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MCA Technical Working Group

Guideline for Clinical Trials in Humans

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1	06 November 2020	New document
2	15 February 2021	Inclusion of Addendum for clarification
3	24 January 2025	Format changed to the current template; editorial changes; principal investigator restricted to medical doctor; DSUR included; non-interventional studies deleted; title of final report and timeline for submission changed; GCP inspection moved to separate guideline.
4	21 February 2025	Editorial changes, inclusion of form for end of CT notification

Comments should be provided by using the template (MCA-F-021/03) for Submission of Comments and sent to info@mca.gm

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Keywords	clinical trial, good clinical practice, GCP, sponsor, principal investigator, ethics committee, clinical trial protocol, informed consent, amendment, investigational product, investigational medicinal product dossier, IMPD, investigator's brochure, development safety update report, DSUR

Guideline for Clinical Trials in Humans

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Abbreviations

ADR	Adverse drug reaction
AE	Adverse Event
AEFI	Adverse Event Following Immunisation
AESI	Adverse Events of Special Interest
AVAREF	African Vaccines Regulatory Forum
CIOMS	Council for International Organizations of Medical Sciences
CRO	Contract Research Organization
CT	Clinical Trial
DSMC	Data and Safety Monitoring Committee
DSUR	Development Safety Update Report
EC	Ethics Committee
EEG	Electroencephalogram
ECG	Electrocardiogram
EU	European Union
EUDRACT	European Union Drug Regulating Authorities Clinical Trials
GCP	Good Clinical Practice
HLT	High Level Terms
IB	Investigator Brochure
ICH	International Council for Harmonisation
ICSR	Individual Case Safety Report
IMP	Investigational Medicinal Product
IRB	Institutional Review Board
IEC	Independent Ethics Committee
LICT	Low-Interventional Clinical Trials
MAH	Marketing Authorisation Holder
MCA	Medicines Control Agency
MSEC	Medicines Safety Experts Committee
NRA	National Regulatory Authority
PL	Package Leaflet
PSUR	Periodic Safety Update Report
PACTR	Pan-African Clinical Trial Registry
SmPC	Summary of Product Characteristics
SUSAR	Suspected Unexpected Serious Adverse (Drug) Reaction
WHO	World Health Organization

Acknowledgement

We duly thank the African Vaccine Regulatory Forum, the Drug Regulatory Authority of Pakistan, the Danish Medicines Agency and the European Medicines Agency for publishing their guidelines that contributed in several aspects relevantly to the development of this guideline.

1 Introduction (background)

1.1. The value of carefully constructed clinical trials (CTs) as the optimum methodology for the testing and evaluation of new medicines is well recognised.

1.2. This and any further guidelines are developed and in line with country and region-specific guidelines as well as major international CT guidance including guidelines from the Declaration of Helsinki, the Nuremberg code, International Council for Harmonisation, and World Health Organization Good Clinical Practices. The recent updates of ICH on GCP (ICH E6 (R2), ICH E6 (R3)) are considered in the development of national guidelines on CT in the Gambia. Any further changes to the international guidelines and recommendations will be considered and incorporated to the current guideline accordingly.

1.3. GCP compliance is to ensure that the rights, safety and well-being of trial participants are protected, and that the results of the clinical trial are reliable.

1.4. Therefore, all stakeholders involved in the initiation, financing, management and conduct of clinical trials such as sponsors, investigators, clinical research organisations (CROs) and all relevant institutions are required to comply with GCP.

1.5. This guide follows the aforementioned standards, including the International Council for Harmonisation Good Clinical Practice (ICH-GCP) Guidelines, International Ethical Guidelines for Biomedical Research Involving Human Subjects issued by the Council for International Organizations of Medical Sciences (CIOMS) and the ethical principles set forth in the Declaration of Helsinki, CIOMS III, VI Working Groups recommendations, and European and FDA guidelines. The guidelines on CTs from WHO Listed Authorities (US FDA, EU/EEA, Singapore) were adopted and adapted in this guideline.

1.6. This guideline is addressed to investigators and sponsors of CTs whether for academic purposes or for generation of data for inclusion in the application for marketing authorisation pre-authorisation (Phase I-III) of a medicine or to gather further insight into a medicine already in the market (post-authorisation phase of the product life-cycle – Phase IV). The guide is available in an open access and can be used by all the relevant stakeholders, including volunteers and patients, investigators and their site staff, pharmaceutical companies and marketing authorisation holders (MAH), other clinical research sponsors and their representatives, NRAs and public health communities, IRBs/IECs members and Data and Safety Monitoring Committees (DSMCs).

1.7. It provides guidance to sponsors and investigators on the procedures for applications and conduct of clinical trials in The Gambia including reporting to the Medicines Control Agency (MCA).

1.8. This guideline can support reliance and mutual recognition procedures for CTA assessment and review of safety and efficacy outcomes of CTs between countries that apply the same standards and procedures.

2 Legal basis

2.1. The regulation of clinical trials of medicines and related products in The Gambia is governed by the provisions and requirements of the Medicines and Related Products Act, 2014 ("Act").

2.2. Part VII of the Act, *Clinical Trials and Safety Monitoring*, requires that a person shall not conduct a clinical trial of a medicine or related product without the written authorisation of the Agency.

2.3. The Medicines and Related Products Regulations, 2020 ("Regulations") details the legal requirements for clinical trial oversight.

