cases SAEs should be reported to the Sponsor, although it is acceptable to specify that certain SAEs do not require immediate reporting, e.g. in trials using a drug with a well known safety profile. Assessment of seriousness, causality and expectedness for trials involving IMPs must be made by the PI or another authorised doctor. If an authorised doctor from the reporting site is unavailable, initial reports without causality and expectedness assessment should be submitted to the Sponsor by a healthcare professional within 24hours of becoming aware of the SAE, but must be followed-up by medical assessment as soon as possible thereafter.

Suggested standard text which may be amended as appropriate

"All [SAEs*/SUSARs* (*delete as appropriate)] occurring from the time of [written informed consent/registration/randomisation/start of trial treatment] until [XXX] days post cessation of trial treatment must be recorded on the [indicate relevant form] Form and faxed to the Sponsor within 24 hours of the research staff becoming aware of the event. Once all resulting queries have been resolved, the Sponsor will request the original form should also be posted to the Sponsor and a copy to be retained on site.

For each [SAEs*/SUSARs* (*delete as appropriate)] the following information will be collected:

- Full details in medical terms and case description
- Event duration (start and end dates, if applicable)
- Action taken
- Outcome
- Seriousness criteria
- Causality (i.e. relatedness to trial drug/investigation), in the opinion of the investigator
- Whether the event would be considered expected or unexpected.

Any change of condition or other follow-up information should be faxed to the Sponsor as soon as it is available or at least within 24 hours of the information becoming available. Events will be followed up until the event has resolved or a final outcome has been reached."

Suggested standard text which may be amended as appropriate

"All SAEs assigned by the PI or delegate (or following central review) as both suspected to be related to IMP-treatment and unexpected will be classified as SUSARs and will be subject to expedited reporting to the Medicines and Healthcare Products Regulatory Agency (MHRA). The Sponsor will inform the MHRA, the REC and the Sponsor of SUSARs within the required expedited reporting timescales."

9.4 Responsibilities

Aim: To define responsibilities

This section should detail the responsibilities for reporting and reviewing toxicity and safety information arising from the trial. Responsibilities for the PI, CI, Sponsor, Trial Steering Committee (TSC) and Data Monitoring Committee (DMC) should always be included. Depending on the trial, if a pharmaceutical company is involved, their responsibilities will also need to be included, for example the company may take on the function of delegated sponsor review.

A process must be in place to review individual SAEs and trends in SAEs will be independently reviewed in addition to usual trial safety monitoring procedures. **The decision regarding the frequency of review of individual and cumulative SAEs will be based on the trial design, risk assessment and advice from the Sponsor/TSC/DMC but may include:**

- Clinical review of a line listing of all life threatening or SAEs resulting in death within 1 week of their occurrence (for lower risk trial).
- Clinical review of a line listing of all other SAEs on a monthly basis (for lower risk trial).
- Clinical review in real time of each SAE as it occurs (for higher risk trial).
- Cumulative review of all safety information by the DMC on a 3 or 6 monthly basis.

- Total numbers of SAEs per month sent to the DMC Chair – in order to expedite a safety review if more SAEs are being seen than would be expected.

An appropriate member of the Trial Management Group (TMG) should also be identified to prepare the written sections of the Development Safety Update Report (DSUR).

If the study has joint- or co-sponsorship, state which party is the lead sponsor, and indicate how the responsibilities have been allocated between the sponsors. Indicate any activities that the sponsor is delegating to a third party and any expectations of the third party when working with the research site(s). Highlight any activities that the sponsor is delegating to the research site(s) and identify any specific requirements that the research site(s) will need to meet to carry out the delegated activities.

NB in a CTIMP the sponsor has legal responsibilities that cannot be delegated.

Suggested standard text

Principal Investigator (PI):

Checking for AEs and ARs when participants attend for treatment/follow-up.

1. Using medical judgement in assigning seriousness, causality and expectedness [in Phase III and late Phase II CTIMPs] using the Reference Safety Information approved for the trial.
2. Using medical judgement in assigning seriousness and causality and providing an opinion on expectedness [in Phase I and early Phase II CTIMPs] using the Reference Safety Information approved for the trial.
3. Ensuring that all SAEs and SARs (including SUSARs) are recorded and reported to the Sponsor within 24 hours of becoming aware of the event and provide further follow-up information as soon as available. Ensuring that SAEs and SARs (including SUSARs) are chased with Sponsor if a record of receipt is not received within 2 working days of initial reporting.
4. Ensuring that AEs and ARs are recorded and reported to the Sponsor in line with the requirements of the protocol.

Principal Investigator (PI)/delegate or independent clinical reviewer:

1. Clinical oversight of the safety of patients participating in the trial, including an ongoing review of the risk/benefit.
2. Using medical judgment in assigning seriousness, causality and expectedness of SAEs where it has not been possible to obtain local medical assessment.
3. Using medical judgment in assigning expectedness [in Phase I and early Phase II CTIMPs].
4. Immediate review of all SUSARs.
5. Review of specific SAEs and SARs in accordance with the trial risk assessment and protocol as detailed in the Trial Monitoring Plan.
6. Assigning Medical Dictionary for Regulatory Activities (MedDRA) or Body System coding to all SAEs and SARs.

7. Preparing the clinical sections and final sign off of the Development Safety Update Report (DSUR).

Sponsor:

1. Central data collection and verification of AEs, ARs, SAEs, SARs and SUSARs according to the trial protocol onto a MACRO database.
2. Reporting safety information to the CI, delegate or independent clinical reviewer for the ongoing assessment of the risk/benefit according to the Trial Monitoring Plan.
3. Reporting safety information to the independent oversight committees identified for the trial (Data Monitoring Committee (DMC) and/or Trial Steering Committee (TSC)) according to the Trial Monitoring Plan.
4. Expedited reporting of SUSARs to the Competent Authority (MHRA in UK) and REC within required timelines.
5. Notifying Investigators of SUSARs that occur within the trial.
6. The unblinding of a participant for the purpose of expedited SUSAR reporting [For double blind trials only].
7. Checking for (annually) and notifying PIs of updates to the Reference Safety Information for the trial.
8. Preparing standard tables and other relevant information for the DSUR in collaboration with the CI and ensuring timely submission to the MHRA and REC.

Trial Steering Committee (TSC):

In accordance with the Trial Terms of Reference for the TSC, periodically reviewing safety data and liaising with the DMC regarding safety issues.

Data Monitoring Committee (DMC):

In accordance with the Trial Terms of Reference for the DMC, periodically reviewing unblinded overall safety data to determine patterns and trends of events, or to identify safety issues, which would not be apparent on an individual case basis.

9.5 Notification of deaths

Aim: To describe the procedure for notification of death

The protocol should state:

- Whether, how and when the Principal investigator will notify deaths (expected or unexpected) to the sponsor e.g.
    - "All deaths will be reported to the sponsor irrespective of whether the death is related to disease progression, the IMP, or an unrelated event". This statement should be used for Phase I/First Time In Man (FTIM) trials.
    - "Only deaths that are assessed to be caused by the IMP will be reported to the sponsor. This report will be immediate".

- "All deaths, including deaths deemed unrelated to the IMP, if they occur earlier than expected will be reported to the sponsor".

The protocol needs to specify the timelines of such reports.

9.6 Pregnancy reporting

Aim: To describe the procedure for notification of pregnancy (where applicable)

The protocol needs to state:

- All pregnancies within the trial (either the trial participant or the participant's partner) should be reported to the Principal Investigator and the Sponsor using the relevant Pregnancy Reporting Form within 24 hours of notification
- Pregnancy is not considered an AE unless a negative or consequential outcome is recorded for the mother or child/foetus. If the outcome meets the serious criteria, this would be considered an SAE.
- Follow-up of pregnant subject: Describe in detail the process for monitoring and managing a pregnancy
- Follow-up of child born to a pregnant trial subject, or to the partner of a male trial subject. (How long will follow-up be for?)

9.7 Overdose

Aim: To describe the procedure for notification of overdose

The protocol should describe:

- How to record and notify overdoses to the sponsor (this information should be placed on the deviation log)
- Where can overdoses be observed from (pill counts, diary cards, drug charts or patient comment)
- How will it affect final analysis e.g. will patients be withdrawn from the trial? (Consider what will constitute an overdose that warrants trial discontinuation)
- If an SAE is associated with the overdose ensure the overdose if fully described in the SAE report form

9.8 Reporting urgent safety measures

If any urgent safety measures are taken the CI/Sponsor shall immediately and in any event no later than 3 days from the date the measures are taken, give written notice to the MHRA and the relevant REC of the measures taken and the circumstances giving rise to those measures.

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

This section needs to describe the type and duration of follow-up care for subjects following an adverse drug reaction.

This section of the protocol also needs to specify how long after the last dose of IMP has been administered to the

subjects will adverse events and reactions be recorded and reported.

Please include 'Any SUSAR related to the IMP will need to be reported to the Sponsor irrespective of how long after IMP administration the reaction has occurred.'

9.10 Development safety update reports

Aim: To demonstrate that the study will comply with reporting requirements

Where appropriate, the IMP manufacturer should be encouraged to submit Development Safety Update Reports (DSURs). **However, in the absence of this**

Either

<Name of Company> will submit DSURs once a year throughout the clinical trial, or on request to the Competent Authority, Ethics Committee, Host NHS Trust and Sponsor.

Or

The PI will provide (in addition to the expedited reporting above) DSURs once a year throughout the clinical trial, or on request, to the Competent Authority, Ethics Committee, Host NHS Trust and Sponsor.

The report will be submitted within 60 days of the Developmental International Birth Date (DIBD) of the trial each year until the trial is declared ended

10. STATISTICS AND DATA ANALYSIS

Where possible the statistician should write this section.

The sub-headings given below are suggestions. However, if a Statistical Analysis Plan is to be produced separately, state this here and condense the most relevant information from the sub sections here.

10.1 Sample size calculation

Aim: To define how the planned number of participants was derived

This section should detail the methods used for the determination of the sample size and a reference to tables or statistical software used to carry out the calculation. Sufficient information should be provided so that the sample size calculation can be reproduced.

For trials that involve a formal sample size calculation, the guiding principle is that the planned sample size should be large enough to have a high probability (power) of detecting a true effect of a given magnitude, should it exist. Sample size calculations are generally based on one primary outcome; however, it may also be worthwhile to plan for adequate trial power or report the power that will be available (given the proposed sample size) for other important outcomes or analyses because trials are often underpowered to detect harms or subgroup effects.

If the planned sample size is not derived statistically, then this should be explicitly stated along with a rationale for the

intended sample size (e.g., exploratory nature of pilot studies; pragmatic considerations for trials in rare diseases).

Formal sample size calculations typically require the power to be specified and the following values with justification:

- Treatment Effect or Alternative Hypothesis: is this the smallest size of effect that would be of clinical interest- how is this justified in the form of appropriate references, pilot data or clinical arguments.
- Null Hypothesis: A clear statement of the hypothesis, in terms of numerical values, of the treatment being ineffective. For example: an absolute difference in response rates between arms of zero.
- Significance level: what risk is acceptable of concluding the treatment is effective, when in reality the treatment is ineffective.
- In trials with continuous outcomes the standard deviation of the primary endpoint should be included: if previous studies or literature are used to estimate or justify the assumptions made to determine this parameter, or any other parameters relevant to the design (e.g. dropout rate, noncompliance rates median survival rate, response rate), provide references.

If one or more interim analysis(es) are planned, it should be considered whether the sample size should be increased to account for multiple testing.

NB an appropriate level of statistical advice should be sought to ensure trial validity.

10.2 Planned recruitment rate

Aim: To estimate the planned recruitment rate

Realistic estimates of expected accrual rate and duration of participant entry based on estimated sample size should be provided. This section may also include information such as the number of recruiting centres, the size/percentage of the population that is captured by the eligibility criteria, the expected consent rate, and the expected screen failure rate. This information will help sites to determine whether they are likely to be able to recruit their target number of participants.

10.3 Statistical analysis plan

Aim: To fully describe the statistical analysis plan

10.3.1 Summary of baseline data and flow of patients

- List variables to be used to assess baseline comparability of the randomised groups including for each factor: a definition, any rules, references or programmes for calculation of derived values, what form it will take for analysis (e.g. continuous, categorical, ordinal) and how it will be reported (e.g. means, standard deviations, medians, proportions)
- Plans to produce a consort flow diagram

10.3.2 Primary outcome analysis

- **Plans for statistical analyses of the primary outcome including:**
- Summary measures to be reported

- Method of analysis (justified with consideration of form of the data, assumptions of the method and structure of the data (e.g. unpaired, paired, clustered) etc.)
- Plans for handling multiple comparisons, missing data, non-compliers, spurious data and withdrawals in analysis
- Plans for predefined subgroup analyses
- Statement regarding use of intention to treat (ITT) analysis
- Description of any non-statistical methods that might be used (e.g. qualitative methods)

10.3.3 Secondary outcome analysis

Plans for statistical analysis of each secondary outcome: In general, the use of hypothesis tests may not be appropriate if the study has not been powered to address these and use of estimates with confidence intervals is preferred. Secondary analyses should be considered as hypothesis generating rather than providing firm conclusions.

10.4 Subgroup analyses

Aim: To describe sub-group analyses

Subgroup analyses explore whether estimated treatment effects vary significantly between subcategories of trial participants. As these data can help tailor healthcare decisions to individual patients, a modest number of pre-specified subgroup analyses can be sensible.

10.5 Adjusted analysis

Aim: To describe any adjusted analysis to account for imbalances between study groups (e.g., chance imbalance across study groups in small trials), improve power, or account for a known prognostic variable.

The protocol should state:

- If there is an intention to perform or consider adjusted analyses
- Any known variables for adjustment (if it is not clear in advance which these should be then the objective criteria to be used to select variables should be pre-specified)
- How continuous variables will be handled
- If unadjusted and adjusted analyses are intended, what the main analysis is

10.6 Interim analysis and criteria for the premature termination of the trial

Aim: To describe any interim analysis and criteria for stopping the trial.

The protocol should describe:

- Any interim analysis plan, even if it is only to be performed at the request of an oversight body (e.g., DMC)
- Include the statistical methods

- Who will perform the analyses
- When they will be conducted (timing and indications)
- The decision criteria—statistical or other—that will be adopted to judge the interim results as part of a guideline for early stopping or other adaptations.
- Who will see the outcome data while the trial is ongoing.
- Whether these individuals will remain blinded (masked) to study groups
- How the integrity of the trial implementation will be protected (e.g., maintaining blinding) when any adaptations to the trial are made
- Who has the ultimate authority to stop or modify the trial e.g. the Principal Investigator, trial steering committee, or sponsor
- The stopping guidelines
    - Criteria for stopping for harm are often different from those for benefit and might not employ a formal statistical criterion
    - Stopping for futility occurs in instances where, if the study were to continue, it is unlikely that an important effect would be seen (i.e., low chance of rejecting null hypothesis)
- If pre-specified interim analyses are to be used for other trial adaptations such as sample size re-estimation, alteration to the proportion of participants allocated to each study group, and changes to eligibility criteria.

