RWANDA FDA
Rwanda Food and Drugs Authority

GUIDELINES FOR CLINICAL TRIALS APPLICATIONS IN RWANDA

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FOREWORD

Rwanda Food and Drugs Authority (Rwanda FDA) is a regulatory body established by Law N° 003/2018 of 09/02/2018, specifically in article 8, paragraphs 7 and 12 to regulate and inspect clinical trials. In reference to the provisions of the technical regulation No DD/PVCT/TRG/001 Version 4 governing the conduct and inspection of pre/clinical trials, the Authority issues Guidelines No DD/PVCT/GDL/005 Version 3 for Clinical Trial Application in Rwanda.

These guidelines have been developed to provide guidance to the applicants and the Authority in preparation and managing applications for clinical trials. These guidelines were developed in reference to the existing guidelines of the World Health Organization (WHO) and the International Conference on Harmonization of Technical Requirements for Good Clinical Practices (ICH E6) and other available literature.

The Authority acknowledges all the efforts of key stakeholders who participated in the development, review and validation of these guidelines.

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Director General

DOCUMENT DEVELOPMENT HISTORY

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Effective date of this revision	Refer to the approval date

Document Revision History

Date of revision	Version number	Changes made and/or reasons for revision
05/02/2021	0	First issue
	1	
18/06/2021	1	1. Provisions for expedited review of Clinical Trial Application (CTA) were included; 2. Provisions for application, review, and approval of clinical Trial during health emergencies; 3. Provisions for reliance pathway approval as the non-routine procedure for clinical trial authorization in Rwanda were incorporated; 4. Requirements for renewal of clinical trial Authorizations were included; 5. The flowchart for the clinical trial was revised and included; 6. The table revision history was included; 7. Necessary editorial changes and formatting were made.
01/04/2023	2	1. The reference number was changed from DIS/GDL/033 to FDISM/PVSM/GDL/005 Rev_2 as per the current SOP on document control 2. Provisions for expedited review of CTA were moved to the Guidelines for Review and Approval of CTAs; 3. Provisions for the application, review, and approval of clinical trials during health, emergencies were moved to the Guidelines for review and Approval of CTA; 4. Provisions for reliance pathway approval as the non-routine procedure for clinical trial authorization in Rwanda were moved to the Guidelines for Review and Approval of CTAs; 5. Criteria to be followed for accepting evidence of GMP compliance for imported IMPs were included; 6. Section 1.3 regarding the review process was moved to the guidelines for the Review and Approval of CTA; 7. Critical requirements for acceptance of CTA were included; 8. Format and content of the CTA updated; 9. Requirements for amendments were included; 10. Requirements for renewal were included; 11. Included necessary editorial changes in line with SOP on Document control.

	3	1. The reference number was changed from FDISM/PVSM/GDL/005 Rev_2 to DD/PVCT/GDL/005 Version 4 as per the current SOP on document control 2. Provisions for risk identification for clinical trials were included; 3. Requirements and provisions for conducting clinical investigations on medical devices, or In Vitro Diagnostics(IVDs) or Software clinical investigations were included; 4. Provisions for submission of clinical trial application and payment were revised; 5. Appendix II regarding clinical trials designs was added; 6. Included necessary editorial changes in line with SOP on Document control.

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ACRONYMS AND ABBREVIATIONS

AE	**Adverse Event**
API	**Active Pharmaceutical Product**
AVAREF	**African Vaccine Regulatory Forum**
CIOMS	**Council of International Organization for Medical Science**
CRO	**Contract Research Organization**
CRF	**Case report form**
CTA	**Clinical Trial Application**
CTA-A	**Clinical Trial Application for Amendment**
DSMB	**Data Safety and Monitoring Board**
EUAL	**Emergency Use Assessment and Listing Procedure**
FPP	**Finished pharmaceutical Product**
GCP	**Good Clinical Practice**
GLP	**Good Laboratory Practice**
GMP	**Good Manufacturing Practice**
IB	**Investigator's Brochure**
ICH	**International Conference on Harmonization**
ICFs	**Informed Consent Forms**
IRB	**Institutional Review Board**
IP	**Investigational Product**
MTA	**Material Transfer Agreement**
NDA	**New Drug Application**
QOS	**Quality Overall Summary**
PI	**Principal Investigator**
RNEC	**Rwanda National Research Ethics Committee**
Rwanda FDA	**Rwanda Food and Drugs Authority**
SAEs	**Serious Adverse Events**
SmPC	**Summary of product characteristics**
SUSARs	**Suspected Unexpected Serious Adverse**
WHO	**World Health Organization**

GLOSSARY / DEFINITIONS

In these Guidelines, unless the context otherwise states:

"Applicant'' means the Sponsor or Principal Investigator or any other authorized person to apply for clinical trial and issued a Clinical Trial Certificate. The applicant shall therefore be responsible for signing the application form.

"Authority" Means Rwanda Food and Drugs Authority or its acronym "Rwanda FDA", established under the article 2 of the Law No 003/2018 of 09/02/2018.

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

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

"Assent" A process by which a child, who is capable of understanding 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 child's decision to participate. Assent is documented by means of a written, signed and dated assent form from the child. As part of the assent process, parents and guardians must give informed consent.

"Audit" A systematic and independent examination of trial related activities and documents to determine whether the evaluated trial related activities were conducted, and the data were recorded, analysed and accurately reported according to the protocol and applicable standard operating procedures (SOPs), the Authority and ICH-GCP requirement(s).

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

"Case Report Form" A printed, optical, or electronic document designed to record all of the protocol required information to be reported to the sponsor on each study participant.

"Clinical Trial" Any investigation in human study participants intended to discover or verify the clinical, pharmacological and/or other pharmacodynamics 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 Report" A written description of a trial/ study of any therapeutic, prophylactic or diagnostic agent conducted in human study participants in which the clinical and statistical description, presentations and analyses are fully integrated into a single report.

"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.

"Data and Safety Monitoring Board" 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.

"Documentation" All records, in any form (including, but not limited t, 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 that individually and collectively permit evaluation of the conduct of a study and the quality of the data produced.

"Ethical Clearance" An authorization to conduct a clinical trial issued by the Rwanda National Research Ethics Committee (RNEC) based on ethical issues related to trials involving human participants in Rwanda.

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

"Good Manufacturing Practice (GMP)" The part of pharmaceutical quality assurance which ensures that products are consistently produced and controlled to quality standards appropriate to their intended use and as required by the marketing authorization.