2.4. The clinical trial of any investigational product (IP), placebo or comparator may only be conducted on humans in The Gambia where:

a) the foreseeable risks and inconveniences are medically justifiable when compared with the benefit on the participant, and the anticipated significance of the investigational product for the advance of medical science; and

b) unjustifiable harmful effects on the health of a third person and the environment, are not to be expected if the clinical trial consists of genetically modified organism, a combination of genetically modified organisms, contains any other organisms;

c) the trial participant-

i is an adult and has been informed in a language that he or she understands, of the nature, significance and implications of the clinical trial,

ii has provided voluntary written informed consent with a signature or a thumb-print on the consent form,

iii is a minor or an incapacitated person, and his or her parents or legal guardians have been informed of the nature, significance and implications of the clinical trial and have provided a written voluntary informed consent and assent,

iv is informed of his or her right to withdraw from the clinical trial at any time,

v is provided with an information sheet with the risks associated to the clinical trials,

vi undergoes a counselling session with an investigator or a person designated by the investigator, and

vii is informed of the purpose and scope of the collection and use of personal data, especially medical data for the purposes of the trial.

viii is unable to read or write English, the informed consent shall be obtained in the presence of at least one impartial witness. The witness, who shall be able to read and write English and understand the local language in which the trial participant is informed, shall not be a member of the investigating team. The consent given by the trial participant shall be documented in writing, dated and

signed by the witness and thumb printed or signed by the trial participant.

d) a declaration of consent to participate in a clinical trial, may be revoked orally or in writing at any time without prejudice to the trial participant, and the data collected and stored data may continue to be used where necessary;

e) the trial is conducted in a high-quality facility by a qualified PI in a professional manner who possesses the required educational training and professional experience to be determined by the Agency to conduct a clinical trial;

f) insurance coverage is provided for the trial participant in the event of an injury or death related to the clinical trial;
Note: The sponsor and PI shall ensure appropriate insurance cover for clinical trial participants. The insurance policy shall grant specific cover associated with the reimbursement of damages and death caused to participants by the clinical trial activities throughout the entire study period, thus covering any civil liability of investigators and sponsor of the clinical trial. Trial participants should be informed about medical insurance provision during the CT. Information should be provided by Sponsor/PI.

g) advantages are not granted to the trial participant with the exception of adequate compensation;

h) a medical doctor is responsible for the enrolment and medical care of the trial participant.

2.5. The principal investigator shall be resident in The Gambia, be a medical doctor registered with the Medical and Dental Council in The Gambia (MDCG) and have sufficient education, training and experience in the conduct of clinical trials (e.g. acted as PI or as an investigator in at least one prior clinical trial). In case of a multi-centre trial the Coordinating Investigator, also called Chief Investigator, does not have to be resident or registered medical doctor in The Gambia.

If the PI is absent from the site, he/she must delegate his/her duties in writing to an adequately trained and experienced investigator, who shall be a registered medical doctor with MDCG.

2.6. A **person** (PI, investigator, study pharmacist, study nurse, monitor, any other study staff and any other stakeholder) involved in a clinical trial of an investigational product on humans, shall fulfill the requirements of:

a) Good Clinical Practice provided under the International Council for Harmonisation Guideline for Good Clinical Practice E6 (R2) ("ICH-E6 GCP-Guideline"); or its subsequent versions (E6 (R3)) etc.

b) The WHO guidelines for Good Clinical Practice for trials on pharmaceutical products; and

c) any other requirements to be determined by the Agency.

2.7. If a marketing authorisation by MCA for a novel medicine or related product is anticipated, the pivotal clinical trials may be conducted in The Gambia. At least the safety and efficacy of the medicine or related product should have been established in previous clinical trials involving participants of similar ethnic or environmental background to the intended population in The Gambia.

2.8. The Agency charges non-refundable fees for clinical trials, including applications, protocol amendment(s) and IP import permit clearance as specified in the in the MCA Fee Schedule published in the *Gazette*. Evidence of payment as bank transfer should be submitted alongside the respective application. Note that any application not accompanied by the requisite proof of completed payment will not be given consideration.

2.9. Applicants are required to familiarise themselves with this document and the above stated Act and Regulations before applying for a clinical trial.

3 Scope

3.1. This guideline applies to any investigational product, placebo or comparator to be used in a clinical trial as defined in this guideline, the Act and Regulations; whether they are unauthorised or marketed products, including observational Phase IV clinical studies (e.g. Post Authoriation Safety Studies and Post Authorisation Efficacy Studies), and to non-investigational products used in the context of a clinical trial (auxiliary medicines).

4 General Conditions for Clinical Trials

All persons involved in review and approval, preparation, conduction and evaluation of CTs following by handling of the data in CTs and publication of the results, should comply with the ICH GCP, The Declaration of Helsinki and the national law and regulations on CTs and international guidelines with the purpose to safeguard the individual and public health and human rights for the population of The Gambia.

4.1 Classification of Clinical Trials

4.1.1. Clinical trials of medicines in humans are generally classified into Phases I to IV. It is not possible to draw distinct lines between the phases, and diverging opinions about details and methodology do exist. A brief description of the individual phases, based on their purposes as related to clinical development of medicines, is given below:

Phase I

4.1.2. These are the first trials of a new active ingredient or new formulation in humans, often carried out in healthy volunteers (20-100). Their purpose is to establish a preliminary evaluation of the safety, and the pharmacokinetic and, where possible, a pharmacodynamic profile of the active ingredient in humans.

Phase II

4.1.3. These trials are performed in a limited number of participants (100-300) 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 participants suffering from a disease or condition (or to prevent the disease or condition in case of vaccines) 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

4.1.4. These are trials in larger (300-3000) and possibly varied participant 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 randomised 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

4.1.5. These are interventional or observational studies performed after marketing of the medicine. Trials/studies in phase IV are carried out on the basis of the product characteristics for which the marketing authorisation 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.
Note: After a product has been placed on the market, clinical trials designed to explore new indications, new methods of administration, new combinations, etc. are normally considered as trials for new medicines.

4.2 Application for a Clinical Trial Authorisation (CTA)

4.2.1. Before commencing a clinical trial in The Gambia, the applicant must obtain a favourable opinion from a nationally established health research Ethics Committee and approval from MCA. An application for a clinical trial can be made to the Ethics Committee and the Agency in either a parallel or sequential submission.