NB in CTIMPs recommendations made by the DMC must be expedited to the NRA where they are deemed relevant for the safety of subjects participating within the trial.

10.7 Subject population

Aim: To describe the subject populations whose data will be subjected to the study analysis.

Protocols should describe:

- The subject populations whose data will be subjected to the study analysis – both for the primary analysis and any applicable secondary analyses e.g.
    - All-randomized population: Any subject randomized into the study, regardless of whether they received study drug
    - All-treated population: Any subject randomized into the study that received at least one dose of study drug
    - Protocol-compliant population: Any subject who was randomized and received the protocol required study drug exposure and required protocol processing
- If the participants to be included in the analysis will vary by outcome e.g. analysis of harms (adverse events) is

sometimes restricted to participants who received the intervention, so that absence or occurrence of harm is not attributed to a treatment that was never received.

To avoid:

- Selection bias, an "as randomised" analysis retains participants in the group to which they were originally allocated
- Attrition bias, out-come data obtained from all participants are included in the data analysis, regardless of protocol adherence

These two conditions (i.e., all participants, as randomised) define an "intention to treat" analysis, which is widely recommended as the preferred analysis strategy.

10.8 Procedure(s) to account for missing or spurious data

Aim: To describe how missing data will be dealt with

The protocol should describe:

- The strategies to maximise follow-up and prevent missing data
- How recording of reasons for missing data will be undertaken
- How missing data will be handled in the analysis and detail any planned methods to impute (estimate) missing outcome data, including which variables will be used in the imputation process (if applicable). Methods of multiple imputation are more complex but are widely preferred to single imputation methods (e.g., last observation carried forward; baseline observation carried forward), as the latter introduce greater bias and produce confidence intervals that are too narrow. Sensitivity analyses are highly recommended to assess the robustness of trial results under different methods of handling missing data.

10.9 Other statistical considerations

Aim: To describe any other statistical consideration pertinent to the trial.

The protocol should describe:

- Procedures for reporting any deviation(s) from the original statistical plan
- Any other statistical considerations e.g. if there is a requirement for an economic analysis plan in which case it should be included in this section

10.10 Economic evaluation

If economic evaluation is to be undertaken this section should include the rationale for inclusion of the economic investigation and means of assessment.

NB it should be written by the health economic investigator

11. DATA HANDLING

11.1 Data collection tools and source document identification

Aim: To describe procedures for data collection, recording and handling

Source Data

ICH E6 section 1.51, defines source data as "All information in original records and certified copies of original records or 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

ICH E6 1.52, defines source documents as "Original documents, data and records (e.g., hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries of evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, 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)."

Case report forms

A case report form (CRF) is a form on which individual patient data required by the trial protocol are recorded. It may be a printed or electronic document. The CRF data is used to perform statistical analysis for the trial. **Design of individual CRFs will vary from trial to trial, but it is essential that the design ensures that:**

- Adequate collection of data has been performed
- Proper paper trails can be kept to demonstrate the validity of the trial (both during and after the trial)
- Only the data required by the protocol are captured in the CRF (using the CRF to capture secondary data not required for the study may be a criminal beach of the Data Protection Act, makes the CRF unnecessarily complicated, and can make it more difficult to extract the primary data for analysis)

CRFs as Source Documents

If the protocol allows data to be entered directly onto the case report forms (CRF), the CRF would then be considered a source document. If the CRF is then transmitted to the sponsor, it is necessary for the trial site to retain a copy to ensure that the principal investigator can provide access to the source documents to a monitor, auditor, or regulatory agency. Additional information can be found in ICH E6, section 6.4.9.

Copied CRFs as Source Documents

Photocopies of the CRFs may be used as source documents. The only drawback to the practice of recording information directly on the photocopied CRF is if the data is then transmitted or transcribed onto the original case report form. This introduces an additional transcription step and additional chance of error, which is also a potential source of error when using other spreadsheets or templates as source documents.

It is recommended that the photocopies are made onto coloured paper so they were easy to find in the case history and will not be mistaken for CRFs. The photocopied case report forms should indicate who collected the data (sign/initial and date) as well as the subject to whom the data applies.

The protocol should:

- Specify whether the data are from a standardised tool (e.g. McGill pain score) or involves a procedure (in which case full details should be supplied).
- Specify if a nonstandard tool is to be used, giving detail on its reliability and validity
- Describe the methods used to maximise completeness of data e.g. telephoning subjects who have not returned postal questionnaires.
- Specify that the investigator/institutions should keep records of all participating patients (sufficient information to link records e.g., CRFs, hospital records and samples), all original signed informed consent forms and copies of the CRF pages

11.2 Data handling and record keeping

The protocol should also describe procedures for data handling and:

- Describe what software (e.g. Access, MACRO) is to be used for data entry.
- NB An Excel spreadsheet is far from ideal for the majority of trials
- Provide details of the methods to be used to ensure validity and quality of data (e.g. double entry, cross validation etc.) which should be proportionate to the trial.
- Describe how data will be stored and backed up securely, including any data storage requirements for sites
- If data will be transferred, describe the method of transfer to be used and the security arrangements in place to ensure the security of the data during transfer where data are transferred electronically this must be in accordance with the National Data Protection Act (where applicable)
- Whether data will be transferred outside of the country of site (note that explicit consent from participants is required if their personal data is to be transferred outside of the country of trial where data protection arrangements may not be as robust)
- Arrangements to anonymise or pseudonymise the data (if, when, and how this will be done; who will do it)document and detail if there is a disaster recovery plan.
- State who is responsible for data entry and quality
- State who is responsible for data analysis

11.3 Access to Data

Direct access will be granted to authorised representatives from the Sponsor, host institution and the regulatory authorities to permit trial-related monitoring, audits and inspections.

11.4 Archiving

Aim: To describe the process for archiving the trial documentation at the end of the trial

The protocol should state:

- Archiving will be authorised by the Sponsor following submission of the end of study report
- Which trial documents the sponsor will be responsible for archiving and which trial documents the site(s) will be responsible for archiving
- The location and duration of record retention for:
    - Essential documents
    - The trial database
- All essential documents will be archived for a minimum of 5 years after completion of trial
- Destruction of essential documents will require authorisation from the Sponsor

12. MONITORING, AUDIT & INSPECTION

Aim: To describe the procedures for monitoring audit and inspection

The protocol should state:

- A Trial Monitoring Plan will be developed and agreed by the Trial Management Group (TMG) and TSC based on the trial risk assessment which may include on site monitoring
- The procedures and anticipated frequency for monitoring
- If monitoring procedures are detailed elsewhere (e.g., monitoring manual), where the full details can be obtained
- The degree of independence from the trial investigators and sponsor of the monitoring personnel
- The processes reviewed can relate to participant enrolment, consent, eligibility, and allocation to trial groups; adherence to trial interventions and policies to protect participants, including reporting of harm and completeness, accuracy, and timeliness of data collection
- Monitoring can be done by exploring the trial dataset or performing site visits
- Any obligations that will be expected of sites to assist the sponsor in monitoring the study. These may include hosting site visits, providing information for remote monitoring, or putting procedures in place to monitor the study internally

- Monitoring might be initially conducted across all sites, and subsequently conducted using a risk based approach that focuses, for example, on sites that have the highest enrolment rates, large numbers of withdrawals, or atypical (low or high) numbers of reported adverse events.

13. ETHICAL AND REGULATORY CONSIDERATIONS

13.1 Research Ethics Committee (REC)/NRA review & reports

Aim: To demonstrate that the study will receive ethical review and approval

The protocol should state that:

- Before the start of the trial, approval will be sought from a REC/NRA for the trial protocol, informed consent forms and other relevant documents e.g. advertisements and GP information letters
- Substantial amendments that require review by REC/NRA will not be implemented until the REC/NRA grants a favourable opinion for the study before they can be implemented in practice at sites)
- All correspondence with the REC/NRA will be retained in the Trial Master File/Investigator Site File
- Quarterly progress report (QPR) will be submitted to the REC/NRA within 21 days of the anniversary date on which the favourable opinion was given, and annually until the trial is declared ended
- It is the Principal Investigator's responsibility to produce the quarterly reports as required.
- The Principal Investigator will notify the REC/NRA of the end of the study
- If the study is ended prematurely, the Principal Investigator will notify the REC/NRA, including the reasons for the premature termination (refer to Guidelines on Authorization)
- Within 90 days after the end of the study, the Principal Investigator will submit a final report with the results, including any publications/abstracts, to the REC/NRA (refer to Guidelines on Authorization)

13.2 Peer review

Aim: To describe the peer review process for the trial which should be instigated or approved by the Sponsor

The protocol should provide details on who reviewed this trial protocol e.g. the funder or an internal Trust department/committee, but not include individual names unless the person in question gives their express permission.

High quality peer review

Peer review must be independent, expert, and proportionate:

a. **Independent:** At least two individual experts should have reviewed the study. The definition of independent used here is that the reviewers must be external to the investigators' host institution and not involved in the study in any way. Reviewers do not need to be anonymous.

b. **Expert:** Reviewers should have knowledge of the relevant discipline to consider the clinical and/or service based aspects of the protocol, and/or have the expertise to assess the methodological and statistical aspects of the study.

c. **Proportionate:** Peer review should be commensurate with the size and complexity of the study. Large multicentre studies should have higher level (more reviewers with broader expertise and often independent review committee or board), and potentially international peer review.

13.3 Public and Patient Involvement

Aim: To describe the involvement of Patients and Public in the research

This section of the protocol should detail which aspects of the research process have actively involved, or will involve, patients, service users, and/or their carers, or members of the public in particular;

- Design of the research
- Management of the research
- Undertaking the research
- Analysis of results
- Dissemination of findings

13.4 Regulatory Compliance

Aim: To demonstrate that the study will comply with regulations

The protocol should state that:

- The trial will not commence until a Clinical Trial Authorisation (CTA) is obtained from the NRA
- The protocol and trial conduct will comply with the *Guidelines for Authorization of Clinical Trials in [the country of submission]* and any relevant amendments

13.5 Protocol compliance

Aim: To demonstrate how protocol compliance will be managed

Protocol deviations, non-compliances, or breaches are departures from the approved protocol.

The protocol should state that:

- Prospective, planned deviations or waivers to the protocol are not allowed under the UK regulations on Clinical Trials and must not be used e.g. it is not acceptable to enrol a subject if they do not meet the eligibility criteria or restrictions specified in the trial protocol
- Accidental protocol deviations can happen at any time. They must be adequately documented on the relevant forms

and reported to the Chief Investigator and Sponsor immediately.

- Deviations from the protocol which are found to frequently recur are not acceptable, will require immediate action and could potentially be classified as a serious breach.

13.6 Notification of Serious Breaches to GCP and/or the protocol

Aim: To demonstrate how serious breaches will be managed

A "serious breach" is a breach which is likely to effect to a significant degree –

a. The safety or physical or mental integrity of the subjects of the trial; or

b. The scientific value of the trial

The protocol should state that:

- The sponsor will be notified immediately of any case where the above definition applies during the trial conduct phase
- The sponsor of a clinical trial will notify the licensing authority in writing of any serious breach of
    a. The conditions and principles of GCP in connection with that trial; or
    b. The protocol relating to that trial, as amended from time to time, within 7 days of becoming aware of that breach

13.7 Data protection and patient confidentiality

AIM: To describe how patient confidentiality will be maintained and how the trial is compliant with the requirements of the Data Protection Act

The protocol should state that all investigators and trial site staff must comply with the requirements of the Data Protection Act with regards to the collection, storage, processing and disclosure of personal information and will uphold the Act's core principles.

The protocol should describe:

- The means whereby personal information is collected, kept secure, and maintained. In general, this involves:
    - The creation of coded, depersonalised data where the participant's identifying information is replaced by an unrelated sequence of characters
    - Secure maintenance of the data and the linking code in separate locations using encrypted digital files within password protected folders and storage media
    - Limiting access to the minimum number of individuals necessary for quality control, audit, and analysis
- How the confidentiality of data will be preserved when the data are transmitted to sponsors and co-investigators
- How long the data will be stored for
- Who is the data custodian

13.8 Financial and other competing interests for the Principal investigator, PIs at each site and committee members for the overall trial management

Aim: To identify and disclose any competing interests that might influence trial design, conduct, or reporting

At a minimum, disclosure should reflect:

- Ownership interests that may be related to products, services, or interventions considered for use in the trial or that may be significantly affected by the trial
- Commercial ties requiring disclosure include, but are not restricted to, any pharmaceutical, behaviour modification, and/or technology company
- Any non-commercial potential conflicts e.g. professional collaborations that may impact on academic promotion.

However the oversight groups should determine what it is appropriate to report.

At the time of writing the protocol not all sites/personnel may have been identified. When this is the case then the protocol should state that this information will be collected and where it will be documented.

13.9 Indemnity

Aim: To fully describe indemnity arrangements for the trial

The following areas should be addressed in the protocol:

1. What arrangements will be made for insurance and/or indemnity to meet the potential legal liability of the sponsor(s) for harm to participants arising from the management of the research?
2. What arrangements will be made for insurance and/or indemnity to meet the potential legal liability of the sponsor(s) or employer(s) for harm to participants arising from the design of the research?
3. What arrangements will be made for insurance and/or indemnity to meet the potential legal liability of investigators/collaborators arising from harm to participants in the conduct of the research? Note that if the study involves sites that are not covered by the NHS indemnity scheme (e.g. GP surgeries in primary care) these investigators/collaborators will need to ensure that their activity on the study is covered under their own professional indemnity
4. Has the sponsor(s) made arrangements for payment of compensation in the event of harm to the research participants where no legal liability arises?
5. If equipment is to be provided to site(s) for the purposes of the study, the protocol should describe what arrangements will be made for insurance and/or indemnity to meet the potential legal liability arising in relation to the equipment (e.g. loss, damage, maintenance responsibilities for the equipment itself, harm to participants or site staff arising from the use of the equipment)

NB Usually the responsibility for sections 1&2 lie with the sponsor, section 3 with the participating site and section 4 with the sponsor. Section 4 is not mandatory and should be assessed in relation to the inherent risks of the trial; however, it may be a condition of REC favourable opinion to have these arrangements in place.