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

"Informed Consent" A process by which a study participant voluntarily confirms his or her willingness to participate in a particular trial, after having been informed of all aspects of the trial that are relevant to the study participant's decision to participate. Informed consent is documented by means of a written, signed and dated informed consent form.

"Inspection" The act of conducting an official review of documents, facilities, records, and any other resources that are deemed by the Authority to be related to the clinical trial and that may be located at the site of the trial, at the sponsor's and/or CRO's facilities or at other establishments deemed appropriate by the Authority.

"Investigational Product" A pharmaceutical product in 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. These include but are not limited to pharmaceutical products, biologicals (e. vaccines), medical devices.

"Investigator" A physician, dentist, or another qualified person who conducts a clinical trial at a trial site. See also Sub-investigator.

"Investigator's Brochure" A compilation of the clinical and non-clinical data on the investigational product(s), which is relevant to the study of the investigational product(s) in human study participants. "Legal representative" The name given to describe the executor, administrator or the person who looks after another person's affairs.

"Materials Transfer Agreement" An MTA is a written contract that governs the transfer of tangible research materials or biological samples between parties.

"Multi-centre 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.

''Notifications" means changes to the details of a trial that have no significant implications for the study participants, conduct, management, and scientific value of the research

"Phase I trials" These are the first trials of a new active ingredient or new formulations in man, often carried out in healthy volunteers. Their purpose is to establish a preliminary evaluation of safety and a first outline of the pharmacokinetic and, where possible, pharmacodynamics profile of the active ingredient.

"Phase II trials" These trials are performed with a limited number of study participants and are often, at a later stage, of a comparative (e.g. placebo-controlled) design. Their purpose is to demonstrate therapeutic activity and to assess the short-term safety of the active ingredient in patients suffering from a disease or condition for which the active ingredient is intended. This phase also aims at the determination of appropriate dose ranges or regimens and (if possible) clarification of dose-response relationships in order to provide an optimal background for the design of extensive therapeutic trials.

"Phase III trials" Trials in larger (and possibly varied) patient groups with the purpose of determining the short and long-term safety/efficacy balance of formulation(s) of the active ingredient, and of assessing its overall and relative therapeutic value. The pattern and profile of any frequent adverse reactions must be investigated and special features of the product must be explored (e.g. clinically relevant investigation product interactions, factors leading to differences in effect such as age). These trials should preferably be of a randomized double-blind design, but other designs may be acceptable, e.g. long-term safety studies. Generally, the conditions under which these trials are carried out should be as close as possible to normal conditions of use.

"Phase IV studies" Studies performed after marketing of the pharmaceutical product. Trials in phase IV are carried out on the basis of the product characteristics on which the marketing authorization was granted and are normally in the form of post-marketing surveillance, or assessment of therapeutic value or treatment strategies. Although methods may differ, these studies should use the same

scientific and ethical standards as applied in pre-marketing studies. After a product has been placed on the market, clinical trials designed to explore new indications, new methods of administration or new combinations, etc. are normally considered as trials for new pharmaceutical products.

"Pharmaceutical product" any substance capable of preventing, treating human or animal diseases and any other substance intended for administration to a human being or an animal in order to diagnose diseases, restore, correct or carry out modification of organic or mental functions.

"Placebo" An inactive substance or sham form of a therapy administered as a control in testing experimentally or clinically the efficacy of a biologically active preparation or procedure.

"Pre-clinical Studies" Biomedical studies not performed on human study participants.

"Principal Investigator" A person responsible for the conduct of the clinical trial at a trial site who is a physician, dentist or other qualified person, resident in Rwanda and a member of good standing of a professional body. If a trial is conducted by a team of individuals at a trial site, the principle investigator is the responsible leader of the team. See also Sub-investigator.

"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.

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

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

"Reliance" is the act whereby the regulatory Authority in one jurisdiction may take into account and give significant weight to regulatory work performed by another regulatory or trusted institution for purposes of reaching its own regulatory decisions.

"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).

"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 study participant. 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 (SOP)" Detailed written instructions to achieve uniformity of the performance of a specific function.

"Substantial amendment" means change to the terms of the protocol or any other trial supporting documentation that is likely to have significant impact and affect the safety and integrity of trial participants, the scientific value of the research, the conduct or management of the research, and the quality or safety of any investigational medicinal product used in research.

"The law" means Law No. 003/2018 of 09/02/2018 establish Rwanda Food and Drugs Authority and Determining its Mission, Organization and Function.

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

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

CHAPTER ONE: INTRODUCTION

Clinical trials are planned scientific investigations conducted in humans and animals to gather information on the safety and efficacy of medical products and health technologies. Such experiments involve the administration of investigational products in patients, healthy volunteers or animal species to generate data which can later on be used for marketing authorization of a product. The regulatory authority mandated to regulate the conduct of clinical trials in Rwanda is Rwanda Food and Drugs Authority.

These guidelines highlight requirements that need to be followed by Investigators and Sponsors when submitting their applications for approval to conduct clinical trials in Rwanda. Good Clinical Practice (GCP) principles and other ethical considerations are also detailed with the aim of ensuring that trial participants are protected and safeguarded against any harm that might arise as a result of participating in clinical trials.

The guidelines are arranged in a modular format as adopted from the ICH guidelines to allow consistent and uniform documentation of submissions. These will in-turn pave-a-way for speedy assessment of applications by the Authority and ultimately decisions on approval/non-approval based on clear and transparent criteria.

These guidelines have been developed and updated to assist applicants to compile clinical trial application dossier for authorization to conduct clinical trials in Rwanda. The clinical trial application dossier is divided into three different modules as follows:

a) **Module I:** administrative and protocol-related information about the trial;
b) **Module II:** Information related to the Quality (Chemistry, Manufacturing, and Control) summaries about the investigational products to be used in the proposed trial;
c) **Module III:** Other Supporting Information.

I.1 SCOPE

The scope of these guidelines applies to the regulatory requirements for clinical trial applications including bioequivalence studies to the Authority for Authorization prior to initiation. They are addressed to investigators, the pharmaceutical industry, Clinical Research Organizations (CROs) and sponsors of clinical trials, whether for academic purposes or for the generation of data, intended for inclusion in the regulatory submissions for investigational products.