4.2.2. An application for the authorisation of a clinical trial shall be made in writing via a completed application form (MCA-F-501/01) available from the MCA website www.mca.gm, dated and signed by the applicant and accompanied by a cover letter.

4.2.3. The duly signed cover letter shall be addressed to the Executive Director, Medicines Control Agency, Off Bertil Harding Highway, Kotu East, Kanifing Municipality, P.O. BOX 3162, Serekunda, The Gambia.

4.2.4. All documentation submitted shall be in English. If documents are written in another language, including e.g. product information for auxiliary medicines, a certified translation is required.

4.2.5. The documents must be submitted electronically in searchable PDF files provided by email or on a DVD/CD-ROM or USB flash drive and in hard copy, one (1) of each document.
Note: The application will only be processed after receipt of the hard copies of the documents.

4.2.6. The documents should be provided in an organised and structured manner clearly indicating the contents of the application dossier.

4.2.7. The applicant shall submit the following documents as part of the clinical trial application dossier:

a) **Clinical Trial Protocol** and Protocol Synopsis whose contents and format should follow the requirements as laid down in the International Council for Harmonisation Guideline for Good Clinical Practice. It shall include site specific addendums and be signed and dated by the sponsor or sponsor's representative and PI showing their agreement and committment to the protocol.

   i. The protocol should contain a statement that the trial will be conducted in compliance with the protocol, ICH GCP and the applicable national and international regulatory requirements and guidelines. If the protocol does not contain such statement or if it contains the statement but is not signed and dated by both parties, a corresponding declaration, signed and dated by both parties shall be provided to the MCA with the application.

   ii. The name, position and full contact details of the **Sponsor/CRO**.

   iii. The name, position and full contact details of the **PI** and Chief Investigator who will be responsible for the site(s) where the trial is to be conducted in The Gambia.

b) **Schematic diagram or flow-chart** of trial design, procedures and stages, if not contained in the protocol.

c) Electronic copies of literature that are relevant to the clinical trial, and that provide background for the clinical trial.

d) **Favourable opinion of the Ethics Committee**. In case of parallel submission, a copy of the application letter to the Ethics Committee and favourable opinion when received including updated versions of documents or information as requested by the Ethics Committee.
Note: The Agency can reach a decision on the application for a clinical trial only when those documents are provided and the favourable opinion of the Ethics Committee is provided.

e) **Informed consent form, assent form(s) and participant information sheet** as applicable, and its translation into local languages, where applicable (e.g. audio translation, adapted pictorial images for children, etc).

f) Copy(ies) of recruitment advertisement(s) and questionnaires, if applicable.

g) **Certificate of Insurance Cover** as evidence of insurance cover for participants and proof of indemnity provision for investigators and trial site (see Sponsor Indemnification for Sites and Investigators template, MCA-T-501/04) or equivalent. Information on Insurance company to be provided and should be Registered in The Gambia.

h) Signed joint **financial declaration** between the sponsor, funding body, if applicable, and the PI concerning sufficient funds to complete the study (see Declaration of sufficient funds, MCA-F-501/05) or equivalent. Where the clinical trial is sponsored by an **individual**, the applicant shall prove the availability of funds to conduct the trial like:

   - co-sponsoring by an institution recognised by the Agency where applicable; and
   - any other conditions as determined by the Agency.

i) **Documentation on the products (including donations) used in the trial**.

i. **Investigator's Brochure (IB)** whose contents and format should follow the requirements as laid down in the International Council for Harmonisation Guideline for Good Clinical Practice. It shall contain a description and brief summary of the relevant chemical, physical and pharmaceutical properties of the IP, and a compilation of the nonclinical and clinical data on the IP relevant to the clinical trial to allow investigators to reach a decision on the safety of its use in the proposed clinical trial. The IB should be reviewed at least annually and submitted to MCA.
Note: If the IMP is used in accordance with the marketing authorisation (registration), an IB and IMPD are not required.

ii. **Investigational Medicinal Product Dossier (IMPD)** or equivalent, as applicable; it shall give detailed information on the quality of any investigational medicinal product including the manufacture and its controls, and data from non-clinical studies and from previous clinical studies, if any. The non-clinical and clinical information shall include data providing sufficient detail to allow assessors to reach a decision on the potential toxicity of the investigational medicinal product. If the IMP is a placebo, the information requirements shall be limited to quality data.
Note: The IMPD can be submitted directly by the sponsor to the MCA for confidentiality reasons.

iii. **Summary of Products Characteristics (SmPC)** or equivalent professional product information for all marketed products used in the trial; if the IMP is used in accordance with the marketing authorisation (registration), an IB or IMPD is not required. If a comparator other than placebo is used that is not a marketed, registered product in The Gambia, a justification is required.

iv. Synopsis of previous trials with the investigational product(s), if applicable and not contained in the protocol or IB.

v. **Good Manufacturing Practice (GMP)** certificate(s) for the manufacturer(s) of the IMPs, Comparator and Placebo, which must be issued from the National Regulatory Authority of the country where the investigational medicinal products, including comparator and placebo, are manufactured. If the GMP certificate is not available for justifiable reasons, sufficient information must be provided that will satisfy the Agency that the product has a defined quality and is safe, stable and consistent.

vi. **Certificates of Analysis** (CoA) for each batch of the IMP(s), Comparator and Placebo.

vii. Product information and CoA for each batch of rescue medications.

viii. Details and, sample of the labelling of the IP, Comparator and Placebo if not provided with the clinical trial protocol.

j) **Documentation on the investigators**.

i. **Signed declaration** by the **principal investigator** (see Declaration and Workload of Principal Investigator, MCA-F-501/02) or equivalent that includes a statement on his/her performance, compliance and on any condition that may influence his/her impartiality and information on his/her current workload.