13.10 Amendments

Aim: To describe the process for dealing with amendments

Refer to Guidelines on Authorization

The protocol should describe:

- The process for making amendments
- Who will be responsible for the decision to amend the protocol and for deciding whether an amendment is substantial or non-substantial
- How substantive changes will be communicated to relevant stakeholders (e.g., REC, trial registries, R&D, regulatory agencies)
- How the amendment history will be tracked to identify the most recent protocol version.

13.11 Post trial care

Aim: To describe what care the sponsor will continue to provide to participants after the trial is completed, including whether funding arrangements are in place.

The Declaration of Helsinki 2013 states that "In advance of a clinical trial, sponsors, researchers and host country governments should make provisions for post-trial access for all participants who still need an intervention identified as beneficial in the trial. This information must also be disclosed to participants during the informed consent process" and that "in clinical trials, the protocol must also describe appropriate arrangements for post-trial provisions."

The protocol should describe any interventions, benefits, or other care that the sponsor will continue to provide to participants after the trial is completed, and provide justification if continued access to the trial treatment(s) will not be funded.

13.12 Access to the final trial dataset

Aim: to describe who will have access to the final dataset

The protocol should:

- Identify the individuals involved in the trial who will have access to the full dataset
- Explicitly describe any restrictions in access for trial investigators e.g. for some multicentre trials, only the steering group has access to the full trial dataset in order to ensure that the overall results are not disclosed by an individual trial site prior to the main publication
- State if the trial will allow site investigators to access the full dataset if a formal request describing their plans is approved by the steering group

14. DISSEMINATION POLICY

14.1 Dissemination policy

Aim: To describe the dissemination policy for the trial

It is highly recommended that the Consort Guidelines and checklist are reviewed prior to generating any publications for the trial to ensure they meet the standards required for submission to high quality peer reviewed journals etc. http://www.consort-statement.org/

The protocol should state

- Who owns the data arising from the trial
- That on completion of the trial, the data will be analysed and tabulated and a Final Study Report prepared
- Where the full study report can be accessed
- If any of the participating investigators will have rights to publish any of the trial data
- If there are any time limits or review requirements on the publications
- Whether any funding or supporting body needs to be acknowledged within the publications and whether they have review and publication rights of the data from the trial
- Whether there are any plans to notify the participants of the outcome of the trial, either by provision of the publication, or via a specifically designed newsletter etc.
- If it possible for the participant to specifically request results from their PI and when would this information be provided e.g. after the Final Study Report had been compiled or after the results had been published
- Whether the trial protocol, full study report, anonymised participant level dataset, and statistical code for generating the results will be made publicly available; and if so, describe where, the timeframe and any other conditions for access.

14.2 Authorship eligibility guidelines and any intended use of professional writers

Aim: To describe who will be granted authorship on the final trial report

The protocol should detail:

- Guidelines on authorship on the final trial report
- Criteria for individually named authors or group authorship (The International Committee of Medical Journal Editors has defined authorship criteria for manuscripts submitted for publication)
- If professional medical writers are going to be hired and how their employment and funding will be acknowledged in trial reports

REFERENCES

List the literature and data that are relevant to the trial, and that provide background for the trial. Please ensure the text contains appropriate cross references to this list

APPENDIX 1c

INVESTIGATIONAL MEDICINAL PRODUCT DOSSIER
<PRODUCT>, VERSION <XX.YY>
<DATE>

AUTHORS

TABLE OF CONTENTS

Explanatory text: *The table of contents for the pharmaceutical part follows the headings as given by the guidelines. The table of contents for the pre-clinical medical parts is based on the assumption that the detailed information will be provided by the Investigational Brochure. Please note that only relevant information will have to be provided and several headings can in general remain empty.*

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LIST OF TABLES

It is recommended to provide a list of table with their titles and page numbers

APPENDIX 1c

CHEMICAL PHARMACEUTICAL AND BIOLOGICAL DATA

Introduction

Explanatory text: *This paragraph should give a short introduction to the compound and its level of pharmaceutical and clinical development.*

Example:

This Clinical Trial Application presents information relating to <PRODUCT> tablets containing 50 mg, 100 mg and 200 mg of <PRODUCT>. <PRODUCT> is an ACE Inhibitor and is being developed for the treatment of hypertension.

<PRODUCT> has been evaluated in 5 clinical studies involving healthy subjects to evaluate the safety and tolerability profile and to assess the pharmacokinetic behavior of the compound. In addition, early clinical development included two Phase IIa studies in hypertensive patients to evaluate efficacy, safety and pharmacokinetics after 12-weeks of exposure. Most early Phase I studies were performed with a capsule formulation, whereas a tablet formulation was used in patients.

DRUG SUBSTANCE

General Information

Nomenclature

Provide Chemical Name, codename and Chemical Abstract number, if available.

Structure

In general the structural formula of the drug substance should be given. Otherwise an adequate description of characteristics including the molecular weight and formula should be given.

General Properties

This paragraph should contain a brief description of the general properties. This could for example be presented as shown below:

Stereochemistry: *example: <PRODUCT> is a single isomer with the R-configuration*

Description: *example: White to pale brownish white crystalline powder*

Crystal form: *example: Two crystal forms (α and β form) have been observed. The α form was selected for the development of <PRODUCT>. All released lots of <PRODUCT> have been the α form, the β form was only observed in early development. The manufacturing process as described yields only the α form.*

Melting range:

Hygroscopicity: *example: <PRODUCT> is not hygroscopic. No weight increase was seen after 7 days storage at 25°C/93% RH*

pKa:

LogD (water):

Solubility: *example: <PRODUCT> is soluble in various organic solvents and slightly soluble in water.*

Additional information can be provided in tabulated form

2.1.S.2 Manufacture

2.1.S.2.1 Manufacturer(s)

The address of the facility where the drug substance is manufactured should be provided.

2.1.S.2.2 Description of Manufacturing Process and Process Controls

A full description of the synthetic process does not have to be provided. A general description including possible by-products that may contaminate the drug substance will suffice.

Example:

<PRODUCT> drug substance is prepared through a three step synthetic process. Three impurities have been detected; one has been qualified, the other two fall below the limit to require qualification.

The methods used to control the conformity of specifications of starting materials for the different steps should be described in general terms.

Example:

Starting Materials

Starting materials used in the preparation process for <PRODUCT> are listed along with their specifications below.

<starting product> (Step 1) Specifications

Identification (IR): *Conforms to reference IR spectrum*

Purity (HPLC): *Not less than 98.0%*

Optical isomer: *Not more than 0.5%*

Where possible and applicable one can also bridge to the impurities sections of both the drug substance and the medicinal product.

2.1.S.2.3 Control of Materials

A list of reagents, solvents and other materials should be provided, including the purity grade and the possibility of residuals contaminating the final drug substance.

Example:

Reagents, Solvents and Other Materials

Reagents, solvents and other materials used in the preparation process for <PRODUCT> are listed in Table 1.

Table 1: Reagents, solvents and other materials

Material	Grade	Specific test item	Possible impurity

2.1.S.2.4 Controls of Critical Steps and Intermediates

In earlier stages of development many parameters are monitored. Not in all cases however, sufficient experience has been gained to assess how critical certain steps are. In case critical steps in the production process have been identified and are pertinent to the safety assessment, it should be described how they are controlled.

Example:

At two points in the preparation process for <PRODUCT>, the reaction progress and the isolated intermediates are monitored by HPLC.

2.1.S.2.5 Process Validation and/or Evaluation

Provide information on the status of validation. Typically more information is required in case of sterile drug substance.

2.1.S.2.6 Manufacturing Process Development

Provide information on the status of validation.

2.1.S.3 Characterization

2.1.S.3.1 Elucidation of Structure and Other Characteristics

This paragraph should list which techniques have been used to elucidate the structure. Detailed structures and spectra should not be provided but should be available on request.

2.1.S.3.2 Impurities

This paragraph should be used to discuss potential impurities and typical levels observed.

2.1.S.4 Control of Drug Substance

2.1.S.4.1 Specification

This paragraph should provide the specification of the final drug product, preferably tabulated and including which methods are used (including referral to international quality standards, where applicable) and the acceptance criteria. Also, the limit of individual and total impurities should be given here. Impurities can be referred to by their in-house code unless their concentration requires qualification and/or identification according to guidelines.

Example:

Individual impurities are ≤ 0.06%; total related substances ≤ 0.2%

Example:

Batches of the active ingredient will comply with the below specification (Table 2). Batches will be released only if the impurity profiles can be supported by available non-clinical data.

Table 1: Specifications for <PRODUCT> drug substance

Attribute	Method	Acceptance criteria
Appearance	*Visual observation*	*Record results*
Identification		
(1)	*UV Absorption*	*Conforms to the reference spectrum*
(2)	*IR Absorption*	*Conforms to the reference spectrum*
(3)	*X-ray powder diffraction method*	*Conforms to the reference X-ray diffraction pattern*
Melting point	*PhEur*	*141 to 145°C*
Purity		
(1) Heavy metals	*Ph.Eur., Method IV*	*≤ 20 ppm*
(2) Related substances	*HPLC*	*Each: ≤ 0.5 %* *Total: ≤ 2.0 %*
(3) Methanol *Ethanol*	*GC*	*Methanol: ≤ 0.3 %* *Ethanol: ≤ 0.5 %*
Water	*Ph.Eur., KF method (coulometric titration)*	*£ 1.0 %*
Residue on ignition	*PhEur*	*£ 0.10 %*
Assay	*Titration*	*97.5 to 102.5 %*

N.B.: Contents of the table are for illustrative purposes only. Specifications used in routine testing are acceptable as well.

2.1.S.4.2 Analytical Procedures

There is no need to fully describe the procedures here. They should be available on request

2.1.S.4.3 Validation of Analytical Procedures.

This paragraph should have a general statement that the analytical procedures are validated (e.g. specificity, quantitation limit, detection limit, linearity, accuracy, repeatability, etc.) and that they are adequate to detect significant deviations from the specifications. It can be considered to add a column with this information to the Table 2 above.

2.1.S.4.4 Batch Analyses

The aim of this paragraph is to provide information on the stability and robustness of the production process. This can be provided by a statement on how many GMP and pre-clinical batches have been produced for pre-clinical safety and clinical use and which proportion of such batches complied with the specifications. Any specific issues identified should be discussed in more detail.

2.1.S.4.5 Justification of specification

Provide justification of the specification provided in section 2.1.S.4.1. In certain cases the justification can be achieved by bridging to the available (pre-)clinical studies.

2.1.S.5 Reference Standards or Materials

Example:

> *The reference standard, Lot KS02 was prepared by division of Lot K2610211. No additional recrystallization or purification was performed.*

[Note: reference standard if applicable to stage of development; otherwise a typical batch may be used.]

2.1.S.6 Container Closure System

The container should be described here.

Example:

> *The bulk drug substance is packaged in polyethylene bags placed inside fiber drums.*

2.1.S.7 Stability

This paragraph should provide information on what has been tested and the conclusions of the stability tests performed. Details should be available on request.

Example

> *The following features of the <PRODUCT> have been tested:*
>
> - *Decomposition Chemistry*
> - *Photostability*
> - *Accelerated stability*
> - *Long term stability*

Conclusions

<PRODUCT> is stable under light protection for three years at 25°C/60% RH. When exposed to D65 light (1000 lux) for 2 months, a small amount of photodegradation products was observed and the endothermic peak broadened. Consequently, <PRODUCT> should be protected from light.

The current retesting period of <PRODUCT> is set at <YY> months/years.

DRUG PRODUCT

2.1.P.1 Description and Composition of the DRUG Product

Provide a physical description of the drug product.

The qualitative composition of the drug product should be provided in a table. Pharmaceutical Standards (e.g. Ph.Eur.) should be provided where applicable. Details on placebo may also be provided in a separate section or a separate document, depending on house style.

Example

The qualitative compositions of <PRODUCT> 50- and 100-mg tablets, the placebo tablets is listed in Table 3. The tablets are round (diameters 7.1 mm (50-mg) and 8.1 mm (100-mg)).

Table 3: Qualitative composition of <PRODUCT> 50- and 100-mg and placebo tablets

Component	Reference to standards	Function
<PRODUCT>	*In house*	*Active ingredient*
D-Mannitol	*Ph.Eur.*	*Filler*
Low Substituted Hydroxypropylcellulose	*Ph.Eur.*	*Disintegrant*
Hypromellose	*Ph.Eur.*	*Binder*
Purified water	*Ph.Eur.*	*Solvent*
Magnesium Stearate	*Ph.Eur.*	*Lubricant*
Purified water	*Ph.Eur.*	*Solvent*

2.1.P.2 Pharmaceutical Development

Provide a qualitative description of the formulation used in the study. Mention if different formulations were used for earlier studies.

Example:

The formulation used for the present clinical trial is an immediate release tablet. For previous clinical studies, other immediate release tablet and capsule formulations were used.

2.1.P.2.1 Components of the Medicinal Product

Additional relevant information with respect to drug substance and excipients should be provided here.

2.1.P.2.2 Medicinal product

Additional relevant information with respect to the formulation development can be provided here.

2.1.P.2.3 Manufacturing Process Development

No development information needs to be provided

2.1.P.2.4 Container Closure System

No development information needs to be provided

2.1.P.2.5 Microbiological Attributes

Provide only relevant information

2.1.P.2.6 Compatibility

Provide only relevant information

2.1.P.3 Manufacture

2.1.P.3.1 Manufacturer(s)

The address of the manufacturing facility having the manufacturing license should be given. In case several facilities with different licences are involved in the process (e.g. for packaging and labeling) these should be mentioned as well.

2.1.P.3.2 Batch Formula

This information does not have to be provided.

2.1.P.3.3 Description of Manufacturing Process and Process Controls

A general description of the manufacturing process should be provided. This should not be a detailed instruction for production, but details/precautions taken, relevant for the safety of the drug product for testing in human subjects should be provided. (Example: actions taken to ensure viral safety in a biotech product)

2.1.P.3.4 Controls of Critical Steps and Intermediates

In earlier stages of development many parameters are monitored. Not in all cases however, sufficient experience has been gained to assess how critical certain steps are. In case critical steps in the production process have been identified and are pertinent to the safety assessment, it should be described how they are controlled.

Example:

> *A single in process control is performed during the manufacturing process of the <PRODUCT> 50- and 100-mg tablets. The moisture content of the granulate after drying is measured and should be not more than 0.7%.*

2.1.P.3.5 Process Validation and/or Evaluation

Provide brief information on the status of validation.

2.1.P.4 Control of Excipients

2.1.P.4.1 Specifications

Refer to the Pharmacopoeias for the excipients used where possible. If this is not possible detailed information how the materials were qualified should be provided in 2.1.P.4.6.

2.1.P.4.2 Analytical Procedures

There is no need to fully describe the procedures here. They should be available on request.

2.1.P.4.3 Validation of Analytical procedures

Provide brief information on the status of validation.