A new application for clinical trial conduct in Rwanda is required for the following categories of products/ circumstances:

1. New Medicines, Vaccines and other biological products, herbal medicines, cosmetics, medical devices and diagnostics for which safety/efficacy profile has not been determined;
2. A clinical investigation of a non-CE-marked (Certificate of European) medical device in the following circumstances:
3. The introduction of a completely new concept of device into clinical practice where components features and/or methods of action, are previously unknown;

a) Where a device incorporates materials previously untested in humans, coming into contact with the human body or where existing materials are applied to a new location in the human body, in which case compatibility and biological safety will need to be considered;
b) Where a device, either CE-marked or non-CE-marked, is proposed for a new purpose or function;
c) Where in vitro and/or animal testing of the device cannot mimic the clinical situation

4. Registered medicines, vaccines and other biological products, herbal medicines, cosmetics, medical devices and diagnostics where the proposed clinical trials are outside the conditions of approval. These may include changes to:

    a) Indications and clinical use
    b) Target patient or animal population(s) e.g. age group and race.
    c) Routes of administration
    d) New dosage scheme/regimen.
    e) The intended use of a device(s)
    f) New combination drug products
    g) New drug delivery/release system

5. Academic clinical trials: clinical trial not funded by pharmaceutical or Biotechnology Company for commercial ends but by public-good agencies (usually universities or medical trusts) to advance medicine.

I.2 GENERAL INFORMATION

All applications and supporting documents shall be in one of the official languages used in Rwanda. Data shall be presented in A4 papers either hard copy or electronic format using New Times, font 12. The clinical trial application documents shall be submitted in modules I, II, and III in hard or soft copies in searchable PDF. Extension sheets, tables, diagrams and other supporting documents shall as far as possible be of the same size, well annotated, numbered and appropriately cross-referenced. The information/data must be compiled in accordance with these guidelines. In case the information is required in the application forms its location shall be cross-referenced in the submission.

CHAPTER II: CLINICAL TRIAL APPLICATION PROCESS AND REQUIREMENTS

II.1 Risk identification for clinical trials

II.1.1 Evaluation of potential risks

Risk is the probability of a potential hazard occurring, leading to harm to participants or compromising the reliability of the trial results. Risk can be broken down into three main components:

1. **Risk to Participant' Rights**: This involves ensuring that patients are properly informed about the trial and that informed consent procedures are followed, including protecting personal data.

2. **Risk to Participant s' Wellbeing and Safety**: This covers the safety of the treatment or intervention, the risks involved in diagnostic procedures, and the vulnerability of the trial participants, which could be influenced by factors such as age, social circumstances, or education level.

3. **Risk to Data Integrity and Public Health**: This relates to the quality and management of data, ensuring its accessibility, credibility, and the robustness of the trial design and methods. It also considers the potential impact of trial outcomes on public health.

When assessing risk in clinical trials, the focus should be on the additional or incremental risk to participants compared to the risks they would face if not participating in the trial (e.g., usual care for patients or everyday life for healthy volunteers).

II.1.2 Risk Categories:

Risk categories refer to different levels of risk associated with clinical studies. A limited number of categories are defined, each addressing a specific aspect of risk, such as the safety of the product for participants. This classification is mainly applicable to clinical trials involving medical products. The recommended stratification divides clinical trials into three categories based on the stage of medical product development:

1. **Usual Care (Category A)**: Trials involving authorized medical products that are used as per their marketing authorization.

2. **Modified Use (Category B)**: Trials testing authorized medical products outside the authorized indications. This can be further divided into (a) trials supported by published evidence, guidelines, or medical practices, and (b) trials without such support.

3. **New Product (Category C)**: Trials testing medical products that have not yet been authorized.

This stratification helps in managing the oversight and risk of clinical trials based on the level of novelty and deviation from established medical practices.

II.2 Requirements for Pre-Submission Meeting Application

An application for a pre-submission consultation meeting is optional and shall be made by the sponsor or Principal investigator who submit to the Authority following documents:

a) The cover letter requesting the pre-submission meeting;
b) A brief synopsis of the proposed trial protocol as per ANNEX-VI
c) A list of preliminary questions to be discussed in the meeting;

The Authority will acknowledge the receipt of the application and will confirm the meeting date, venue and time of meeting within fifteen (15) calendar days after the receipt of meeting request. After the meeting, the sponsor should prepare and send to the Authority a written record of the discussions and conclusions of the meeting within 14 calendar days.

II.3 Clinical Trial Application requirements

A Clinical Trial Application for conducting clinical trials in Rwanda including bioavailability studies should be made to the Authority prior to the initiation. The content and format of clinical trial application is composed of three modules:

a) **Module I**: Administrative and protocol related information about the trial;
b) **Module II**: Information related to the Quality (Chemistry, Manufacturing and Control) summaries about the investigational products to be used in the proposed trial;
c) **Module III**: Other Supporting Information.

The contents of each module of clinical trial application dossier are summarized in the table provided below:

Module I	**Administrative Information and Protocol Related Information**
1.1	**Administrative Information**
1.1.1	Signed and dated Clinical Trial Application Cover letter
1.1.2	Signed and dated clinical trial application form (**Doc No: DD/PVCT/FOM/007)**
1.1.3	Valid Ethical Clearance Certificate from Rwanda National Ethics Committee
1.1.4	Curriculum vitae (CVs) of Principal investigator(s) and Co-investigator(s)
1.1.5	Copy of Valid GCP Certificates for both Principal Investigator(s) and co-Principal investigator (s)
1.1.6	Signed and dated Joint declaration between Sponsor & Principal Investigator for sufficient funds in the prescribed format (**Doc No: DD/PVCT/FOM/033**)
1.1.7	Signed and dated declarations by the Principal investigator and/or Co-investigators (**Doc No: DD/PVCT/FOM/034**)