ii. **Signed declaration** by all (**other) investigators** (see Declaration -Investigator MCA-F-501/11) named in the protocol (e.g. coordinating investigator, clinical trial coordinator, research clinicians, contract research affiliate(s), if applicable, etc), that includes a statement with any condition, that may influence their impartiality; they must have no conflict of interest and no history of GCP serious and/or persistent noncompliance or malpractice.

iii. Signed **Curriculum Vitae** in a format recommended by MCA (see CVs MCA-T-501/03) or equivalent and copies of the educational certificates (qualifications) for all key personnel named in the clinical trial protocol participating in the conduct of the clinical trial including contract research affiliate(s), if applicable. The investigators have to show evidence of previous training or experience obtained from work with clinical trials and/or patient care.

iv. **Good Clinical Practice (GCP) certificates** (not older than two years at the time of application) and proof of training or experience in other relevant areas in accordance with the delegated tasks and duties for all trial staff.

v. Proof of registration of the PI and key study staff with a professional statutory body, if applicable.

k) Details of the location where the trial is to be conducted including:

- a statement on the suitability of the clinical trial site relating to the nature and use of the investigational product, and
- a description of the suitability of the facilities, equipment, human resources and expertise to be issued by the head of the clinic/hospital or institution or another responsible person of the clinical trial site (medical superintendent or medical officer); the statement can be included in the cover letter, as appropriate.

l) Licence or equivalent of central and local laboratories to be used in the clinical trial, evidence of appropriate laboratory quality management systems or valid certificates of accreditation and normal ranges to be used for assays of clinical samples.

m) **Material Transfer Agreement (MTA)**, if external laboratories will be used to analyse samples.

n) Proof of registration on the **Pan African Clinical Trials Registry (PACTR)** is mandatory prior to trial approval. Also, registration in any other international CT registry such as EUDRACT, Clinicaltrials.gov is optional though preferable.

o) **Data Safety Monitoring Committee** (DSMC) charter and composition, where applicable.

p) **Summary** of the clinical trial (100-150 words) to be made publicly available on the MCA website.

q) Case Report Form, patient's/participant´s Diary, patients/ participant Reminder Card, Questionnaires, Advertisement materials for CT, where applicable.

4.2.8. The following should be submitted to the Agency once the trial is authorised and before database lock:

- Data Management Plan;
- Statistical Analysis Plan; and
- Plan for publication.

4.2.9. The MCA may ask the applicant to supply other information as may be additionally required to enable reaching a decision on the application.

4.3 Clinical Trial Protocol

4.3.1. According to Part I (2) of the Regulations, the clinical trial protocol is 'a document that describes the objectives, design, methodology, statistical considerations and organisation of a trial'. Thus, the protocol shall provide the background and rationale for the trial, although these could be provided in other protocol referenced documents.

4.3.2. The protocol shall be identified by the title, the sponsor's protocol number specific for all versions of it (if available), a date and number of version that will be updated when it is amended, and a short title or name assigned to it.

4.3.3. The content and format of the protocol shall follow the requirements as laid down in the International Council for Harmonisation Guideline for Good Clinical Practice and shall thus contain the relevant information for the assessment of the quality, safety, efficacy and the statistical considerations regarding the sample size and required IMP/placebo/comparator for the clinical trial.

4.4 Clinical Trial Amendments

4.4.1. Changes to the approved CT can be made. Depending on the nature of a change, amendments to the trial are regarded as substantial or non-substantial/ minor amendments.

4.4.2. Following cases are not considered as amendments:

- a change to the documentation submitted to the MCA during the ongoing assessment (before approval) of the request for clinical trial authorisation by the MCA, and
- a change to the documentation submitted to the Ethics Committee during the ongoing assessment (before approval) of the request for favourable opinion by the Ethics Committee.

4.4.3. Without prejudice to the points listed below, the Agency reserves the right to direct for an amendment to the clinical trial.

Substantial Amendments

4.4.4. Amendments to a CT are regarded as 'substantial' where they are likely to have a significant impact on the safety or physical or mental integrity of the CT participants, and/or the scientific value of the trial.

4.4.5. A substantial amendment is an amendment:

(a) Which changes a sponsor or principal investigator of the trial or

(b) Which is likely to affect to a significant degree.

(i) The safety, or physical or mental integrity, of any participant of the trial

(ii) The scientific value of the trial

(iii) The conduct or management of the trial; or

(iv) The quality or safety of any investigational product used in the trial.

4.4.6. Substantial amendments to the conduct of the CT may arise from changes to the protocol, study documentation such as participant information sheets, consent forms, questionnaires, letters of invitation, or from new information relating to the scientific documents in support of the trial.

4.4.7. Sponsors are required to submit all substantial amendments of the trial to MCA and EC for approval or acceptance of notification. The sponsor must not implement any substantial amendment before MCA and EC approval or acceptance of notification of the non-substantial amendment, unless the amendment is to protect any participant of a clinical trial against any immediate hazard to the health or safety of the participant (i.e. urgent safety measure). In addition, the sponsor is required to keep records of all substantial and non-substantial amendments to the trial, and provide such records to MCA if requested.

4.4.8. As for any change to a specific clinical trial protocol, the sponsor should make an in-depth analysis of the specific items, degree and scope of change according to the specific trial protocol design, relevant non-clinical and pharmaceutical research results. In addition, the sponsor should evaluate whether the change indeed have a significant adverse impact on the safety, scientific or data reliability of the trial. If so, it should be judged as a substantial change. For example, if the increased dosage does not exceed the safety range suggested by the nonclinical safety studies and existing clinical studies, it is a non-substantial change; if the increased dosage exceeds the safety range suggested by the non-clinical safety studies and existing clinical studies, then it is a substantial change.

4.4.9. Progress reports including safety data as well as annual update of the IB is not necessarily a substantial amendment. However, the PI and sponsor have to verify whether data presented or updates require a change to the documentation submitted with the request for authorisation of the CT. If this amendment is substantial, the rules for approval of substantial amendments apply to these changes.