2.1.P.4.4 Justification of Specifications

Only when different from internationally accepted pharmaceutical standards.

2.1.P.4.5 Excipients of Human or Animal Origin

Provide necessary details if applicable.

2.1.P.4.6 Novel Excipients

Provide necessary details if applicable.

2.1.P.5 Control of DRUG Product

2.1.P.5.1 Specifications (s)

Provide release and shelf life specifications in tabulated form.

Example:

> *Clinical trial batches of the <PRODUCT> 50-mg and 100-mg and corresponding placebo tablets will meet the following specifications.*

Table 4: Release and shelf-life specifications for <PRODUCT> 50-mg and 100-mg tablets

Test Item	Method	Acceptance Criteria
Description	*Visual observation*	*Light yellow film-coated tablet*
Identification	*HPLC/UV spectrum*	*The <PRODUCT> retention time and UV spectrum are the same as those of reference standard.*

Test Item	Method	Acceptance Criteria
Related Substances	*HPLC*	*Each: NMT 0.5%* *Total: NMT 2.0%*
*Content Uniformity**	*HPLC*	*Conforms to Ph. Eur.*
Assay	*HPLC*	*Release:* *NLT 95.0% and NMT 105.0%* *Shelf-life* *NLT 93.0% and NMT 107.0%*
Dissolution Test	*USP apparatus 2,* *50 rpm, 900 mL of simulated gastric fluid without pepsin (USP),* *UV spectrophotometry*	*Q = 75% at 30 minutes* *Conforms to USP*

**Only applied at release; NMT: Not more than; NLT: Not less than*

Table 5: Release and shelf-life specifications for placebo tablets

Test Item	Method	Acceptance Criteria
Description	*Visual observation*	*Light yellow film-coated tablet*
Identification	*HPLC*	*No peak of <PRODUCT> is observed.*
Disintegration	*Ph. Eur. Test A*	*Conforms to Ph. Eur.* *(30 min)*

N.B. Details on placebo may also be provided in a separate section or a separate document, depending on house style.

2.1.P.5.2 Analytical Procedures

There is no need to fully describe the procedures here. They should be available on request.

2.1.P.5.3 Validation of Analytical Procedures

This paragraph should have a general statement that the analytical procedures are validated (specificity, quantitation limit, detection limit, linearity, accuracy, repeatability, etc.) and that they are adequate to detect important deviations from the specifications. It can be considered to add a column with this information to the Tables 4 and 5 above.

2.1.P.5.4 Batch Analyses

The aim of this paragraph is to provide information on the stability and robustness of the production process. This can be provided by for example a statement on how many GMP batches have been produced for validation and clinical use and which proportion of such batches complied with the specifications. Any specific issues identified should be discussed in more detail.

2.1.P.5.5 Characterization of Impurities

The results should be described.

Example:

In stability studies using the present and other formulations, no impurities have been found above the quantitation limit (0.1%), which is also the reporting threshold. The only exception is a photostability study using the present formulation (see Section 2.1.P.8).

2.1.P.5.6 Justification of Specification(s)

Provide a statement in relation to the safety of the drug products for the testing in human subjects. In certain cases the justification can be achieved by bridging to the available (pre-)clinical studies.

Example:

Batches will be released for clinical trial purposes only if the impurity profiles can be supported by available non-clinical data.

2.1.P.6 Reference standards

Usually the same as in section 2.1.S.5.

Example:

The reference standard, Lot KS02 was prepared by division of Lot K2610211. No additional recrystallization or purification was performed.

2.1.P.7 Container Closure System

Describe the packaging of the drug product.

Example:

The tablets used in the clinical trial will be packed in PVdC/aluminum laminate blisters strips. The blisters will be packed in cardboard boxes to protect the tablets from light.

2.1.P.8 Stability

The objective of this section is to demonstrate that the drug product is stable for the expected duration of the clinical trial and (if applicable) is stable during preparation for administration. The stability conclusion should be limited to statements supported by the available data. The conclusions of the program can be presented first followed by a list of which tests have been performed. Full data must be available on request.

Example:

Conclusion

The stability data for the drug substance (see section 2.1.S.7) show that <PRODUCT> is intrinsically very stable.

Preliminary stability studies show that the <PRODUCT> 50 mg and 100 mg Phase-II tablets are also very stable. No

significant change was observed at any of the time points at any condition for any of the parameters tested. There is no indication that any degradation occurs, even after storage in open bottles at 40°C/75%RH for 6 months. The only exception is the photostability study, where some formation of degradation products was observed.

Considering the above, a shelf life of 24 months at is set for <PRODUCT> 50 mg and 100 mg (P-II) tablets packed in PVdC/Alu blisters. The storage instruction will be to store the tablets below 30°C, and the blisters must be kept in the outer cartons to protect them from light.

Stability data for the formulations in the present clinical trial

Tablets in dosage strengths of 50-mg and 100-mg of <PRODUCT> are described in this IMPD. Preliminary stability studies were conducted with 50-mg and 200-mg tablets. The active:excipient ratio of the 50-mg, 100-mg and 200-mg core tablets is the same, and the manufacturing process is identical. Therefore, the stability information on the 50-mg and 200-mg tablets is also considered representative for the 100-mg tablets.

These studies were performed under the following storage conditions. Both tablet strengths were stored in high density polyethylene (HDPE) bottles with or without metal screw caps, or in a petri dish wrapped in polyvinylidene chloride film.

(1) 25°C/60%RH, 12 months, HDPE bottles sealed with metal screw caps

(2) 40°C/75%RH, 6 months, HDPE bottles sealed with metal screw caps

(3) Light 1000 Lux, 2 months, Petri dish wrapped in polyvinylidene chloride film

(4) 40°C/75%RH, 6 months, HDPE bottles open

(5) 50°C/ambient, 6 months, HDPE bottles sealed with metal screw caps

Results of the stability study are shown in Table 6. No significant change was observed in any of the samples under various storage conditions. The only exception was the photostability study, where some formation of degradation products was observed, indicating a need for protection from light.

Table 6: Preliminary Stability of <PRODUCT> 50-mg tablets (Lot No. M50-1)

Storage Condition	Packaging	Storage Period	Appearance	Dissolution (%) *	Assay (%)	Related Substances (%)
Initial			*Light yellow film-coated tablets*	*99.5*	*99.1*	*NT***
25°C, 60%RH	*HDPE Bottle closed*	*12M*	*Not changed*	*97.3*	*98.7*	*<QL ****
Light 1000 Lux	*Petri dish*	*2M*	*Not changed*	*99.6*	*98.2*	*Max ind.: 0.54%* *Total: 0.60%*

Storage Condition	Packaging	Storage Period	Appearance	Dissolution (%) *	Assay (%)	Related Substances (%)
40°C, 75%RH	*HDPE Bottle closed*	*6M*	*Not changed*	*96.6*	*99.0*	*<QL ****
40°C, 75%RH	*HDPE Bottle open*	*6M*	*Not changed*	*97.6*	*98.6*	*<QL ****
50°C	*HDPE Bottle closed*	*6M*	*Not changed*	*98.6*	*98.5*	*NT***

**Dissolution rate (%) at 50 rpm after 15 min using 900 mL of MacIlvaine buffer (pH 6.8) as medium; **Not tested; ***Quantitation Limit (0.1 %)*

Non-clinical pharmacology, pharmacokinetics and toxicology

For the summaries of non-clinical studies on <PRODUCT>, reference is made to the Investigators Brochure, version 3, 14 January 2004 , which is an integral part of this IMPD.

2.2.1 Test Materials used in toxicity studies

Table 7: Impurities in <PRODUCT> drug substance

Impurities	Batches used in Toxicity Studies
No impurities >0.1% were found in the non-clinical toxicity studies	*K02; K1780005; K1780006; K1780107*

2.2.2 Integrated assessment of the data package

For this section reference is made to the Investigators Brochure(provide version number and date)

2.2.3 List of studies Conducted & References

A table of referenced non-clinical studies and references should be provided. They should be available on request

Table 36: List of referenced non-clinical studies for <PRODUCT>

Study or Report Number	Author(s)	Title of report

Study or Report Number	Author(s)	Title of report

*) Report in preparation

2.2.4 GLP statement and bioanalytical methods

A GLP statement for the relevant non-clinical studies should be provided. Any relevant information on non-clinical studies not covered in the Investigator's Brochure should be provided here.

APPENDIX 1c

REFERENCES

APPENDIX 1c

CLINICAL DATA

Referral should be made to the Investigator's Brochure for all clinical data.

2.3.5 Clinical pharmacology

2.3.5.1 Brief summary

A brief summary can be provided here, but a referral to the Investigator's Brochure should be sufficient.

2.3.6 Clinical pharmacokinetics

Example:

Details of the pharmacokinetic profile of <PRODUCT> in healthy subjects and hypertensive patients are presented in section 8.2 of the Investigator Brochure (14 January 2004).

2.3.7 Human exposure

Example:

Details of these studies are presented in the Investigator Brochure (14 January 2004), section 8.

APPENDIX 1c

OVERALL RISK AND BENEFIT ASSESSMENT

This section should give a justification of the proposed study and discuss why the data provided do allow this study to be performed. It is recommended to make this section a part of the Investigator's Brochure and refer to it from the IMPD if possible as it is considered relevant information for an investigator.

APPENDIX 1c

APPENDICES

APPENDIX 1d

INVESTIGATOR'S BROCHURE

The investigator's brochure like any other clinical trial essential document must be appropriately labelled and identified with the following information;

Investigational Product Number:_____

Chemical or Approved Generic Name:_____

Trade Name (if applicable):_____

Effective Date:

Previous Version Number	Effective Date

Author	Department	Company

SPONSOR SIGNATURE PAGE

Sponsor Signatory:

_____ _____

Name and qualifications Date

Position

APPENDIX 1d

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APPENDIX 1d

ABBREVIATIONS

APPENDIX 1d

SUMMARY

This section should contain a brief summary highlighting the significant points included in the document. The following subheadings should be addressed. If they are not applicable then it must be stated.

- Physical, Chemical and Pharmaceutical Properties and Formulation
- Preclinical Pharmacology
- Preclinical Pharmacokinetics
- Toxicology
- Metabolic Information
- Clinical Experience

INTRODUCTION

Background

The chemical name, generic name (if approved) and trade name (if approved) of the investigational product must be briefly described. The active ingredients must be listed and the pharmacological class the IP is in confirmed. The expected position within this class (i.e., the advantages it is expected to have over other products in that class) must also be discussed.

The anticipated prophylactic, therapeutic or diagnostic indication(s) that the IP is being developed to address must also be identified.

Rationale for investigational product

The rationale for performing research with the IP must be briefly discussed. Information on the general approach to be followed in developing/evaluating the IP should be provided.

REFERENCES

References relating to this section should be listed here.

Alternatively, if there are not a large number of references, a single reference section may be at the end of the document.

APPENDIX 1d

PHYSICAL, CHEMICAL AND PHARMACEUTICAL PROPERTIES AND FORMULATION

Pharmaceutical Presentation

The description of the IP substance including a brief summary of the relevant pharmaceutical properties should be provided.

Physical and Chemical Properties of the Drug Substance

Compound Number:	
Approved Name (USAN):	
Other Names:	
Chemical Name (IUPAC):	
Molecular Formula:	
Molecular Weight:	
Physical Form:	
Solubility (at ambient temperature):	

Formulation Including Excipients

The description of the formulation to be used including the excipients should be provided. Justification of the use of this formula if clinically relevant must be outlined. Information on structural similarities to other known compounds must also be provided.

Storage and Handling

The instructions for the storage and handling of the IP in its dosage form should be provided under this section.

REFERENCES

The references relating to this section must be listed here.

APPENDIX 1d

PRECLINICAL STUDIES

Preclinical Test Material

What material was used in the Preclinical studies and what form that material took should be provided here.

Preclinical Pharmacology

This section should include the results of all relevant Preclinical pharmacology studies. Summaries of the pharmacological aspects of the IP studied in animals and those of its significant metabolites must be provided. The methodology used and the study results must be outlined. The relevance these findings have to the proposed therapeutic use in humans should be discussed. Any possible unfavourable or unintended effects these results indicate and which might occur in humans should be highlighted.

Preclinical Pharmacology Studies Performed

The range of in vitro and in vivo studies performed in order to characterise the pharmacodynamics of the IP is require under this section. A table (sample below) may be included to present a list of the Preclinical pharmacology studies conducted to date.

Species tested	Number/sex of animals per group	Unit dose	Dose interval	Route of administration	Duration of dosing	Duration of post-exposure follow-up

There must be a discussion of the results of these studies including the following information:

- *Nature and frequency of pharmacological effects.*
- *Severity or intensity of pharmacological effects.*
- *Time to onset of effects.*
- *Reversibility of effects.*
- *Duration of effects.*
- *Dose response.*

If applicable there must be a comparism and discussion of the therapeutic index (i.e., the effective and nontoxic dose findings) in the same animal species. The subheadings below may be helpful.

- Primary Pharmacodynamics

- Secondary Pharmacodynamics
- Safety Pharmacology
- Overt central and peripheral effects
- Effects on the cardiovascular system
- Effects on the respiratory system
- Effects on the kidney

REFERENCES

References relating to this section should be provided here.

APPENDIX 1d

PHARMACOKINETICS AND PRODUCT METABOLISM IN ANIMALS

It is relevant that the pharmacokinetics and disposition of the IP characterised in adequate animal species be presented under this section. The main species used in Preclinical safety assessment studies must be listed. A summary table like that presented below that lists all pharmacokinetic studies performed with the IP may suffice.

Type of Study	Route of Administration	Dose or Concentration (mg/kg)	Species	No./Sex/Group
Pharmacokinetic				
Toxicokinetic				
Distribution				
Metabolism				
Excretion				

Analytical Methods and Validation

The analytical methods used to measure the blood and tissue levels of the IPmust be succinctly described. The validation process relating to these methods should also be duly outlined.

Absorption and Pharmacokinetics

Single dose pharmacokinetic studies

The absorption and pharmacokinetic results of any single dose pharmacokinetic studies must be discussed here.

Repeat dose toxicokinetic studies

Discussion of the absorption and pharmacokinetic results of any repeat-dose toxicokinetic studies.

Distribution

A review both local and systemic bioavailability including a discussion of the results of studies in all species in which the IP and metabolite distribution have been investigated should be provided here. The following subheadings may serve as a guide.

- In vitro studies
- In vivo studies

Metabolism

This section summarises the biological transformation of the IP both in vitro and in vivo.

In vitro studies

In vivo studies

Toxicology

Evidence of the evaluation of the toxicity of the IP in single and repeat dose oral studies of up to 12 months' duration must be provided here (time duration of such studies are normally within a context. The evidence provided must include results of investigations of the reproductive and genetic toxicity of the product. A listing of these studies may be provided in a tabular form.