1.1.8	**Valid Local Insurance Policy Covering trial participants**
1.1.9	Signed and dated Sponsor/ Principal investigator contractual Agreement
1.1.10	Letters of Access authorizing Authority to access related files (Drug Master Files, Site Reference Files) must be submitted
1.1.11	Clinical Trial Site Agreement/contract
1.1.12	Collaborative note from Rwanda Biomedical Center for clinical trial on products used under public health programs(HIV,TB, Malaria, etc.),if applicable
1.1.13	Minutes of the discussions and conclusions of the pre-submission meeting or other relevant correspondence with the Authority, if applicable
1.1.14	List of Competent Authorities to which the same application has been submitted and details of decisions, if available
1.1.15	Proof of registration of the trial with a WHO recognized Clinical Trial Registry. Preferably, trials may be registered with the Pan African Clinical Trials Registry (PACTR)
1.1. 1 6	Evidence of payment of prescribed fees
1.2	**Clinical Trial Protocol-related Information**
1.2.1	A copy of the final proposed protocol(s), including the version number. The trial protocol must be signed by the sponsor and the investigator prior to the start of the clinical trial (ICH E6 8.2.2)
1.2.2	A copy of the Informed Consent Forms (ICFs) in English, French and Kinyarwanda signed and stamped by the Rwanda National Ethics Committee that includes a statement regarding the risks and anticipated benefits to the clinical trial participants as a result of their participation in the clinical trial
1.2.3	Copy of Participant Information Leaflet (PIL)
1.2.4	Copy of Case Report Forms (CRFs) to be used for data collection
1.2.5	Capacity building plan including training and updating of staff involved in the trial
1.2.6	Good Clinical Laboratory Practice (GCLP) accreditation certificate
1.2.7	Signed Charter of DSMB and CVs of Members if applicable
1.2.8	Signed and dated Materials Transfer Agreement (MTA) if applicable
Module II	**Information related to the Quality of Investigational Product** (Chemistry, Manufacturing, and Control Summaries)
2.1	Investigational Product (IP) Dossier containing the Quality Overall Summary and showing the chemistry, manufacture, and control (CMC) as per Common technical document (CTD) format in ANNEX-V, non-clinical data, and Data from previous clinical use (if applicable). Non-clinical data reports should be included in the dossier as per the requirements in the latest version of ICH M3.
2.2	A copy of the current Investigator's Brochure (IB), supplemented as appropriate with up-to-date safety, non-clinical, and available clinical data

2.3	Copy of valid Good Manufacturing Practice (GMP) Certificate or Confirmation document of the authority that the manufacturer complies with PIC/S or GMP inspection report or ISO Certificate for medical device/IVD
2.4	A copy of the identification labels for both primary and secondary packaging (outer and inner packaging) of Investigational product labels
2.5	Investigational product package Insert/s for mark if applicable
2.6	Mock-up labels for the Investigational Product(s)
2.7	Copy of the summary of product characteristics (SmPC) or a copy of the certificate of pharmaceutical product (COPP) of the investigational products if applicable
2.8	Copy of Certificate of analysis or certicate/declaration of conformity for the batches of the investigational products to be used in a clinical trial if applicable
2.9	Composition of the placebo (placebo-controlled trials**,** information on the placebo is also required including a description of the manufacturing process, a qualitative and quantitative list of ingredients, specifications, batches, stability and facility information) or diluent if applicable
2.10	Copy of the import authorization in case the investigational product is not imported directly to the trial site
Module III	**Other Supporting Information**
3.1	Additional supporting quality information such as publications
3.2	Literature References

Note:

1. Clinical trial applications requirements shall be considered based on identified risk to the participants including the type, dosage form (if applicable) and the development stage of the proposed investigational product or intervention, population as well as the design of clinical trials.

2. Non-compliance and non-conformity to the regulatory requirements prescribed in these guidelines shall lead to the clinical trial application rejection. The Clinical Trial Application shall be accepted for review if more than 70% of the applicable required documents are provided. This shall include but not be limited to the signed, dated application letter and forms, duly signed protocol, updated IB, proof of payment of applicable fees, declarations, and agreement between the sponsor and principal investigator. Therefore, sponsors, investigators and Clinical Research Organizations (CROs) are encouraged to submit a completed clinical trial application dossier to avoid rejection and delays in the review process.

3. Application for compassionate use of unauthorized investigational products shall follow requirements set out in the latest version of AVAREF Guidance and Considerations on Compassionate Use Access Application for compassionate use of unauthorized investigational products shall follow requirements set out in the latest version of AVAREF Guidance and Considerations on Compassionate Use Access.

Additional requirements for medical devices, or In Vitro Diagnostics(IVDs) or Software clinical investigations.

In addition, the following documentation will be required for clinical trials of medical devices or in Vitro Diagnostics(IVDs) or Software:

1. Device description, intended use, design and materials such as User manual, catalogue of IFU of the device.
2. Marketing status from other countries if applicable
3. Risk assessment and standard list
4. Toxicology and biological safety
5. Sterilization validation certificate if applicable
6. Electrical safety certificate if applicable
7. Safety and usefulness of medicinal substance
8. Safety and appropriateness of use of tissues of animal origin
9. Certificate of ISO/ Quality audit (ISO 13485) for manufacture of the device if applicable.
10. The Investigational product dossier with data compiled in a common submission template (CSDT)
11. Medical devices or Software as medical device classification

II.3.1 Conduct of clinical investigations involving medical devices, In Vitro Diagnostics OR software

The design, conduct, recording and reporting of clinical investigations carried out in human subjects to assess the safety, performance and effectiveness of investigational products should be as prescribed in accordance with international standards and regulations including:

- ISO 14155:2020/Clinical investigation of medical devices for human subjects — Good clinical practice;
- ISO 13485:2016 / Medical devices — Quality management systems — Requirements for regulatory purposes;
- ISO 20916:2019/ In vitro diagnostic medical devices — Clinical performance studies using specimens from human subjects — Good study practice
- ISO 14971:2019/ Medical devices — Application of risk management to medical devices
- Sterilization standards including ISO 11135:2014, ISO 17665:2024, ISO 11137-1:2006, ISO 20857:2010, etc.;
- ISO 10993-1:2018/ Biological evaluation of medical devices;
- IEC 62304:2006/ Medical device software — Software life cycle processes

II.3.2 Submission of clinical trial application dossier and payment

The clinical trial application dossier and invoice payment shall be processed through Rwanda FDA online portal or following any other guidance as provided on the Rwanda FDA official website.

II.3.3 Clinical Trial Protocol

The content and format of the clinical trial protocol and its amendments should comply with the requirements set out in the latest version of the ICH-GCP guidelines. Site specific information may be provided on separate protocol page(s) or addressed in a separate agreement for multicenter clinical trials. The protocol and its amendment should be those reviewed by the Rwanda National Ethics Committee and signed by both sponsor and principle investigator. The clinical trial protocol template **(Doc No: DD/PVCT/FMT/037)** is provided as a guide capturing key section of ICH-GCP guidelines.

II.3.4 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 trial of the product(s) in human participants. The content and format of the Investigator's Brochure (IB) and its updates should comply with the requirements set out in the latest version of the ICH GCP guidelines. The approved summary of product characteristics (SmPC) may be used in place of the Investigational Brochure (IB) if the investigational product is marketed and is used according to the terms of the marketing authorization. If the conditions of use in the clinical trial differ from those authorized, the SmPC should be supplemented with a summary of relevant non-clinical and clinical data that support the use of the IP in the clinical trial.

II.3.5 Informed Consent and Assent

The informed consent informed consent should comply with regulatory requirements and abide with ICH GCP guidelines and the ethical principles that have their origin in the Declaration of Helsinki. Note that, the language used in the ICF shall be in English, French and Kinyarwanda and approved by Rwanda National Ethics Committee.