4.4.10. Any substantial changes to the clinical trial protocol, the trial arrangements or any supporting documents or the IMP or IP shall be approved by the Ethics Committee and MCA before such amendments are carried out. The PI, sponsor or sponsor's representative should apply for amendment to the Ethics Committee at the same time as to the MCA.

4.4.11. If such amendments are necessary to eliminate an immediate hazard to trial participants, the urgent amendment may be carried out and the PI, sponsor or sponsor's representative shall inform the MCA and Ethics Committee by writing as soon as possible but not later than 72 hours.

4.4.12. The submission of amendment(s) shall be indicated in a cover letter signed by the applicant identifying the clinical trial, sponsor and applicant, and shall include:

- A summary of the nature and explanation of the amendment(s);
- Possible consequences for participants already included in the trial; and
- Possible consequences for the evaluation of the results.

4.4.13. The amendment(s) shall be described in a completed Clinical Trial Amendment form (see Protocol Amendment Form MCA-F-501/08) or equivalent, and the new versions of the documents, identified by an updated version number and date, shall be provided.

4.4.14. Where applicable, supporting information shall be included with the submission.

4.4.15. The favourable opinion of the Ethics Committee is required before MCA can reach a decision on an amendment. MCA shall provide the decision within ten (10) working days of receipt of the favourable opinion.

Non-substantial/minor Amendments

4.4.16. Non-substantial/ minor amendments (except substantial) can be implemented immediately by the sponsor and should always be documented and notified to the MCA and the Ethics Committee.

4.4.17. For example, a change of the contact person or in the contact details of the contact person (e.g. a change of e-mail or postal address) is not considered as a substantial amendment, if the sponsor and legal representative remain identical. However, the sponsor should ensure that the MCA is aware of this change as soon as possible, in order to allow the Agency to exercise its clinical trial oversight function. Documentation of non-substantial amendments should also be available on request for inspection at the trial site or the sponsor premises as appropriate.

4.4.18. Non-substantive changes can be made upon being reviewed or put on records by the MCA and the EC.

4.5 Clinical Trials in Case of Emergency Situations

4.5.1. Under certain circumstances MCA may deviate from the routine procedure and accept an expedited application and review process for clinical trials. Examples of such situations are epidemics, pandemics or other urgent public health interests that require fast utilisation of new medicines or related products and/or fast gathering of information on products.

4.5.2. The Ministry of Health shall declare a national public health emergency (PHE) where there is a situation that poses an immediate risk to health or life.

4.5.3. The following documents must at least be submitted in such situations together with a cover letter and a completed application form, both signed and dated by the applicant:

- Clinical Trial Protocol;
- Investigator's Brochure or a corresponding product information containing available chemical, physical and pharmaceutical information about the investigational product, non-clinical and clinical data on safety and efficacy, as available;

- Certificate of Analysis (CoA);
- GMP certificate, if available;
- The name, position and full contact details of sponsor;
- A list of the planned clinical trial site(s) and the planned number of participants at the site(s);
- The name, position and full contact details of the PI who will be responsible for the sites where the trial is to be conducted and shall be-
  - resident in The Gambia; and
  - registered with the Medical and Dental Council in The Gambia (MDCG);
- Proof of current, relevant and appropriate study insurance for all participants or professional indemnity provision for all investigators in the event of an injury or death related to the clinical trial;
- Participant information sheet and informed consent form including assent information, where applicable;
- Recruitment arrangements;
- The favourable opinion of the Ethics Committee and updated version(s) of documents or information as requested by the Ethics Committee, if applicable; and
- Proof of payment of the appropriate application fee.
- Full CT application package should be submitted to the Agency. The acknowledgement of receipt or notification of missing documents to be shared with applicant. Time clock for the assessment starts after the submission of the full dossier accepted by the agency.

4.5.4. Depending on the phase and nature of the trial, the MCA shall prescribe other relevant information to be provided.

4.5.5. The Agency shall upon initial communication with a prospective applicant, and upon receipt of an application, liaise with relevant stakeholders (including relevant ethics and other oversight bodies) to draw an appropriate plan to facilitate a holistic review of an application in a fast-track manner.

4.5.6. The under listed criteria shall be applied in the emergency clinical trial applications for review:

- Epidemiology of the emergency
- Morbidity / mortality associated with the emergency and/or condition understudy
- Supporting scientific data/information available of the investigational product at the time of submission
- Feasibility of the implementation of the trial design within the context of the emergency
- Risk-Benefit impact of the intervention and/or trial design;

4.5.7. The MCA will review expedited application within 21 working days (excluding clock stops).

4.5.8. As part of the application, the sponsor may request an AVAREF Emergency Joint Review Process of the application.-Such applications shall be considered

by the MCA on a case-by-case basis.

4.5.9. Applications for the AVAREF Emergency Joint Review Process shall be submitted at least 14 working days before the proposed date of the joint review.

4.6 Special Pre-Conditions for Clinical Trials

4.6.1. In an emergency where consent cannot be obtained and treatment is required without delay to save the life of the trial participant, restore good health or alleviate suffering, the treatment may be commenced and consent shall be obtained for continued participation.

4.6.2. Where a clinical trial is to be conducted on a minor who suffers or may suffer from a disease, to be treated by the investigational product the-

a) use of the investigational product shall be indicated according to the findings of medical science to save the life of the person, restore health and alleviate suffering, or prevent disease;

b) clinical trial shall be of direct benefit to a group of patients suffering from the same disease as the trial participant;

c) research shall be considered necessary in order to confirm data obtained in clinical trials on other persons or by means of other research methods;

d) research shall relate to a clinical condition from which the minor concerned is suffering or may suffer; and

e) research may cause only a minimal risk and minimal burden to the trial participant.