Type of Study/Dose Duration	Route of Administration	Species (IP Dosage)	Animals/ Sex/Group
Single Dose			
Repeat Dose			
Genotoxicity			
Reproductive Toxicity			
Local Tolerance			
Other Toxicity			
Key: **DRF** = Dose range finding **M** = male; **F** = female **NA** = Not applicable			

There must be a discussion of the results of these studies to include the following information:

- *Nature and frequency of toxic effects.*
- *Severity or intensity of toxic effects.*
- *Time to onset of effects.*
- *Reversibility of effects.*
- *Duration of effects.*
- *Dose response.*

The subheadings below may be useful.

a. Single Dose Studies

Include information on single dose studies under the appropriate species heading.

- Rat
- Dog

b. Repeat Dose Studies

Include information on repeat dose studies under the appropriate species heading.

- Mouse
- Rat
- Dog

c. Genotoxicity (Mutagenicity)

d. Reproductive Toxicity

- Fertility and early embryonic development
- Embryofetal development

e. Local Tolerance

f. Carcinogenicity

g. Other Toxicity Studies

For example irritancy and sensitisation.

REFERENCES

References relating to this section should be provided here.

APPENDIX 1d

PRECLINICAL ASSESSMENT OF SAFETY

The class of the IP must be stated.

The extent of preclinical safety evaluation including safety pharmacology, single and repeat dose toxicity, and reproductive and genetic toxicity studies done should be outlined. The key toxicological findings may be presented in a table.

	Mouse		Rat		Rabbit		Dog	
Findings	**Effect Dose (mg/kg)**	**No Effect Dose (mg/kg)**	**Effect Dose (mg/kg)**	**No Effect Dose (mg/kg)**	**Effect Dose (mg/kg)**	**No Effect Dose (mg/kg)**	**Effect Dose (mg/kg)**	**No Effect Dose (mg/kg)**

If human studies have been performed the following information should be provided. A comparison of systemic exposure to the IP achieved in the toxicology species and in humans, Refer to table below for guide.

Species (Duration)	**Dose (mg/kg)**	**Sex**	**Cmax (ng/mL) [range]**	**AUC(0-t) (ng.h/mL) [range]**	**Ratio of Animal to Human Exposure**	
					Cmax	**AUC(0-t)**
Mouse (3 months)	30	M				
		F				
	100 (NOAEL)	M				
		F				
	300	M				
		F				
Rat (6 months)	3	M				
		F				
	15 (NOAEL)	M				
		F				
	100	M				
		F				

Dog (12 months)	3	M				
		F				
	10 (NOAEL)	M				
		F				
	30	M				
		F				
Rabbit (EFD)	3	F				
	10	F				
	30 (NOAEL)	F				
Human						
Single dose	100	M				
10 days	100	M				

REFERENCES

References relating to this section should be provided here.

APPENDIX 1d

EFFECTS IN HUMANS

This section should include a thorough discussion of the effects of the IP in humans. A summary of each completed clinical trial should be provided as well as any additional information obtained through alternative methods e.g., experience during marketing.

For first-time-in-human IBs this section can be deleted. Alternatively, if dose selection for human studies is based on pharmacokinetic modelling, any relevant modelling data can be presented in this section.

The following areas should be covered where the information is available:

- *Pharmacokinetics:*
    - *Pharmacokinetic summary including metabolism, absorption, plasma protein binding, distribution and elimination.*
    - *Bioavailability of the IP (absolute and/or relative).*
    - *Differences in pharmacokinetic profile in population subgroups such as the elderly, renally impaired etc.*
    - *The effect of food on the pharmacokinetic profile.*
    - *The effect of other drugs on the pharmacokinetic profile. It is particularly important to investigate drugs known to affect the cytochrome P*450 (CYP) pathway as well as drugs commonly co-prescribed for the condition being investigated.
- *Safety and Efficacy*
    - Summarise the safety profile of the IP and its metabolites.
    - Summarise the pharmacodynamic profile of the IP and its metabolites.
    - Summarise the efficacy of the IP and its metabolites.
    - Discuss the observed dose response.
    - It can be helpful to use tables to summarise adverse drug reactions (ADRs).
    - Discuss the important differences in ADR incidence and patterns across subgroups or indications.
    - Describe the possible risks and anticipated ADRs in future studies based on the current experience with the IP.
    - Describe any precautions that should be taken or special clinical monitoring that should be performed.

A listing of clinical studies conducted may be summarised in a table like that below;.

Study ID	Objectives	Study Design	Population	No. of subjects	Dose Regimens

Phase I Data

A Summary of Phase I Clinical Safety

Phase II Data

Overall Conclusions of Phase II Clinical Trial Safety and Efficacy In these studies provided the following evidence regarding:

- **Efficacy**

  1.

  2.

- **Safety**

  1.

  2.

Phase III Data

Marketing (Phase IV) Data

- *List of countries where regulatory approval has been granted or rejected.*
- *List of countries where the IP is currently being marketed and has been withdrawn from the market.*
- *Discuss any additional information gained through the marketing process.*

APPENDIX 1d

SUMMARY OF DATA AND GUIDANCE FOR THE INVESTIGATOR

For first-time-in-human IBs, the Applicant must state that no data are available on the relationship of AEs to administration of the IP, because no studies have yet been conducted in human subjects. For IPs in early phase development, it must be stated that limited data are available on the relationship of AEs to administration of the IP, because clinical experience is limited. In this case, the guidance for the investigator is based on Preclinical data and on the results of any Phase I/II studies.

Development Core Safety Information

The Development Core Safety Information (DCSI) for an investigational product is derived from all of the available safety information at the time of compilation; this includes Preclinical safety data and data available from the clinical study programme.

The DCSI is an integral part of the Investigator's Brochure and documents the adverse events which, based on the information available so far, could be reasonably assumed to be associated with the IPand therefore considered expected for the purposes of expedited reporting to regulatory authorities and investigators. Because the product is investigational, the DCSI is provisional and can be updated and amended at any time. As further information becomes available, the DCSI will be reviewed to assess the appropriateness of continued inclusion of any events or the addition of new events in the document.

Some events presented in the DCSI may have been identified from ongoing, blinded clinical studies. If this is the case, these data may not be presented elsewhere in the Investigator's Brochure, however they will be described more fully once the studies have been completed and the final data have been unblinded and analysed.

This section should provide an overall discussion of the Preclinical and clinical data and summarise the information from various sources on different aspects of the IP. If reports on related products have been published then these may be discussed if appropriate (i.e., if it could help the investigator to anticipate ADRs relating to this drug class).

The following subheadings may be helpful.

- Posology and Method of Administration
- Contraindications
- Special Warnings and Special Precautions for Use
- Interactions
- Use during Pregnancy and Lactation
- Undesirable Effects
- Overdose
- Drug Abuse and Dependency
- Other Potentially Clinically Relevant Information for the Investigator

REFERENCES

References relating to this section should be provided here.

APPENDICES

Add appendices may have been added as appropriate.

APPENDIX 1e

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

{(Invented) name of product <strength> <pharmaceutical form>}

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

For excipients, see section 6.1.

3. PHARMACEUTICAL FORM

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

<This medicinal product is for diagnostic use only.>

4.2. Posology and method of administration

4.3. Contraindications

<Hypersensitivity to the active substance(s) or to any of the excipients <or {residues}>.>

4.4. Special warnings and special precautions for use

4.5. Interaction with other medicinal products and other forms of interaction

4.6. Pregnancy and lactation

[Pregnancy and Lactation statements]

4.7. Effects on ability to drive and use machines

<{Invented name} has <no or negligible influence> <minor or moderate influence> <major influence> on the ability to drive and use machines.> [describe effects where applicable]

<No studies on the effects on the ability to drive and use machines have been performed.>

<Not relevant.>

4.8. Undesirable effects

[MedDRA frequency convention and system organ class database]

4.9. Overdose

<No case of overdose has been reported.>

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: {group}, ATC code: {code}

5.2. Pharmacokinetic properties

5.3. Preclinical safety data

<Preclinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, toxicity to reproduction.>

<Preclinical effects were observed only at exposures considered sufficiently in excess of the maximum human exposure indicating little relevance to clinical use.>

<Adverse reactions not observed in clinical studies, but seen in animals at exposure levels similar to clinical exposure levels and with possible relevance to clinical use were as follows.>

6. 6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

6.2. Incompatibilities

<Not applicable.>

<In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.>

<This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.>

6.3. Shelf life

<...> <6 months> <...> <1 year> <18 months> <2 years> <30 months> <3 years> <...>

6.4. Special precautions for storage

[Storage condition statements]

6.5. Nature and contents of container

<Not all pack sizes may be marketed.>

6.6. Instructions for use and handling <and disposal>

<No special requirements.>

<Any unused product or waste material should be disposed of in accordance with local requirements.>

7. MARKETING AUTHORISATION HOLDER

{Name and address}

8. MARKETING AUTHORISATION NUMBER(S)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10. DATE OF REVISION OF THE TEXT

APPENDIX 1f

Informed Consent Form Template for Clinical Studies

(This template is for either clinical trials or clinical research)

(Language used throughout form should be at the level of a local student of class 6th/8th)

Notes to Researchers:

1. It is important that Principal Investigators adapt their own ICFs to the outline and requirements of their particular study.
2. The informed consent form consists of two parts: the information sheet and the consent certificate.
3. Do not be concerned by the length of this template. It is long only because it contains guidance and explanations which are for you and which you will not include in the informed consent forms that you develop and provide to participants in your research.
4. This template includes examples of key questions that may be asked at the end of each section,that could ensure the understanding of the information being provided, especially if the research study is complex. These are just examples, and suggestions, and the investigators will have to modify the questions depending upon their study.
5. In this template:
    - square brackets indicate where specific information is to be inserted
    - bold lettering indicates sections or wording which should be included
    - standard lettering is used for explanations to researchers only and must not be included in your consent forms. The explanation is provided in black, and examples are provided in red in italics. Suggested questions to elucidate understanding are given in black in italics.

[Name of Principle Investigator]

[Informed Consent form for_____]

Name the group of individuals for whom this informed consent form is written. Because research for a single project is often carried out with a number of different groups of individuals - for example healthcare workers, patients, and parents of patients - it is important that you identify which group this particular consent is for.

(Example: This Informed Consent Form is for men and women who attend clinic Z, and who we are inviting to participate in research on X. The title of our research project is ".....")

You may provide the following information either as a running paragraph or under headings as shown below.

[Name of Principal Investigator]

[Name of Organization]

[Name of Sponsor]

[Name of Proposal and version]

This Informed Consent Form has two parts:

- Information Sheet (to share information about the research with you)
- Certificate of Consent (for signatures if you agree to take part)

You will be given a copy of the full Informed Consent Form

APPENDIX 1f

PART I: INFORMATION SHEET

Introduction

Briefly state who you are and explain that you are inviting them to participate in the research you are doing. Inform them that they may talk to anyone they feel comfortable talking with about the research and that they can take time to reflect on whether they want to participate or not. Assure the participant that if they do not understand some of the words or concepts, that you will take time to explain them as you go along and that they can ask questions now or later.

(Example: I am X, working for the Y Research Institute. We are doing research on Z disease, which is very common in this country. I am going to give you information and invite you to be part of this research. You do not have to decide today whether or not you will participate in the research. Before you decide, you can talk to anyone you feel comfortable with about the research.

There may be some words that you do not understand. Please ask me to stop as we go through the information and I will take time to explain. If you have questions later, you can ask them of me, the study doctor or the staff.)

Purpose of the research

Explain in lay terms why you are doing the research. The language used should clarify rather than confuse. Use local and simplified terms for a disease, e.g. local name of disease instead of malaria, mosquito instead of anopheles, "mosquitoes help in spreading the disease" rather than "mosquitoes are the vectors". Avoid using terms like pathogenesis, indicators, determinants, equitable etc. There are guides on the internet to help you find substitutes for words which are overly scientific or are professional jargon.

(Example: Malaria is one of the most common and dangerous diseases in this region. The drugs that are currently used to help people with malaria are not as good as we would like them to be. In fact, only 40 out of every 100 people given the malaria drug XYZ are completely cured. There is a new drug which may work better. The reason we are doing this research is to find out if the new drug ABX is better than drug XYZ which is currently being used.)

Type of Research Intervention

Briefly state the type of intervention that will be undertaken. This will be expanded upon in the procedures section but it may be helpful and less confusing to the participant if they know from the very beginning whether, for example, the research involves a vaccine, an interview, a biopsy or a series of finger pricks.

(Example: This research will involve a single injection in your arm as well as four follow-up visits to the clinic)

Participant selection

State why this participant has been chosen for this research. People often wonder why they have been chosen to participate and may be fearful, confused or concerned.

(Example: We are inviting all adults with malaria who attend clinic Z to participate in the research on the new malaria drug.)

→ **Example of question to elucidate understanding:** *Do you know why we are asking you to take part in this study? Do you know what the study is about?*

Voluntary Participation

Indicate clearly that they can choose to participate or not. State, what the alternative - in terms of the treatment offered by the clinic - will be, if they decide not to participate. State, only if it is applicable, that they will still receive all the services they usually do whether they choose to participate or not. This can be repeated and expanded upon later in the form as well, but it is important to state clearly at the beginning of the form that participation is voluntary so that the other information can be heard in this context.

(Example: Your participation in this research is entirely voluntary. It is your choice whether to participate or not. Whether you choose to participate or not, all the services you receive at this clinic will continue and nothing will change. If you choose not to participate in this research project, you will offered the treatment that is routinely offered in this clinic/hospital for disease Z, and we will tell you more about it later. You may change your mind later and stop participating even if you agreed earlier.)

→ **Examples of questions to elucidate understanding:** *If you decide not to take part in this research study, do you know what your options are? Do you know that you do not have to take part in this research study, if you do not wish to? Do you have any questions?*

Include the following section only if the protocol is for a clinical trial:

Information on the Trial Drug [Name of Drug]

1. Give the phase of the trial and explain what that means. Explain to the participant why you are comparing or testing the drugs.
2. Provide as much information as is appropriate and understandable about the drug such as its manufacturer or location of manufacture and the reason for its development.
3. Explain the known experience with this drug
4. Explain comprehensively all the known side-effects/toxicity of this drug, as well as the adverse effects of all the other medicines that are being used in the trial

(Example: The drug we are testing in this research is called ABX. It has been tested before with people who do not have malaria but who live in areas where malaria is common. We now want to test the drug on people who have malaria. This second research is called a "phase 2" trial.

The drug ABX is made by Company C. You should know that it has a few side effects. One of the side effects, or problems, is that you may feel tired for the first day after being given the drug. Also, 20% of the people who tried the drug in previous research experienced temporary swelling where the injection entered the skin. We know of no other problem or risks.