II.3.6 Ethical Clearance

A valid Ethical Clearance certificate issued by RNEC is required for all phases of clinical trials. The Authority shall give its position after the applicant has submitted ethical clearance. The Authority shall allow parallel submission of clinical trial applications to facilitate the sponsor and principal investigators. In this case, the evidence of submission to RNEC shall be required and any change made to the protocol by RNEC will be submitted to the Authority.

II.3.7 Insurance cover of trial participants.

All trial participants must be satisfactorily insured against possible injuries that must arise during the conduct of clinical trial. The valid evidence insurance policy issued by the local insurance company for participants shall be submitted to Authority prior to the study initiation.

The insurance certificate shall contain at least the following elements:

a) Policy number,
b) Starting date and expiry date,
c) Insured (policy holder/sponsor),
d) Title of insured protocol or protocol number,
e) Number of trial participants and
f) List all events that are covered by the insurance policy e.g. deaths, permanent and temporary impairment of health conditions, etc.

II.3.8 Data and Safety Monitoring Board/Committee (DSMB/C)

An Independent Data Monitoring committee 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. The Sponsor shall include charter of work, membership and curriculum vitae of all the DSMB members when applicable. DSMB shall sign the

charter and copy of updated CVs shall be submitted. It is required that for national clinical trials conducted in Rwanda, at least one member of the Data and Safety Monitoring Board (DSMB) be of Rwandan nationality. In the case of multi-country clinical trials, the DSMB shall include at least one member from the African region where the trial is taking place.

II.3.9 Materials Transfer Agreement (MTA)

Where applicable, an appropriate MTA which defines the rights, obligations and restrictions for the provider (PI) and recipient(s) (External Laboratory) with respect to the materials and any derivatives to be Transferred, as well as any confidential information exchanged with the material shall be provided. The MTA shall specify:

a) The type of materials to be transferred
b) The local laboratory or institution from which the samples shall be transferred
c) The destination of the samples (intermediary and final destination)
d) The type of analyses to be carried out by the recipient(s)
e) Competence of the recipient(s) of the materials for the listed analyses to be carried out

The MTA shall be duly signed and dated by the Sponsor, PI and the recipient(s) of the materials at external laboratory.

II.3.10 Investigational Product (IP) Dossier

The investigational product dossier (IPD) gives information related to the quality of any IP (i.e. including reference product and placebo), manufacture and control of the IP, and data from non-clinical studies and from its clinical use shall be provided according to the ICH CTD format. The applicant shall fill in the summary of the quality of the Investigational product in the Quality Overall Summary as per template **(Doc No: DD/PVCT/FMT/038)** as well as additional Quality information as outlined in the template, should be completed as stipulated in the guidelines.

Any additional information that can support the chemistry, manufacturing and control (CMC) of the Investigational Product including but not limited to non-clinical studies, clinical studies and the relevant batch analysis results should be provided as attachments.

Non-clinical data shall be required together with the application package according to the latest version ICH M3 Non-clinical safety studies for the conduct of human clinical trials. Generally, in many cases where the IP has a marketing authorization, the investigational product dossier is not required and summary of product characteristics shall be sufficient. However, for placebo-controlled studies, a qualitative list of the ingredients in the placebo shall be submitted.

II.3.11 Evidence of Good Manufacturing Practices (GMP) compliance

To support the quality of the investigational product (s), the Authority shall rely and accept a valid GMP certificate or confirmation of GMP compliance or GMP inspection report issued by but not limited to:

a) Stringent Regulatory Authorities/WHO listed authorities;
b) Competent Authority of countries that are standing PIC/s members;
c) World Health Organization (WHO) prequalification program;
d) Authorities operating at least at maturity level 3(ML3)
e) Competent Authority that has a recognition agreement with the Authority;
f) EAC Joint GMP inspection procedure.

In case the investigational product is manufactured in a country whose GMP control system is not recognized by the Authority, but the clinical trial has been authorized by one of the above-stated bodies a, b, c, d, e, and f, the decision from that body may be considered.

CHAPTER III: REQUIREMENTS FOR AMENDMENT AND RENEWAL OF APPROVED CLINICAL TRIAL

III.1 Substantial amendments

The substantial amendment are major changes to the terms of the protocol or any other trial-supporting documentation that is likely to have significant impact and affect the safety and integrity of trial participants, the scientific value of the clinical trial, the conduct or management of the clinical trial, and the quality or safety of any investigational product. All substantial amendment require approval by the Authority.

Sponsors and investigators are required to file Clinical Trial Application Amendment (CTAA) for changes after the approval of original CTA; that will impact on the safety of the trial participants or will affect the analysis and the interpretation of the safety and efficacy of the drug(s) under investigation. CTAA must be filed and approved by the Authority before such amendments are implemented when the proposed amendments to the protocol or investigational product (s):

a) Affect the selection, assessment, or dismissal of a clinical trial participants;
b) Affect the evaluation of the clinical efficacy of the investigational products;
c) Alter the risk to the health of a clinical trial participants;
d) Affect the safety evaluation of the investigational products;
e) Extend the duration of the treatment.

If such amendments are necessary to protect the life of participants, an urgent amendment may be implemented but the investigator shall inform the ethics committee and the Authority of such amendments with immediate communication (e-mail) within 48 hours. An application for approval of the amendment, which clearly identifies the change and the rationale for immediate implementation of the change, shall be submitted within 15 days after the date of implementation of the amendment.

The substantial amendments submitted when the CTA is under review will not be accepted. The sponsor should withdraw the active CTA and submit the amendment as a new CTA. However, non-substantial amendments shall be notified and shall be handled as additional information to the application.

III.2 Non-substantial amendments

The non-substantial amendments shall not require the approval of the Authority, but, shall be submitted as notification including the rationale of the change and supporting document must be submitted within 15 days of the implementation of the change. A line list of all notifications must be submitted along with the annual progress report.
The changes may be implemented and notify to the Authority. The recorded changes shall be availed to the Authority upon request during GCP inspection at the trial site.