4.6.3. Where a clinical trial is to be conducted on an adult who is incapable of comprehending the nature, significance and implications of the clinical trial and suffers or may suffer from a disease, to be treated by the investigational product the

a) use of the investigational product shall be indicated, according to the findings of medical science to save the life of the trial participant, restore health and alleviate suffering;

b) research shall relate directly to a life-threatening or highly debilitating clinical condition suffered by the trial participant;

c) degree of burden and the risk threshold shall be defined specifically in the trial protocol and monitored constantly by the investigator;

d) clinical trial may only be conducted if there is a justified expectation that the benefits of the investigational product for the trial participant outweigh the risks;

e) consent by the authorised representative may be provided after he or she has been duly informed; and

f) research shall be absolutely necessary for the confirmation of data obtained from clinical trials conducted on persons capable of granting informed consent or by means of other research methods.

4.7 Application for an observational Phase IV Clinical Study Approval

4.7.1. Before the commencement of an observational Phase IV clinical study like e.g. a post-authorisation safety or efficacy study (PASS/PAES) in The Gambia, the responsible person must obtain a favourable opinion from a nationally established health research Ethics Committee and approval from MCA. An application for such a Phase IV clinical study can be made to the Ethics

Committee and the Agency in either a parallel or sequential submission.

4.7.2. The responsible person is a natural or juristic person responsible for the initiation, organisation, planning, conducting, supervising and financing of the non-interventional study.

4.7.3. An application for the authorisation of such a Phase IV clinical study shall be made in writing via a completed application form (see Application Form MCA-F-501/12) available from the MCA website www.mca.gm, dated and signed by the applicant and accompanied by a cover letter.

4.7.4. The duly signed cover letter shall be addressed to the Executive Director, Medicines Control Agency, Off Bertil Harding Highway, Kotu East, Kanifing Municipality, P.O. BOX 3162, Serekunda, The Gambia.

4.7.5. All documentation submitted shall be in English. If documents are written in another language, including e.g. product information for auxiliary medicines, a certified translation is required.

4.7.6. The documents must be submitted electronically in searchable PDF files provided by email or on a USB flash drive and in hard copy, one (1) of each document.

4.7.7. The applicant shall submit the following documents:

- Observation plan of the Phase IV clinical study;
- Case Report Forms (CRF), patient´s diaries and questionnaires;
- In case of parallel submission, a copy of the application letter to the Ethics Committee and favourable opinion when received including updated versions of documents or information as requested by the Ethics Committee;
- The Summary of the Product Characteristics or other product information of the products under observation.

4.7.8. In case of a substantial amendment the new version of the oberservation plan and other changed documents should be submitted.

4.7.9. The responsible person should submit a study summary report (MCA-F-501/10) or equivalent after six (6) months of the completion of the data collection and analysis.

4.7.10. If products used in the study are to be imported or exported, the responsible person should apply for the import or export in accordance with the MCA *Guideline for Import and Export of Medicines and Related Products* (MCA-GL-103).

Publication

4.7.11. For studies that are fully or partially conducted by investigators who are not employees of the marketing authorisation holder, the marketing authorisation holder and the investigator should agree in advance on a publication policy allowing the investigator to independently prepare publications based on the study results irrespective of data ownership. The marketing authorisation holder should be entitled to view the results and interpretations included in the manuscript and provide comments prior to submission of the manuscript for publication.

4.7.12. In order to allow MCA to review in advance the results and interpretations to

be published, the marketing authorisation holder initiating, managing, or financing a clinical trial should communicate to the Medicines Control Agency the final manuscript of the article within two (2) weeks after first acceptance of publication.

4.8 Application for Low-interventional Clinical Trial Approval

4.8.1. A low-interventional clinical trial (LICT) like e.g. a phase IV clinical trial, is a trial that fulfils the following conditions:

a) The investigational medicinal products (IMP), excluding placebos, are authorised;

b) Their use should be in accordance with the protocol of the Clinical Trial;

c) The IMPs are used in accordance with the terms of the marketing authorisation; or

d) The use of the IMPs is supported by published scientific evidence on the safety and efficacy including high quality data published in scientific journal articles, national, regional or institutional treatment protocols, health technology assessment reports or other appropriate evidence.

4.8.2. A LICT is a trial where the risk is similar to that of standard medical care and/or established medical practice.

4.8.3. Any additional procedures or additional diagnostics and/or monitoring procedures must not pose more than minimal additional burden or risk to the safety of the study participants compared to normal local clinical practice. Examples of minimal additional burden: analysis of saliva, urine, stool samples, measuring weight and/or height, questionnaires, ECG and EEG measurements, blood withdrawal with minimal additional venepuncture or through a pre-existent catheter.

4.8.4. LICTs are used for instance to investigate safety and efficacy questions that have arisen since the issue of marketing authorisation.

4.8.5. LICTs are subject to less stringent rules.

4.8.6. LICT are subject to the same application procedure as any other CT.

4.8.7. The applicant shall submit the following documents:

- Clinical Trial Application Form;
- Cover letter which shall indicate if the CT is considered to be a LICT and shall contain a detailed justification thereof;
- Clinical Trial protocol;
- SmPC of the already authorised investigational medicinal products (IMPs);
- Labelling.

5 Investigational Products (IPs), Investigational Medicinal Products (IMPs)

5.1 Manufacturing of IMPs

5.1.1. IMPs must be manufactured in accordance with the Regulations and internationally recognised current Good Manufacturing Practice requirements, unless

it is justified otherwise and approved by MCA.

5.1.2. It is the responsibility of the sponsor to supply the clinical trial site with IMPs produced in compliance with GMP, where applicable.