Some participants in the research will not be given the drug which we are testing. Instead, they will be given the drug XYZ, the drug which is most commonly used in this region to treat malaria. There is no risk associated with that drug and no known problems. It does not, however, cure malaria as often as we would like.)

Procedures and Protocol

Describe or explain the exact procedures that will be followed on a step-by-step basis, the tests that will be done, and any drugs that will be given. Explain from the outset what some of the more unfamiliar procedures involve (placebo, randomization, biopsy, etc.) Indicate which procedure is routine and which is experimental or research.Participants should know what to expect and what is expected of them. Use active, rather than conditional, language. Write "we will ask you to…." instead of "we would like to ask you to…."

In this template, this section has been divided into two: firstly, an explanation of unfamiliar procedures and, secondly, a description of process.

A. Unfamiliar Procedures

This section should be included if there may be procedures which are not familiar to the participant.

If the protocol is for a clinical trial:

1. Involving randomization or blinding, the participants should be told what that means and what chance they have of getting which drug (i.e. one in four chances of getting the test drug).

(Example: Because we do not know if the new malaria drug is better than the currently available drug for treating malaria, we need to compare the two. To do this, we will put people taking part in this research into two groups. The groups are selected by chance, as if by tossing a coin.

Participants in one group will be given the test drug while participants in the other group will be given the drug that is currently being used for malaria. It is important that neither you nor we know which of the two drugs you are given. This information will be in our files, but we will not look at these files until after the research is finished. This is the best way we have for testing without being influenced by what we think or hope might happen. We will then compare which of the two has the best results.

The healthcare workers will be looking after you and the other participants very carefully during the study. If we are concerned about what the drug is doing , we will find out which drug you are getting and make changes. If there is anything you are concerned about or that is bothering you about the research please talk to me or one of the other researchers)

2. Involving an inactive drug or placebo, it is important to ensure that the participants understand what is meant by a placebo or inactive drug.

(Example: A placebo or inactive medicine looks like real medicine but it is not. It is a dummy or pretend medicine. It has no effect on a person because it has no real medicine in it. Sometimes when we want to know whether a new medicine is good, we give some people the new medicine and some people the pretend or dummy medicine. For the research to be good, it is important that you do not know whether you have been given the real medicine or the pretend or dummy medicine. This is one of the best ways we have for knowing what the medicine we are testing really does.)

3. Which may necessitate a rescue medicine, then provide information about the rescue medicine or treatment such as what it is and the criterion for its use. For example, in pain trials, if the test drug does not control pain, then intravenous morphine may be used as a rescue medicine.

(Example: If we find that the medicine that is being used does not have the desired effect, or not to the extent that we wish it

to have, we will use what is called a "rescue medicine." The medicine that we will use is called QRS and it has been proven to control pain. If you find that the drug we are testing does not stop your pain and it is very uncomfortable for you, we can use the rescue medicine to make you more comfortable.)

If the protocol is for clinical research:

Firstly, explain that there are standards/guidelines that will be followed for the treatment of their condition. Secondly, if as part of the research a biopsy will be taken, then explain whether it will be under local anesthesia, sedation or general anesthesia, and what sort of symptoms and side effects the participant should expect under each category.

(Example: You will receive the treatment of your condition according to national guidelines. This means that you will be (explain the treatment). To confirm the cause of your swelling, a small sample of your skin will be taken. The guidelines say that the sample must be taken using a local anesthesia which means that we will give you an injection close to the area where we will take the sample from. This will make the area numb so that you will not feel any pain when we take the sample.)

For any clinical study (if relevant):

If blood samples are to be taken explain how many times and how much in a language that the person understands. It may, for example, be inappropriate to tell a tribal villager that blood equal to a wine-glass full will be taken but it may be very appropriate to use pictures or other props to illustrate the procedure if it is unfamiliar.

If the samples are to be used only for this research, then explicitly mention here that the biological samples obtained during this research procedure will be used only for this research, and will be destroyed after ____years, when the research is completed. If the tissues/blood samples or any other human biological material will be stored for a duration longer than the research purpose, or is likely to be used for a purpose other than mentioned in the research proposal, then provide information about this and obtain consent specifically for such storage and use in addition to consent for participation in the study - (see last section)

(Example: We will take blood from your arm using a syringe and needle. Each time we will take about this much blood (show a spoon, vial or other small container with a small amount of water in it. In total, we will take about ____this much blood in x number of weeks/months. At the end of the research, in 1 year, any left over blood sample will be destroyed.)

B. Description of the Process

Describe to the participant what will happen on a step-by-step basis. It may be helpful to the participant if you use drawings or props to better illustrate the procedures. A small vial or container with a little water in it is one way of showing how much blood will be withdrawn.

(Example: During the research you make five visits to the clinic.

- *In the first visit, a small amount of blood, equal to about a teaspoon, will be taken from your arm with a syringe. This blood will be tested for the presence of substances that help your body to fight infections. We will also ask you a few questions about your general health and measure how tall you are and how much you weigh.*
- *At the next visit, which will be two weeks later, you will again be asked some questions about your health and then you will be given either the test drug or the drug that is currently used for malaria. As explained before, neither you nor we*

will know whether you have received the test or the dummy/pretend drug.

- *After one week, you will come back to the clinic for a blood test. This will involve….)*

Duration

Include a statement about the time commitments of the research for the participant including both the duration of the research and follow-up, if relevant.

(Example: The research takes place over_____ (number of) days/or _____ (number of) months in total. During that time, it will be necessary for you to come to the clinic/hospital/health facility _____ (number of) days, for _____ (number of) hours each day. We would like to meet with you three months after your last clinic visit for a final check-up.

In total, you will be asked to come 5 times to the clinic in 6 months. At the end of six months, the research will be finished.)

→ **Examples of questions to elucidate understanding:** *Can you tell me if you remember the number of times that we are asking you to come to the hospital to complete the treatment? The research project? How many injections will you be given? How many tablets? How much blood will be taken from your veins, using a syringe and needle? Over how many weeks? Etc. Do you have any other questions? Do you want me to go through the procedures again?*

Side Effects

Potential participants should be told if there are any known or anticipated side effects and what will happen in the event of a side effect or an unexpected event.

(Example: As already mentioned, this drug can have some unwanted effects. It can make you tired and it can cause some temporary swelling around the place where the injection goes into your arm. It is possible that it may also cause some problems that we are not aware of. However, we will follow you closely and keep track of any unwanted effects or any problems. We may use some other medicines to decrease the symptoms of the side effects or reactions. Or we may stop the use of one or more drugs. If this is necessary we will discuss it together with you and you will always be consulted before we move to the next step.)

Risks

Explain and describe any possible or anticipated risks. Describe the level of care that will be available in the event that harm does occur, who will provide it, and who will pay for it. A risk can be thought of as being the possibility that harm may occur. Provide enough information about the risks that the participant can make an informed decision.

(Example: By participating in this research it is possible that you will be at greater risk than you would otherwise be. There is, for example, a risk that your disease will not get better and that the new medicine doesn't work even as well as the old one. If, however, the medicine is not working and your fever does not go down in 48 hours we will give you quinine injections which will bring your fever down and make you more comfortable.

While the possibility of this happening is very low, you should still be aware of the possibility. We will try to decrease the chances of this event occurring, but if something unexpected happens, we will provide you with_____ .)

→ **Example of question to elucidate understanding:** *Do you understand that, while the research study is on-going, no-one may know which medicine you re receiving? Do you know that the medicine that we are testing is a new medicine,*

and we do not know everything about it? Do you understand that you may have some unwanted side-effects from the medicines? Do you understand that these side-effects can happen whether or not you are in the research study? Etc. Do you have any other questions?

Benefits

Mention only those activities that will be actual benefits and not those to which they are entitled regardless of participation. Benefits may be divided into benefits to the individual, benefits to the community in which the individual resides, and benefits to society as a whole as a result of finding an answer to the research question.

(Example: If you participate in this research, you will have the following benefits: any interim illnesses will be treated at no charge to you. If your child falls sick during this period he/she will be treated free of charge. There may not be any benefit for you but your participation is likely to help us find the answer to the research question. There may not be any benefit to the society at this stage of the research, but future generations are likely to benefit.)

Reimbursements

State clearly what you will provide the participants with as a result of their participation. The recommendation is that reimbursements for expenses incurred as a result of participation in the research be provided. These may include, for example, travel costs and money for wages lost due to visits to health facilities. The amount should be determined within the host country context.

(Example: We will give you [amount of money] to pay for your travel to the clinic/parking and we will give you [amount] for lost work time. You will not be given any other money or gifts to take part in this research.)

Examples of question to elucidate understanding: Can you tell me if you have understood correctly the benefits that you will have if you take part in the study? Do you know if the study will pay for your travel costs and time lost, and do you know how much you will be re-imbursed? Do you have any other questions?

Confidentiality

Explain how the research team will maintain the confidentiality of data, especially with respect to the information about the participant which would otherwise be known only to the physician but would now be available to the entire research team. Note that because something out of the ordinary is being done through research, any individual taking part in the research is likely to be more easily identified by members of the community and is therefore more likely to be stigmatized.

(Example: With this research, something out of the ordinary is being done in your community. It is possible that if others in the community are aware that you are participating, they may ask you questions. We will not be sharing the identity of those participating in the research.

The information that we collect from this research project will be kept confidential. Information about you that will be collected during the research will be put away and no-one but the researchers will be able to see it. Any information about you will have a number on it instead of your name. Only the researchers will know what your number is and we will lock that information up with a lock and key. It will not be shared with or given to anyone except [name who will have access to the information, such as research sponsors, DSMB board, your clinician, etc].)

→ **Example of question to elucidate understanding:** *Did you understand the procedures that we will be using to make sure that any information that we as researchers collect about you will remain confidential? Do you have any questions about them?*

Sharing the Results

Where it is relevant, your plan for sharing the information with the participants should be provided. If you have a plan and a timeline for the sharing of information, include the details. You should also inform the participant that the research findings will be shared more broadly, for example, through publications and conferences.

(Example: The knowledge that we get from doing this research will be shared with you through community meetings before it is made widely available to the public. Confidential information will not be shared. There will be small meetings in the community and these will be announced. After these meetings, we will publish the results in order that other interested people may learn from our research.)

Right to Refuse or Withdraw

This is a reconfirmation that participation is voluntary and includes the right to withdraw. Tailor this section to ensure that it fits for the group for whom you are seeking consent. The example used here is for a patient at a clinic.

(Example: You do not have to take part in this research if you do not wish to do so and refusing to participate will not affect your treatment at this clinic in any way. You will still have all the benefits that you would otherwise have at this clinic. You may stop participating in the research at any time that you wish without losing any of your rights as a patient here. Your treatment at this clinic will not be affected in any way.)

OR

(Example: You do not have to take part in this research if you do not wish to do so. You may also stop participating in the research at any time you choose. It is your choice and all of your rights will still be respected.)

Alternatives to Participating

Include this section only if the study involves administration of investigational drugs or use of new therapeutic procedures. It is important to explain and describe the established standard treatment.

(Example: If you do not wish to take part in the research, you will be provided with the established standard treatment available at the centre/institute/hospital. People who have malaria are given_____ .)

Who to Contact

Provide the name and contact information of someone who is involved, informed and accessible (a local person who can actually be contacted. State also that the proposal has been approved and how.

(Example: If you have any questions you may ask them now or later, even after the study has started. If you wish to ask questions later, you may contact any of the following: [name, address/telephone number/e-mail])

→ **Example of question to elucidate understanding:** *Do you know that you do not have to take part in this study if*

you do not wish to? You can say No if you wish to? Do you know that you can ask me questions later, if you wish to? Do you know that I have given the contact details of the person who can give you more information about the study? Etc.

You can ask me any more questions about any part of the research study, if you wish to. Do you have any questions?

APPENDIX 1f

PART II: CERTIFICATE OF CONSENT

This section should be written in the first person and have a statement similar to the one in bold below. If the participant is illiterate but gives oral consent, a witness must sign. A researcher or the person going over the informed consent must sign each consent. **The certificate of consent should avoid statements that have "I understand..." phrases. The understanding should perhaps be better tested through targeted questions during the reading of the information sheet (some examples of questions are given above), or through the questions being asked at the end of the reading of the information sheet, if the potential participant is reading the information sheet him/herself.**

I have read the foregoing information, or it has been read to me. I have had the opportunity to ask questions about it and any questions that I have asked have been answered to my satisfaction. I consent voluntarily to participate as a participant in this research.

Print Name of Participant_____

Signature of Participant_____

Date_____
Day/month/year

If illiterate

A literate witness must sign (if possible, this person should be selected by the participant and should have no connection to the research team). Participants who are illiterate should include their thumb-print as well.

I have witnessed the accurate reading of the consent form to the potential participant, and the individual has had the opportunity to ask questions. I confirm that the individual has given consent freely.

*Print name of witness*_____ *AND Thumb print of participant*

*Signature of witness*_____

Date_____
Day/month/year

Statement by the researcher/person taking consent

I have accurately read out the information sheet to the potential participant, and to the best of my ability made sure that the participant understands that the following will be done:

1.

2.

3.

I confirm that the participant was given an opportunity to ask questions about the study, and all the questions asked by the participant have been answered correctly and to the best of my ability. I confirm that the individual has not been coerced into giving consent, and the consent has been given freely and voluntarily.

A copy of this ICF has been provided to the participant.

Print Name of Researcher/person taking the consent_____

Signature of Researcher/person taking the consent_____

Date_____
Day/month/year

APPENDIX 1g

GUIDE FOR IMPORTING PRODUCTS FOR CLINICAL TRIAL

1. An application for importation of investigational products and trial products, should receive prior approval from the NRA.
2. Approval to import products for clinical trials should only be granted to recognized clinical research entities whose protocol has been reviewed and accepted/approved by The NRA.
3. Application to import investigational products shall be made to The NRA by submitting:
    a. A letter stating the quantities of each investigational products and trial related products to be imported.
    b. The letter should bear the full name and address of the innovator, the Sponsor and the recognized clinical research entity, the name/description of the investigational product, placebo
    c. Certificates of analysis for all batches of the investigational products that to be imported.
    d. Lot Release certificate(s) (where applicable) for all batches to be imported.
4. On approval of an application for importing IPs, the necessary required permits must be processed through the local agency as pertains at the approved ports of entry for the product.
5. The Principal Investigator should notify The NRA within 48 hours of each consignment of investigational product batches received on site. The notification shall include the following details:
    a. Name of product(s),
    b. Quantities received and
    c. Batches received
6. The investigational product should be appropriately labeled with the approved labels to indicate they are samples for the conduct of clinical trials only. The label shall bear the following as the basic information:
    a. For Clinical Trial purposes ONLY
    b. Trial name
    c. Investigational Product identity number
    d. Expiry date (if applicable)
    e. Dosage (if applicable)
7. Products imported may be inspected by officials of The NRA at the port of entry before they are released to the recognized clinical research entity.