III.3 Filing a Clinical Trial Application Amendment

The CTAA (**Doc No: DD/PVCT/FOM/035)** shall be submitted to the Authority in the same way as a new CTA. The regulatory requirements shall differ depending on the type of amendment. The sponsor or principal investigator shall submit the following documents:

a) Signed and dated cover letter of Clinical Trial Application for amendment
b) Copy of the Clinical Trial Approval Certificate
c) Signed and dated clinical trial application form for an amendment
d) Valid Ethical Clearance Certificate from Rwanda National Ethics Committee
e) Copy of the most recently authorized protocol, including version number.
f) Updated protocol highlighting the proposed amendments if applicable
g) Copy of ICF with changes clearly highlighted if the amendment affects the ICF
h) Addendum to the IB describing any new Quality information, if applicable
i) Supporting data as required depending the amendment of quality of the investigational products (revised CMC information with track changes that have been submitted in the initial clinical trial application, and summary of changes on the CMC information) as applicable.
j) Evidence of payment of prescribed fees.

The authority reserves the rights to request any other documents deemed necessary to support the safety of the trial participants.

Note: Each amendment related to an IP and that leads to a new potential risk for the trial participants must be considered as a substantial amendment. However, any IP change that affects the clinical development phase(s) and/ or the replacement or addition of the new IP contrary to the previous approved CTA, shall be considered as a new CTA.
In addition, the responsibility of assessing whether an amendment is regarded as substantial or not lies with the sponsor. Therefore, the sponsor shall notify the Authority of the reasons for, and content of these amendments. The Authority shall however recommend a reassessment of a Sponsor's classification of an amendment when necessary.

III.4 Requirements for Renewal of Clinical Trial Authorization

In case the implementation period of the trial is more than one (1) year, the sponsor or principal investigator apply for renewal of Clinical Trial Authorization to continue the implementation of the trial one (1) month before the expiration of the certificate previously issued. The application shall consist of the following documents:

a) Signed and dated Clinical Trial Application letter for renewal;
b) Copy of the Clinical Trial Approval Certificate to be renewed;
c) Valid Ethical Clearance Certificate from Rwanda National Ethics Committee;
d) Valid Local Insurance Policy Covering trial participants;
e) Copy of protocol and its amendments (if applicable) that is being implemented;
f) Updated investigational brochure if applicable;
g) Updated progress report of the implementation of the trial according to the format provided in the specific guidelines.

In case of the extension of the trial implementation period, the applicant shall provide justification, all above-mentioned documents, and any other documentation deemed necessary by the Authority.

III.5 Application for import of Investigational Products

The sponsor or principal investigator shall be required to obtain an import permit for importation of Investigational products after authorization of the trial. A copy of the import authorization is required if the investigational product is not directly imported from the manufacturing country to the trial site.

The full requirements for importation and exportation of IP are detailed in guidelines for importation and exportation of Pharmaceutical products. In case of exportation of leftover for the Investigational Products after the completion of the trial, the sponsor or principal investigator shall obtain export permit or destruction certificate from the Authority.

III.6 Requirements for labelling and blinding of Investigational Products

The following information shall be labelled on the carton, inner label and the blisters or strips of the investigational drug product for a clinical trial:

Parameters	**Unit carton or subject kit**	**Inner Labels**	**Blister/Strips/ Vials**
Clinical Trial Protocol Number	√	√ *	√
No, of Subjects or Initial of subject	√**	√**	√**
Investigational Drug Product name or code	√	√	√
Dosage form	√	√*	√**
Name of Active substance	√	√	√
List of excipients	√	√*	√*
Strength	√	√	√
Instructions for use	√**	√ **	√**
Lot number	√**	√	√
Batch number	√	√**	√**
Manufacturing date	√	√**	√
Expiry date	√	√	√
For clinicalTrial use only/Cautionary statement	√	√*	√
Name and address of Manufacturer	√***	√***	√***
Route of administration	√	√	√
Storage condition	√	√	√
Pack size (Unit/Vol)	√	√	√

NA Not Applicable
* Exempted for small label such as ampoule and vial.
** Where applicable
*** With letter of authorization where it applies

If the product is supplied without an outer carton, the information that is required on the outer carton should be stated on the inner carton. In blinded trials, the coding system for the investigational product(s) should include a mechanism that permits rapid identification of the product(s) in case of a medical emergency, but does not permit undetectable breaks of the blinding.