5.2 Labelling of IMPs, Placebo or Comparator

5.2.1. The following information should be included on labels of the primary and/or secondary packaging:

a) Reference number allowing identification of the trial, site, PI and sponsor;

b) Medicine(s) to be used by name/identification number, dosage form, route of administration, quantity of dosage units, and in the case of open trials the strength/potency;

c) Trial participant identification number to whom the medicine is to be administered;

d) Name, address and telephone number of the investigator who is the main contact for information on the product, clinical trial and emergency unblinding;

e) Directions in regard to the manner in which such medicine should be used or reference to where this information is provided;

f) Date of dispensing, if applicable and use-by or expiry or re-test date, as applicable;

g) Storage conditions;

h) Batch number or code number;

i) Labelled with "For Clinical Trials Only";

j) "keep out of reach of children" except when the product is for use in trials where the product is not taken home by participants; and

k) Any other information as may be required by the Agency.

5.2.2. If the primary container takes the form of blister packs or small units such as ampoules, the secondary packaging should be provided bearing a label with the required particulars listed above. The primary container should nevertheless bear the following:

- name of the investigator who is the main contact for information on the product, clinical trial and emergency unblinding.
- route of administration (may be excluded for oral solid dosage forms) and in the case of open trials, the name/ identifier of the IP and strength/ potency;
- batch and/or code number to identify the contents and packaging operation;
- a trial reference code allowing identification of the trial, site, principal investigator and sponsor if not given elsewhere;
- the trial participant identification number/treatment number and where relevant, the visit number.

5.2.3. If the IMP is authorised (registered) to be marketed in The Gambia and used in accordance with its approved indications and dosage regimen, MCA may make exemptions from the label requirements as listed in 5.2.1, if justified by

the applicant.

Donated IMPs

5.2.4. If the IMP has been donated it must be manufactured in accordance with the Regulations and internationally recognised current Good Manufacturing Practice requirements, unless it is justified otherwise and approved by MCA. The labelling of the donated IMP must follow label requirements as listed in 5.2.1 & 5.2.2 above.

5.3 Importation and Exportation/Re-exportation of IPs, Placebo or comparator

Importation

5.3.1. If the IP , placebo, comparator or any auxiliary medicine is to be imported, the clinical trial must be approved by the MCA before the import can be permitted. A parallel submission for approval of the clinical trial and permit for the import is possible. In this case, application for import permit can be included in the clinical trial application package.

5.3.2. The protocol title, duration of the CT, sample size and required IPs, placebo comparator or any auxiliary medicine for the clinical should be provided in the application for importation.

5.3.3. IPs, placebo, comparator or auxiliary medicines may only be imported in a quantity as required by the clinical trial.

5.3.4. Authorised or registered IPs, placebo, comparator or auxillary medicines may only be imported if they are not locally available or if the need for importation is otherwise justified.

5.3.5. The import application form (MCA-F-501/06) available from the MCA website: www.mca.gm must be completed and duly signed and dated by the PI or sponsor's representative.

5.3.6. Application for import permit must include at least, the following information:

- The title and identification number of the CT for which the application is made;
- The planned CT sites and the planned number of participants at the sites;
- Description of the IP(s), Placebo or Comparator by name or code, strength and dosage form, as applicable;
- Unit of issue, total quantity, batch number and expiry dates of the product(s);
- Justification of the quantity of the IP , Placebo, Comparator,or auxiliary medicines to be imported relative to the timelines as stated in the CT protocol (sample size, phase of the protocol and duration of the study, reasons for additional supply, if necessary); and
- Letter of authorisation of the CT including the MCA CT number.

5.3.7. The completed application form and required documents can be sent electronically, but a hard copy must be hand delivered or posted to: Executive Director, Medicines Control Agency, Off Bertil Harding Highway, Kotu East,

Kanifing Municipality, P.O. BOX 3162, Serekunda, The Gambia

5.3.8. Approval of an import permit application by the Agency may take up to five (5) working days.

Exportation/re-exportation

5.3.9. If the IP or any auxiliary medicine needs to be exported/re-exported out of The Gambia upon completion of the clinical trial, an approval from MCA is required.

5.3.10. Before exportation or re-exportation, the delivered, used and recovered quantities of IP should be recorded.

5.3.11. Application for export/re-export permit shall be submitted in a letter to the MCA and must include at least, the following information:

- The title, clinical trial identification number and MCA authorisation number of the CT concerned;
- Description of the IP(s) or auxiliary medicine concerned;
- Unit of issue, total quantity, batch number and expiry dates of the products concerned; and
- Justification of the quantity of the IP(s) or auxiliary medicines to be exported/re-exported and reason for export/re-export.

5.4 Repackaging and Re-labelling of IMPs Placebo or Comparator

5.4.1. Approval for repackaging and/or re-labelling of IPs is required from MCA and the reason for it must be provided.

5.4.2. If it becomes necessary to change the expiry/use-by date, an additional label should be affixed to the IP which should state the new use-by date and repeat the batch number. It may be superimposed on the old date, but for quality control reasons, not on the original batch number.

5.4.3. The operation should be performed at an appropriately authorised manufacturing site, but when justified, may be performed at the investigational site by or under the supervision of preferably the clinical trial site pharmacist, or the PI or by the clinical trial monitor(s) who should be appropriately trained.

5.4.4. Further re-labelling or repackaging of IPs may be carried out in health facilities or other clinical trial sites by pharmacists if the IPs are intended to be used exclusively in the facilities taking part in the same clinical trial.

5.4.5. Pharmacists must be registered with the Pharmacy Council of The Gambia and must have at least two years' experience in manufacturing or quality management of medicines or related products.

5.4.6. The repackaging or re-labelling operations of IPs should be performed in accordance with Good Manufacturing Practice principles and specific standard operating procedures and should be checked by a second person.

5.4.7. Repackaging or re-labelling should be properly documented. To avoid mistakes the activities should be carried out in an area which is partitioned or separated from other activities. A line clearance at the start and end of activity should be carried out and reconciliation performed. Any discrepancies observed during reconciliation should be investigated and accounted for before release.