8. The above notwithstanding, all other statutes governing importation procedures and tax liabilities in the respective countries should apply to imported investigational products.

9. For investigational products purchased locally, the Principal Investigator should document the source, proof of purchase, quantities purchased and Certificate of Analysis for each batch of Investigational Products purchased for the trial.

APPENDIX 1h

CHECKLIST FOR SUBMITTING DOCUMENTS FOR ETHICS REVIEW

PRE-ASSESSMENT FORM FOR CLINICAL TRIALS APPLICATION

Name of trial_____

Phase_____

Principal Investigator (PI)_____

Contact/Tel no_____

Applicant's Name_____

Sponsor's Name & Contact_____

PARAMETER	SUBMITTED	NOT SUBMITTED	COMMENTS
Covering Letter			
Application fees			
Fully completed application form			
Institutional Support letter for the study			
Confirmation letter from participating/ collaborative institution involved in the study			
A statement that the researcher(s) agree to comply with ethical principles set out in relevant guidelines			
Material Transfer Agreement (MTA) for shipment of specimen/biological materials (where applicable)			
Signatures of key persons			
Trial Protocol			
• Signed agreement between sponsor and PI (where applicable)			
• Signatory page of key persons of the collaborative institutions involved in the study i.e. Sponsor Signatory Approval Page duly signed, with date (where applicable)			

PARAMETER	SUBMITTED	NOT SUBMITTED	COMMENTS
• Written Informed Consent form (with dates and version number) and translations into the local language (where necessary)			
• Written Parental Consent form & Assent form for older children (if study involves Minors)			
• All data collection forms to be used in the research including but not limited to case report forms, diary cards, questionnaires, interview schedules, etc. clearly indicated and dated			
• Referral forms for treatment (where applicable)			
• All forms, documents, advertisements to be used in the recruitment of potential participants			
• Budget for the study			
• Time line for the study			
• Profile on previous study i.e. Phase 1 & Phase II studies (where applicable)			
• Investigator Agreement (PI's responsibility), Page duly signed, with name and date.			
• Current Certificate of Training in Good Clinical Practice (GCP) for PI(s)			
• Investigational Product Brochure for the study			
• Data Safety Monitoring Board (DSMB) membership and Charter of Work/Current Curriculum Vitae of members.			
• Insurance cover for study participants			
• Scientific review approval			
• NRA approval letter for use of the Investigational Product/Devices and clinical trial approval			
• Current CVs of PI & Co-Investigators			

PARAMETER	SUBMITTED	NOT SUBMITTED	COMMENTS
• Any other information deemed necessary to facilitate the review process.			
Protocol amendments			
• Reasons for the amendment(s)			
• Possible consequences for participants already in the trial			
• Possible consequences for data analysis and study outcome			
• Fees			

Note: All documents should be submitted as per the national requirements of the Ethics Committee

Remarks:_____

Name/signature of receiving officer_____

Date_____

APPENDIX 1i

GUIDE TO ETHICAL REVIEW OF REQUIRED DOCUMENTS

PARAMETER	GUIDE	COMMENTS
1. Protocol	*If study is a multi-centre and original protocol is generic, submit country specific protocol*	
2. General Information	*Include administrative information (trial title, names, contacts and signatures of key persons, document identification number, list of abbreviations, table of contents etc)*	
3. Project summary	*Include a brief synopsis of the trial for quick reference; a flow chart of the trial may be included*	
4. Background and Literature review	*It should be written so it is easy to read and understand by someone with a basic sense of the topic who may not necessarily be an expert in the area.* *Include relevant information on any previous studies conducted which may be related to the proposed study*	
5. Study rationale	*It should explain why the research questions being asked are important and why closely related questions are not being covered*	
6. Study goals and objectives: These should be clearly outlined	*These should define the primary research question, to address a specific hypothesis and to clearly define the secondary objectives*	
7. Study design	*It should describe the ideal design for the research question and what the trial is designed to show.* *Ensure that this is suitable for the purpose of the trial and can answer the question under research in order to achieve goals and objectives. The following should be taken into consideration: adequacy/suitability of choice of control (placebo or standard care), sample size, study endpoints*	
8. Eligibility criteria (Study population)	*It should set out precise definitions of which participants are qualified for the trial, defining both inclusion and exclusion criteria.* *The eligibility criteria should be clear so they can be applied consistently through the trial and definitions for the timelines and flexibility of each eligibility criterion must be carefully considered to ensure that arbitrary or un-workable definitions are not used.*	
9. Study area(s)	*It should describe where the study will be run and any site specific requirements*	

PARAMETER	GUIDE	COMMENTS
10. Methodology	*Describe what the procedures/assessments are at each visit and where they will be undertaken i.e. hospital/GP surgeries/at home and if not at the trial site the timelines for notification of these results to the trial team, especially if they are outside of the range etc*	
11. Ethical and Safety Considerations (Problems anticipated and solutions proposed)	*General good practice in research (and the basis of legal frameworks relating to both CTIMPs and non-CTIMPs) require that persons incapable of giving legal consent should be given special protection.*	
12. Plans for Follow-up(s)	*Clearly described long term follow-up of participants should be indicated.* *If participants will be monitored after the active treatment phase has closed, the protocol should describe how and when this would be done.*	
13. Data management considerations and statistical analysis	*Data management describes procedures and the tools for data collection, recording and handling* *If a Statistical Analysis Plan is to be produced separately, it should be stated in the protocol and the most relevant information should be condensed in this section.*	
14. Quality assurance	*Include all 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) e.g. DSMB, Robust database system etc*	
15. Expected Outcomes of the study	*Primary and secondary endpoints/outcomes for the trial usually appear in the objectives and sample size calculation.* *An ideal endpoint/outcome is valid, reproducible, relevant to the target population, and responsive to changes in the health condition being studied. Endpoints should be measurable.*	
16. Dissemination of results	*A statement in the protocol that indicates that the findings of the study would be publically made available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the study will be given; any discrepancies from the study as planned in the protocol will be explained.* *A publication plan should be clearly outlined.*	

PARAMETER	GUIDE	COMMENTS
17. Duration of the Project	*It should provide a clear and concise timeline for all trial related activities from trial commencement to submission of Final report to relevant bodies (NRAs, Ethics Committees etc.).* *The activities include trial visits, enrolment process, interventions, and assessments performed on participants etc.*	
18. Project Management	*A system put in place to effectively maintain and manage planning, performing and reporting functions, along with tracking deadlines and milestones. This ensures that all trial related activities are coordinated in a chronological manner.* *Includes informed consent, participant recruitment and enrolment, monitoring visits and source document verification.*	
19. Informed-Consent Form	*Refer to appendix 1g for the guide to ICF*	
20. Budget	*A detailed breakdown of all trial related costs/expenditures to be made within the trial period. This includes cost of equipment, investigational products, logistics etc.*	
21. Funding source(s)	*Names and contact details of ALL organisations providing funding and/or support in kind for this trial*	
22. References	*This section should list the literature and data that are relevant to the trial, and provide background for the trial. Ensure the text contains appropriate cross references to this list.*	
23. Curriculum Vitae of PI and co PIs	*Latest signed and dated CVs of investigators and study team members*	
24. Profile on Previous study	*If study is in phases, the results and any other relevant information from the previous phases should be provided.*	
25. Insurance cover for participants	*It should be current, valid for the full duration of the trial (or there must be a written commitment for renewal for the duration of the trial) and follow-up period.* *The certificate should contain a reference to the trial Protocol number and the countries to which cover is extended.* *The insurance cover should be provided from a company which is ABPI compliant.*	

PARAMETER	GUIDE	COMMENTS
26. Material Transfer Agreement (MTA) - if specimen has to be transported outside Ghana	*The MTA should describe the procedure for dealing with biological sample.* • *include details of the arrangements for this (e.g. on dry ice), indicate whether the sponsor or the site(s) will be responsible for arranging the courier to transport the samples* • *what will happen to the samples after they have been analysed; will they be stored or destroyed* • *should be signed by the key parties involved*	
27. Indicate if samples will be stored (where and for how long)	*The protocol should describe the procedure for dealing with biological samples:* • *the criteria for the collection, analysis, storage and destruction of biological samples* • *the arrangements for sample collection*	
28. Membership of Data Safety Management Board (DSMB), CVs, and Charter of Work	*Submit membership, CVs and Charter of Work.* *Members should be qualified and be expert in the area related to the trial.*	
29. GCP certificates for PI and Co PIs	*GCP certificates should be current and valid (as per the applicable NRA guidelines)*	
30. Registration with clinical trials registry	*All clinical trials to be conducted in Africa must be registered with the Pan African Clinical Trial Registry*	

Note: For further details on the Guide to reviewing the Protocol section, refer to Appendix 1b

APPENDIX 2a

GUIDE TO INFORMED CONSENT/ASSENT FORM REVIEW

PARAMETER	GUIDE	COMMENTS
1. Heading	This should read "Trial Information Sheet"	
2. Title of Trial	The full trial title should be stated. A short or abbreviated name may be included	
3. Introduction	A brief introduction about the Principal Investigator(s), that is, name, address, local telephone number, Email and work location.	
4. Nature of Trial	Indicate what the trial is about. A brief explanation (in simple language) on what the trial is interested in finding should be provided. Procedures that are experimental should be mentioned (if applicable)	
5. Participants involvement		
a. Duration/what is involved	What and how much of the time of participants would be required should be stated	
b. Potential Risks	Participants should be given a fair idea about the consequences (risk or harm) of participation, that is, if there will be discomforts, emotional upset, psychological, among others.	
c. Benefits	Any direct or indirect benefit from the study should be explained. This includes description of the scientific or other benefit hoped from the trial	
d. Costs	Any costs involved in the trial and who is expected to bear these costs should be clearly stated e.g. transportation	
e. Compensation/ Payment	Any remuneration to be given for participation in the trial should be stated.	
f. Confidentiality	How participants' confidentiality will be preserved should be stated. If recording of interview or taking photographs of participant is intended, permission for this should be sought and how anonymity would be ensured should be stated.	
g. Voluntary participation/ withdrawal	A statement clarifying that participation is voluntary and that their right to withdraw from the trial at any time without penalty.	
h. Outcome and Feedback	What will happen to data and whether any feedback will be given to participants should be explained.	

PARAMETER	GUIDE	COMMENTS
i. Appropriate alternative Procedures and Treatment	Any appropriate alternative procedures and treatment etc. that may serve as possible alternate options to study participation (if applicable) should be disclosed in full.	
j. Funding information	A brief and clear statement of who is/are funding or sponsoring the study/research should be made.	
k. Additional Information	Any other relevant information which is of importance to the participant could be included.	

GUIDE TO GOOD CLINICAL PRACTICE INSPECTION – TRAINING TOOL

Abbreviations/Acronyms

ADR Adverse Drug Reaction

ALS Advanced Life Support

CRF Case Report Form

CoA Certificate of Analysis

CPR Cardio-pulmonary resuscitation

CRO Clinical Research Organisation

CV Curriculum Vitae

DSMB Data Safety Monitoring Board

GCP Good Clinical Practice

GLP Good Laboratory Practice

ICH International Conference on Harmonisation

IEC Independent Ethics Committee

IRB Institutional Review Board

IP Investigational Product

NA Not checked or not applicable

PI Principal Investigator

RA Regulatory Authority

SAE Serious Adverse Event

SOP Standard Operating Procedures

IMPORTANT:

- *The site must show evidence, preferably documentation, to prove availability or conduct of the underlisted considerations. Interviews may be conducted as part of the verification process.*
- *All observations made during the inspection must be document ONLY on the GCP Inspectors notes form*
- *There must be SOPs for all study procedures required by the approved protocol.*
- *All equipment used for the conduct of any trial activity must be calibrated, validated and functional.*

1. FACILITY INSPECTION

1.1. Reception Area

a. This area must be of an adequate size and must be accessible for participants.

b. Consider the trial population e.g. babies, disabled participants

c. There must be a receptionist or team member who has the first contact with a potential participant.

d. This person must be trained to encounter a potential participant.

e. He/she must also be trained in basic knowledge in clinical trials.

1.2. Informed consent area

a. This area must be of an adequate size.

b. The settings of the room or area must allow for optimum privacy and confidentiality of participants.

1.3. Consulting/Screening Area

a. This area must be of an adequate size.

b. There should be lock-up cupboards for confidential documents, this should be access controlled.

c. The room/area must have the required trial specific equipment. If not, the area where required procedures are performed adequate and easily assessable?

d. All equipment available must be calibrated, validated and functional

e. There must be SOPs on how to use the equipment available.

f. The blood sampling area must be kept according to infection control procedures, that is, if blood sampling is conducted in the room.

g. SOPs for procedures conducted in the area must be boldly displayed.

h. There must be evidence the PI recruits, manages and maintains the trial visits as per the approved protocol.

i. A delegated team member must plan and organize visits according to the visits schedule in the protocol.

1.4. Injection and/or resuscitation area (if applicable)

a. This area must be of an adequate size.

b. There must be a specific area where participants could be evaluated for reactogenicity as per protocol.

c. There must be appropriate waste handling according to applicable guidelines, e.g. from the RA or site or government.

d. There must be an emergency trolley available in the area.

e. The trolley must be under lock and key and must be access controlled.

f. The content of the emergency trolley must be frequently checked and documented.

g. Expiry dates of products kept in the area must be checked regularly and controlled.

h. Oxygen and accessories must be available

i. There must be evidence to show that functionality of this is regularly checked and maintained.

j. Evidence of training of staff to administer CPR must be available.

k. The room/area must have the required trial specific equipment (s). If not, the area where required procedures are performed adequate and easily assessable

l. All equipment available must be calibrated, validated and functional

m. There must be SOPs on how to use the equipment available.

n. SOPs for procedures conducted in the area must be boldly displayed.

1.5. Pharmacy (Investigational Product storage area)

a. Access to the pharmacy or storage area must be controlled.

b. Temperature and humidity in the area must be monitored and controlled. Appropriate logs must be available for this.

c. Products must be stored as per required temperature and humidity.

d. There should be an SOP on how to handle electricity or temperature failure in the area.

e. Preparation of investigational product must be done according to the approved protocol by suitable qualified staff.

f. In case of vaccines, there must be an SOP for spillage and the study team must be trained to handle such incidences.

g. The different study investigational products must be kept in separate storage areas and clearly identified.

h. Transported and handling of IPs must be as per cold chain requirements.

i. Documents regarding shipment, receipt, administration, destruction and/or return of IP must be available. This should be detailed enough to allow for complete IP accountability.

j. Administration of IP to respective participants must be as per randomization procedure.