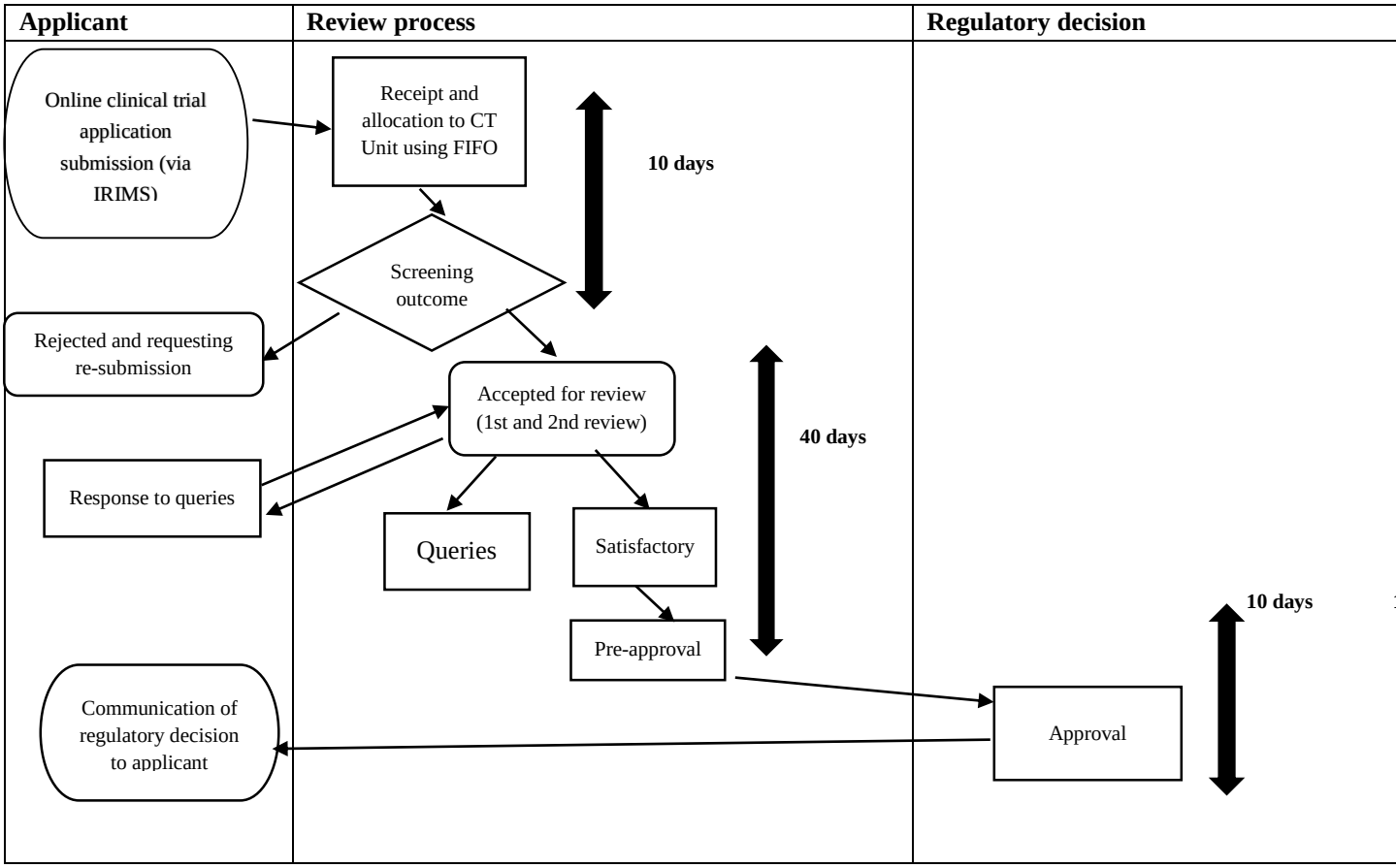
ENDORSEMENT OF THE GUIDELINES

	Prepared by	**Checked by**		**Approved by**
Title	**Division manager**	**Head of Department**	**QMS Division Manager**	**Director General**
Names	Mr.Lazare NTIRENGANYA	Dr. Védaste HABYALIMANA	Ms. Marie Ange Uwase	Prof. Emile BIENVENU
Signature				
Date				

APPENDICES

APPENDIX I: CLINICAL TRIAL APPLICATION PROCESS FLOW

RWANDA FDA Rwanda Food and Drugs Authority	**Title: CLINICAL TRIAL APPLICATION REVIEW PROCESS FLOW CHART**	Doc. No	:DPT/DIV/CHT/XXX
		Revision Number	:
		Effective Date	:DD/MM/YYYY
		Review Due Date	: D/MM/YYYY



	Prepared by	**Checked by**	**Approved by**
Names and Title	Mr. Lazare NTIRENGANYA	Mrs. Marie Ange UWASE	Dr. Védaste HABYALIMANA
Signature and Date			

APPENDIX II: Clinical Trial Designs

I. Based on control group presence:

Uncontrolled Trials: Efficacy/toxicity compared in a single group, with no control. Typically used in Phase I/II for dose tolerance or pharmacokinetics.

Controlled Trials: Study group compared to a control group (placebo or active treatment). Common in Phase III.

II. Based on participant allocation method:

Non-Randomized Trials: Investigator assigns participants to treatment/control groups.

Randomized Controlled Trials (RCTs): Participants randomly assigned to treatment/control groups, using randomization tools (e.g., computer-generated sequences) to prevent bias.

III. Based on participant/investigator awareness:

Open-Label Studies: Both participants and investigators know the assigned group, possibly introducing bias.

Blind Studies: Reduces bias by keeping participant/investigator group assignments concealed.

Single-Blind: Participants unaware of their group, but investigators know.

Double-Blind: Neither participants nor investigators know the group assignments.

IV. Based on result significance:

Superiority Trials: Aimed at demonstrating that the investigational drug is superior to the control.

Equivalence Trials: Aimed at showing that the investigational drug is similar to the control.

Non-Inferiority Trials: Aimed at proving the investigational drug is not worse than the control.

V. Based on treatment structure:

Parallel Trials: Each group receives one treatment for comparison.

Cross-Over Trials: Each participant receives all treatments sequentially, with potential ethical concerns about switching effective treatments.

Sequential Trials: Patients allocated to investigational/control groups in pairs, with sample size determined based on accumulating results**.**

APPENDIX III: Phases of Clinical

Trials Phase I

These are the first trials of a new active ingredient or new formulations in man, often carried out in healthy volunteers. Their purpose is to establish a preliminary evaluation of safety, and a first outline of the pharmacokinetic and, where possible, a pharmacodynamics profile of the active ingredient in humans. These trials are tested in a small group of people between 20 to 100 health volunteers.

Phase II

These trials are performed in a limited number of subjects and are often, at a later stage, of a comparative (e.g. placebo-controlled) design. Their purpose is to demonstrate therapeutic activity and to assess short-term safety of the active ingredient in patients suffering from a disease or condition for which the active ingredient is intended. This phase also aims at the determination of appropriate dose ranges or regimens and (if possible) clarification of dose response relationships in order to provide an optimal background for the design of extensive therapeutic trials. These trials are tested in a larger group of people generally 100–300 participants with a specific disease.

Phase III

Trials in larger (and possibly varied) patient groups with the purpose of determining the short and long- term safety/efficacy balance of formulation(s) of the active ingredient, and of assessing its overall and relative therapeutic value. The pattern and profile of any frequent adverse reactions must be investigated and special features of the product must be explored (e.g. clinically-relevant drug interactions, factors leading to differences in effect such as age). These trials should preferably be of a randomized double-blind design, but other designs may be acceptable, e.g. long-term safety studies. Generally, the conditions under which these trials are carried out should be as close as possible to normal conditions of use generally in 300 to 3,000 volunteers who have the disease or condition.

Phase IV

Studies performed after marketing of the pharmaceutical product. Trials in phase IV are carried out on the basis of the product characteristics on which the marketing authorization was granted and are normally in the form of post-marketing surveillance, or assessment of therapeutic value or treatment strategies. Although methods may differ, these studies should use the same scientific and ethical standards as applied in premarketing studies. After a product has been placed on the market, clinical trials designed to explore new indications, new methods of administration or new combinations, etc. are normally considered as trials for new pharmaceutical products.