1.6. Document storage/archiving area

a. The study documentation must be appropriately archived.

b. The area must be access controlled.

c. There must be a person designated to control the handling of documents and appropriate records maintained.

d. There should be an agreement between Sponsor and Trial Site/CRO on the archiving of documentation (this may be part of the protocol).

e. The archiving area must be waterproof, fireproof and pest controlled.

1.7. Clinical Laboratory

a. There must be procedures and documentation of transfer of biological samples to the designated lab.

b. All equipment used in the laboratory must be calibrated.

c. Testing procedures used in the laboratory must be validated.

d. There should be a routine equipment maintenance plan in place.

e. The laboratory must be accredited and/or approved for the tests performed.

f. There must be documentation to prove that all test results are quality assured.

1.8. Waste disposal

a. There must be a dedicated and suitable area for disposal of all waste generated from the study.

b. There should be an appropriate system in place for the disposal of especially biological specimens and sharps.

c. There should be separate disposal containers for different waste.

d. Per international coding, the following should apply:

- Black for non-infectious waste.
- Red for infectious waste.
- Yellow containers for sharps.

2. QUALITY ASSURANCE SYSTEM

2.1. There should be SOPs for all critical procedures.

2.2. SOPs must be adhered to.

2.3. There must be a system in place for an internal self-assessment of the quality assurance system.

2.4. Training records for staff must be available.

2.5. Superseded SOPs must be available in a history file.

2.6. Revision periods of SOPs must be adhered to as required.

2.7. If there is a contract between the sponsor/CRO and PI, delegated responsibilities must be clearly identified and listed and a copy of the contract must be available on site.

2.8. The organogram of the Trial Site/CRO must indicate the following:

a. Number and categories of people employed

b. Description of the qualifications, training and experience of the personnel

c. Work load of study team

d. Number of concurrent clinical studies performed on site and identification of participants to avoid confusion and mix-ups of IP's administration

2.9. The quality system for the study must be duly described in a document and must be available for verification.

2.10. Check the existence, availability, accessibility and validity of the Standard Operating Procedures for ALL protocol required procedures used for the trial.

2.11. Quality control procedures must be applied to each stage of data handling to ensure that all data is reliable and has been processed correctly.

2.12. There must be evidence that the sponsor monitors the trial regularly.

2.13. The monitoring visit log must be duly signed to prove this.

2.14. Check to verify if the monitor adheres to the monitoring plan as per protocol.

2.15. Verify that AE and SAE are handled according to SOPs and regulatory requirements.

3. 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).

3.1. Check the availability of the following essential documents:

- An approved, signed and final version of the Protocol (including amendments) available.
- Type of information which must be reported between sponsor/EC/investigator and the NRA/sponsor.
- Final version of the Investigator's Brochure.

- Information Leaflet i.e. information regarding the trial in lay terms.
- The Informed Consent Form (translation) and applicable procedure.
- Sample of the case report forms (CRF) as per protocol requirements.
- Any other written information (e.g. advertisements).
- IEC approval of advertisement for participant recruitment.
- Financial aspects of the trial as predefined in an agreement between the Investigator and the sponsor available.
- Guaranteed indemnity/insurance document/statement available.
- The insurance must be valid for the duration of the trial.
- The signed agreements between involved parties e.g. Investigator/CRO, Investigator/Sponsor/ laboratories.
- List of source documents/signed source document agreement between the sponsor and investigator.
- Documentation of transfer of responsibilities if applicable.
- Independent Ethics Committee approval (Clearly stated which dated version of protocol and informed consent is approved, Minutes of meeting available where relevant documentation were reviewed and approved, List of members voted for approval (Conflict of interest), List of Ethics Committee members and their disciplines).
- Regulatory approval. (Clearly stated which dated version of protocol and informed consent is approved.)
- Verify the importation/sourcing dates of IPs versus NRA approval dates.
- Latest signed and dated CVs of investigators and study team members.
- Proof of valid GCP training (PI, local monitor, pharmacist, lab manager and data manager must have NRA certificate of not more than 2 years) of all study team members.
- List of DSMB members (National or international).
- Local Safety Monitor's CV (signed and dated).
- Trial initiation visit, agenda and study team attendance list.
- Serious Adverse Event reporting forms and reporting procedures/timelines (including supporting SOPs).
- Standard Operating Procedures.
- Training records for staff on SOPs, protocol and protocol specific procedures.
- Normal values/ranges for medical/laboratory/technical procedures as supplied by the laboratory/contract laboratory.
- Evidence of quality assessment of local laboratory by the sponsor.
- Process validation protocols and reports where applicable.

- Investigational Product (IP)
  - IP labelled according to GMP and regulatory requirements
  - IP labelled for clinical trial use only
  - Shipping records of IPs (dates, batch numbers) including copy of GCNET approval
  - Records of delivery, receipt of the IP
  - Proof that the correct diluent has been packed according to the correct storage condition and shipped with the vaccine
  - Proof that conditions as stated in the protocol have been maintained during shipment and storage of products
  - CoA of IPs (Check stability, batch number, expiry dates) for compliance
  - IP accountability record e.g. quantities ordered and received available
  - SOP/instructions available for handling of IP and trial related materials
  - Decoding procedure for blinded trials available.
- Randomization procedure referring to the master list according to sponsor instructions.
- Communications other than monitoring visits: Letters, Meeting minutes and agenda, notes of telephone calls.
- Signed Informed Consents.
- Source documents, e.g. X-rays, serology printout, diary cards.
- Signed and dated CRFs.
- SAE reporting to sponsor.
- Reporting of any serious unexpected ADR and relevant safety information to NRA and IEC where required.
- Progress reports to regulatory and other oversight body.
- Participant screening log.
- Participant identification code list.
- Participant enrolment log.
- Study team signature sheet with delegated functions by PI.
- Retained biological samples (records, storage conditions).
- All deviations e.g. inclusive/exclusive criteria (waiver) recorded.
- IP accountability at site (final reconciliation).
- Documentation on disposal of IPs.
- Audit Certificate (if applicable), i.e. if carried out.

- Final trial close-out monitoring report.
- Final report by investigator to IEC and regulatory authority.
- Clinical study report (refer to ICH GCP section 5.22).
- Treatment allocation and decoding documentation that have occurred.
- Follow up plan available (post-trial period) for participants with adverse events related to the IP as per protocol.

4. INFORMED CONSENT PROCESS

- The informed consent form version used must be the same as the one approved.
- Soliciting of informed consent should be conducted as per SOP.
- All participants must be given a copy of a signed informed consent form.
- All participants must sign the consent form prior to any study related procedure.

5. REFERENCES

5.1. **ICH Guideline for Good Clinical Practice E6,with step 4 version 10 June 1996**

5.2. **Guidance on General Considerations for Clinical Trials (ICH-E8)**

5.3. **Code of Federal Regulations CFR Title 45 - Public Welfare United States Code of Federal Regulations (CFR). Title 21 Code of Federal Regulations (CRF) that establishes the United States Food and Drug Administration (FDA) regulations**

5.4. **Guidelines for Good Pharmacoepidemiology Practice (GPP). Pharmacoepidemiology and Drug Safety 2016;25:2-19**

5.5. **The Council for International Organizations of Medical Science (CIOMS) 2000**

5.6. **Guidelines for phase 1 clinical trials 2012 Edition, Association of British Pharmaceutical Industry (ABPI)**

5.7. **Insurance and compensation in the event of injury in phase 1 clinical trials, Association of British Pharmaceutical Industry (ABPI) June 2012 International Ethical Guidelines for Biomedical Research Involving Human Subjects CIOMS and WHO 2002**

APPENDIX 2bii

CLASSIFICATION/GRADING OF INSPECTION FINDINGS

Observations should be classified into the categories **"Critical", 'Major"** or **"Minor**

- **Critical observation:**
  Conditions, practices, processes or regulatory offences that adversely affect the rights, safety or well-being of the participant(s) and/or the quality and integrity of data.
- **Major observation:**
  Conditions, practices, processes or regulatory offences that may adversely affect the right, safety or well-being of the participant(s) and/or the quality and integrity of data.
- **Minor observation.**
  Conditions/practices or processes that will not be expected to adversely affect the right, safety or well-being of the participant(s) and/or the quality and integrity of data.
- **Comments:**
  Observations that might lead to suggestions on how to improve quality or reduce the potential for a deviation to occur in the future.

Implication of grading

- It can lead to the conclusion that the study is not of a satisfactory level of compliance with GCP/GCLP.
- Several major observations can lead to the conclusion that a study is not of a satisfactory level of compliance with GCP/GLP.
- Minor observations need to be addressed in order to sustain confidence in the trial.
- Minor observations indicate the need for improvement of conditions, practices and processes.
- Lots of minor non-compliances may add up to a major non-compliance.

APPENDIX 2bii

GCP OBSERVATION & GRADING SHEET

OBSERVATION	GRADING	REFERENCE (ICH & National Laws/ Guidelines)	RESPONSIBILITY
Personnel			
Facilities			
Equipment			
Application/notification to competent authority			
Contacts with the independent ethics committee (IEC)			
Contacts with other committees, any other validation or authorisation			
Contract(s), Agreement(s)			
Trial Documents			
Conduct of the Trial			
Documentation and Reporting of Efficacy Data			
Documentation and Reporting of Safety Data			
Investigational Medicinal Product(s) (IMPs)			
Data handling			
Laboratories, Technical Departments			
Monitoring and Auditing			

*Observations made under the respective sections should be listed and addressed individually.

APPENDIX 3

LIST OF ICH OBSERVERS

Standing Observers

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

Observers

Legislative or Administrative Authorities

- The Agência Nacional de Vigilância Sanitária (ANVISA, Brazil)
- The Central Drugs Standard Control Organization (CDSCO, India)
- The Comisión Federal para la Protección contra Riesgos Sanitarios (COFEPRIS, Mexico)
- The Health Sciences Authority (HSA, Singapore)
- The Ministry of Food and Drug Safety (MFDS, South Korea)
- The Roszdravnadzor (Russia)
- The Food and Drug Administration (TFDA, Chinese Taipei)
- The Therapeutic Goods Administration (TGA, Australia)

Regional Harmonization Initiatives (RHIs)

- The Asia-Pacific Economic Cooperation (APEC)
- The Association of Southeast Asian Nations (ASEAN)
- The East African Community (EAC)
- The Gulf Cooperation Council (GCC)
- The Pan American Network for Drug Regulatory Harmonization (PANDRH)
- The Southern African Development Community (SADC)

International Pharmaceutical Industry Organizations

- The Biotechnology Innovation Organization (BIO)

International Organizations with an Interest in Pharmaceuticals

- The Council for International Organizations of Medical Sciences (CIOMS)
- The European Directorate for the Quality of Medicines & HealthCare (EDQM)
- The International Pharmaceutical Excipient Council (IPEC)
- The United States Pharmacopeia (USP)

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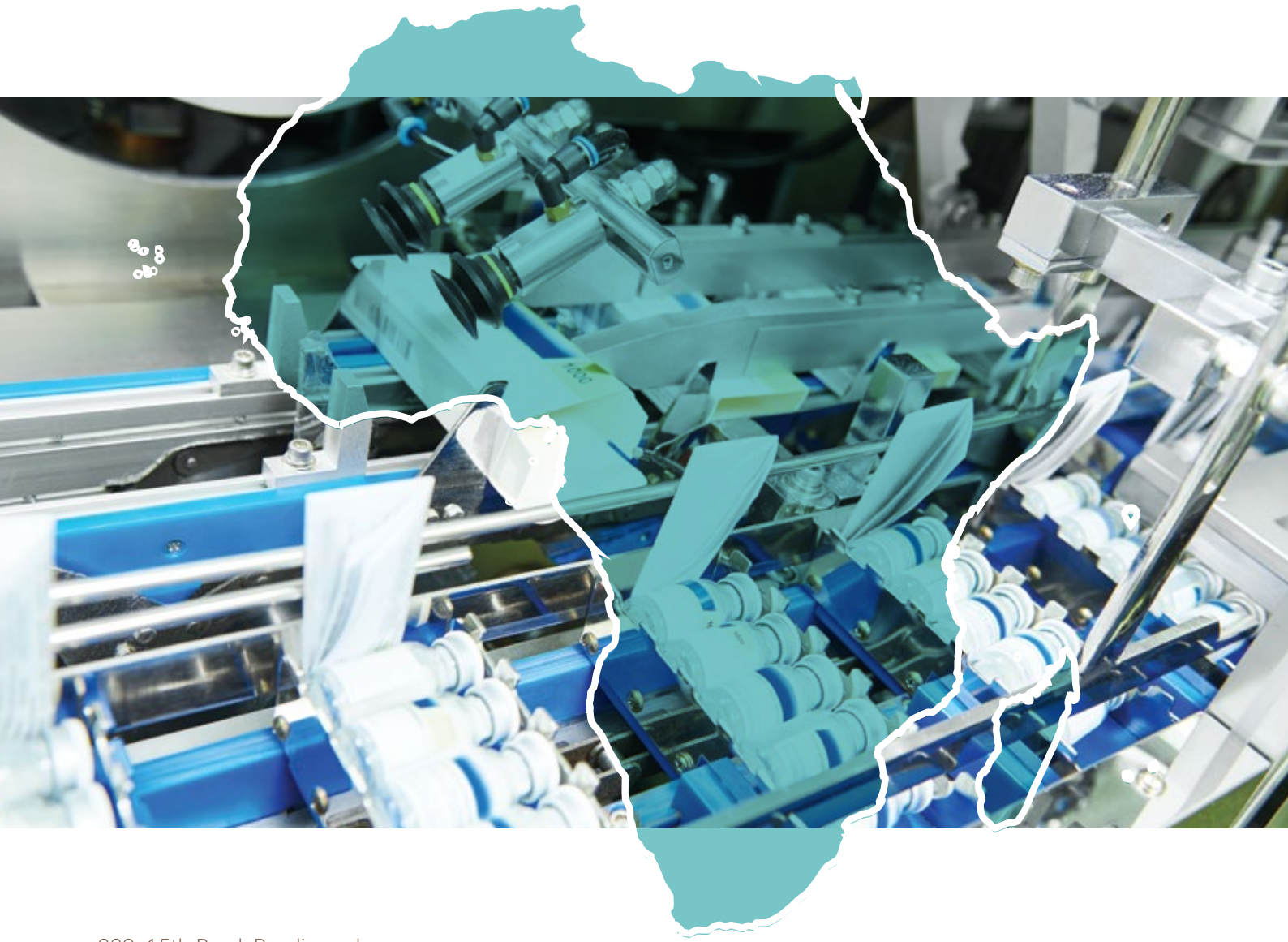

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