APPENDIX IV: List of possible amendments to an approved trial

CHANGES RELATED TO CLINICAL PROTOCOL		
#	**Example of changes include but are not limited to the following:**	**Type**
1	Changes to eligibility criteria, tests or procedures for selecting the study population, tests or procedures required for the ongoing assessment of safety and /or efficacy of clinical trial participants. This includes protocol changes as a result of serious unexpected ADRs;	Amendment
2	Study design, study population, objectives, or hypotheses, including adding or discontinuing a study arm that was not included as a provision in the original CTA protocol;	Amendment
3	Changes in the primary efficacy endpoint(s), important secondary efficacy endpoints (e.g., those that could be used in support of a marketing application), safety endpoints, sample size estimation, or addition of interim analyses that will affect the analysis and interpretation of the study results;	Amendment
4	Dose level, dosage schedule, or treatment duration;	Amendment
5	Changes to the post-treatment follow-up period that may affect the safety evaluation of the drug.	Amendment
6	Adding or removing a concomitant medication, which may impact on the analysis of efficacy or increase the risk to clinical trial participants;	Amendment
7	Criteria for expedited reporting of severe expected; and serious unexpected adverse drug reactions;	Amendment
8	Increases in blood volume, changes in procedures, enrolling additional subjects in PK studies or confirmatory testing in PK studies that were not specified in the original CTA protocol;	Amendment
10	Increasing the screening period or other administrative changes to accommodate logistical constraints in study conduct that do not affect the safety of the trial participants	Notification
11	Minor changes to the inclusion and exclusion criteria, such as laboratory chemistry cut-off values that reflect clinical practice and improve the safety of clinical trial subjects;	Notification
12	Changes to administrative information such as Sponsor, PI or CRO contact names and organizations, or other entities, involved in the conduct of the trial	Amendment
13	Updating the ICF with new information that does not require a protocol amendment;	Notification
14	Annual Investigator Brochure updated with new information that does not require a protocol amendment	Notification
15	Changes to the quality information that does not affect the quality or safety of the investigational product	Notification

	DRUG SUBSTANCE (Biologics and Radiopharmaceuticals)	
#	**Example of changes include but are not limited to the following:**	
1	Replacement or addition of a manufacturing site involving:	
	a. production of the starting material, intermediate, or drug substance	Amendment
	b. testing	Amendment
2	Change in the manufacturing process for the drug substance intermediate, involving:	

	a. the fermentation process [for example (e.g.), scale-up, new bioreactor technology, use of new raw materials of biological origin]; or change in the route of synthesis of the radiopharmaceutical drug substance or critical component*	Amendment
	b. the purification process (e.g., addition/removal/replacement of a purification step)	Amendment
3	Change in the specifications for the drug substance involving:	
	a. deletion or replacement of a test, relaxation of an acceptance criterion or addition of a test for a new impurity	Amendment
	b. addition of a test (other than a test for new impurity) or tightening of an acceptance criterion	Notification
4	Change in the primary container closure system(s) for the storage and shipment of the drug substance provided the proposed container closure system is at least equivalent to the approved container closure system with respect to its relevant properties, and the change does not concern a sterile drug substance	Notification
5	Change in the shelf life for the drug substance, involving:	
	a) Extension i) if the approved shelf life and supporting stability data provided up to18 months	Amendment
	ii) if the approved shelf life and supporting stability data provided beyond 18 months	Notification
	b) Reduction (due to stability concerns)	Amendment
DRUG PRODUCT (Biologics and Radiopharmaceuticals)		
#	**Type of Change**	**Type**
1	Replacement or addition of a drug product manufacturing site involving:	
	a. production of a drug product (including primary packaging)	Amendment
	b. secondary packaging	Amendment
	c. testing	Amendment
2	Change in the drug product manufacturing process (e.g., scale-up, changes to the formulation process); change from manual synthesis of positron-emitting radiopharmaceutical to use of automatic synthesis unit or change in type.	Amendment
3	Deletion of a drug product manufacturer / manufacturing site, primary or secondary packaging site or testing site	Notification
4	Change in the specifications for the drug product, involving:	
	a) deletion or replacement of a test, relaxation of an acceptance criterion or addition of a test for a new impurity	Amendment
	b) addition of a test (other than a test for new impurity) or tightening of an acceptance criterion	Notification
5	Change in the shelf life for the drug product, involving:	
	a. Extension i) if the approved shelf life and supporting stability data provided up to18 months	Amendment
	ii) if the approved shelf life and supporting stability data provided beyond 18 months	Notification
	b. Reduction (due to stability concerns)	Amendment
6	Change in the storage conditions for the drug product	Amendment

7	Changes in final product dosage form (e.g., liquid to lyophilized formulation)	Amendment
8	Changes in final product strength	Amendment
9	Change in diluent, involving replacement or addition of a diluent for a lyophilized powder or concentrated solution	Amendment
10.	Change in radiolytic protective agent or antioxidant	Amendment
DRUG SUBSTANCE (Pharmaceuticals)		
#	**Type of Change:**	**Type**
1	Replacement or addition of a manufacturing site involving:	
	a. production of drug substance	Amendment
	b. testing	Amendment
2	Change in the manufacturing process for the drug substance intermediate or starting material (e.g., reaction conditions, solvents, catalysts, synthetic routes, reagents, etc.)	Amendment
3	Change in the batch size for the drug substance (no impact on quality)	Notification
4	**Change in the specification for the drug substance involving test and acceptance criteria:**	
	a. Deletion or replacement of a test, relaxation of an acceptance criterion, or addition of a test for a new impurity	Amendment
	b. addition of a test (other than a test for a new impurity) or tightening of an acceptance criterion	Notification
5	Change in the re-test period (or shelf life) for the drug substance, involving:	
	a. Extension i. if the approved shelf life and supporting stability data provided up to18 months	Amendment
	ii. if the approved shelf life and supporting stability data provided beyond 18 months	Notification
	b. Reduction (due to stability concerns)	Amendment
DRUG PRODUCT (Pharmaceuticals)		
1	Addition of a dosage form or strength	Amendment
2	Change in the composition of a dosage form	Amendment
3	Qualitative or quantitative addition, deletion or replacement of a colour or flavour with no negative impact on stability	Amendment
4	Change in diluent, involving replacement or addition of a diluent for a lyophilized powder or concentrated solution	Amendment
5	Replacement or addition of a drug product manufacturer / manufacturing site involving:	
	a. Production of an immediate release drug product (tablet, capsule, liquids, semi-solids) to a new Manufacturer	Amendment
	b. Production of a modified release product	Amendment
	c. Production of a sterile drug product	Amendment
	d. Primary packaging (non-sterile products)	Amendment
	e. Testing (e.g., release, stability)	Amendment

6	Change in the drug product manufacturing process	Amendment
7	Change in the specification for the drug product tests and acceptance criteria, involving:	
	a. Deletion or replacement of a test, relaxation of an acceptance criterion, or addition of a test for a new impurity	Amendment
	b. addition of a test (other than a test for a new impurity) or tightening of an acceptance criterion	Notification
8	Change in the shelf life for the drug product, involving:	
	a. Extension i. if the approved shelf life and supporting stability data provided up to18 months	Amendment
	ii. if the approved shelf life and supporting stability data provided beyond 18 months	Notification
	b. Reduction (due to stability concerns)	Amendment