5.5 Disposal of IPs Placebo or Comparator

5.5.1. Before disposal, the delivered, used and recovered quantities of IP should be recorded and an IP(s), placebo or comparator accountability report sent to MCA, reconciled and verified by or on behalf of the sponsor for each trial site and each trial period in The Gambia.

5.5.2. The PI must apply to MCA for approval before destruction, indicating the procedure of disposal and the name, dosage form/strength, batch number, expiry date and amount of the IP to be destroyed and reason for destruction.

5.5.3. Destruction of unused investigational products should be carried out for a given trial site or a given trial period only after any discrepancies have been investigated and satisfactorily explained and the reconciliation has been accepted by the sponsor.

5.5.4. The disposal of investigational products at investigational site(s) in The Gambia shall be recorded and conducted in a professional manner by the PI or sponsor's representative like the clinical trial monitor.

5.5.5. Recording of destruction operations should be carried out in such a manner that all operations may be accounted for. The record of disposal shall clearly identify the batch for disposal, the participant numbers and the quantities to be destroyed.

5.5.6. The disposal exercise must be witnessed by MCA. When destruction of investigational products takes place, the MCA shall issue a dated certificate of, or receipt for destruction, to the sponsor. These documents should clearly identify, or allow traceability to, the batches and/or participant numbers involved and the actual quantities destroyed.

6 Timelines for Clinical Trial Applications

6.1. All clinical trial applications and applications for substantial clinical trial amendments shall be screened by the MCA for completeness.

6.2. MCA shall inform the applicant in writing about the receipt of a valid or complete clinical trial application or amendment within 10 working days from the receipt of the complete application. However, if deficiencies are identified at screening, these would be addressed by a Request for Clarification or a Screening Rejection Letter specifying the formal grounds for non-acceptance, also within 10 working days from the receipt of the application. The applicant shall address formal grounds for non-acceptance within 10 working days.

6.3. The MCA shall inform the applicant in writing about the outcome of the assessment of the clinical trial within a maximum of sixty (60) calendar days after validation of a formally complete clinical trial application, or 120 calendar days if the IP contains a genetically modified organism.

6.4. During evaluation, additional documents or changes may be requested through a query letter. Once a query has been raised and issued to the applicant, the process stops until when MCA receives a written response to the query. If the applicant fails to modify the application correspondingly within a maximum of 30 calendar days, following the reasoned objections, the application shall be deemed to be rejected.

6.5. In general, CT applications should be processed as per the prescribed

timelines presented in the flowchart.

6.6. Applications on substantial amendments to the clinical trial should be processed by MCA within thirty (30) calendar days after submission of all required information and documents.

7 Opinion from the Ethics Committee

7.1. Parallel clinical trial applications to the Ethics Committee and the MCA are encouraged to streamline or minimise the timelines for the clinical trial authorisation process in The Gambia. A favourable opinion from the Ethics Committee is required before the MCA can issue the clinical trial authorisation.

7.2. The principal investigator is required to submit the favourable opinion from the Ethics Committee when issued to the MCA.

7.3. Sequential clinical trial application submission can also be done where the principal investigator submits first to the Ethics Committee and when the favourable opinion is issued by the Ethics Committee the clinical trial application along with this is submitted to the MCA for request of the clinical trial authorisation.

7.4. An application for a favourable opinion shall be made by the principal investigator to the Ethics Committee in the prescribed form.

7.5. The principal investigator shall submit any other information as determined by the Ethics Committee to assess the application.

7.6. The Ethics Committee:

a) may rely on its personal scientific findings, consult experts or request for an expert opinion to assess any application;

b) shall provide its opinion on an application for a clinical trial based on its written standard operating procedures;

c) may refuse to grant a favourable opinion where the-

i documents submitted are incomplete and the PI fails to submit the appropriate documents within the time frame provided by the Ethics Committee,

ii documents submitted, including the trial protocol, the investigator's brochure, the modalities for selection of trial participants and the informed consent documents, do not correspond with the scientific knowledge available and the clinical trial is considered unsuitable to provide proof of the safety and efficacy of an investigational product;

iii requirements specified under Section 73 of the Regulations are not fulfilled.

7.7. The Agency shall provide the Ethics Committee with any information of significance, if required for the assessment of any application for a favourable opinion.

7.8. The Agency shall provide information to the Ethics Committee, when required, on aborted or prematurely discontinued investigations.

8 Decision on Clinical Trial Applications

8.1. All clinical trial applications shall be evaluated with the same set of criteria based on the up-to-date scientific knowledge and ethics standards, regardless of the applicant.

8.2. During the CT assessment process, relevant CT decisions, reports or information from other national regulatory authorities or regional and international bodies can be recognised or used by the MCA.

8.3. MCA has established the Medicines Safety Experts Committee (MSEC) as an external advisory committee, for the review of a clinical trial application, if special expertise is required. The MCA shall establish an Internal Advisory Committee whose expertise would be utilised for the ad hoc review of clinical trial applications.

8.4. The MSEC will convene meetings anytime, a minimum of two (2) and a maximum of four (4) regular meetings per year and when the need is expressed by the Executive Director of MCA, or ad hoc meetings, if necessary.

8.5. The MSEC will diligently carry out its functions in accordance with the Terms of Reference (TOR), Code of Practice, and Guidelines provided by the Agency. The provision of scientific advice by the MSEC will be conducted based on the necessity as determined by the Agency and will be completed within the 60-day Clinical Trial Application (CTA) evaluation period. The committee members will adhere to the established protocols and procedures outlined in the TOR, Code of Practice, and Guidelines to ensure the quality and timeliness of their recommendations. The MSEC's commitment to upholding professional standards and regulatory compliance will guide their decision-making process in providing accurate and reliable scientific advice. The Agency can rely on the expertise and dedication of the MSEC members to fulfil their responsibilities effectively and contribute to the overall safety and efficacy of medicinal products under evaluation.

8.6. All MSEC meetings will be planned and agreed with the Director of Clinical Trials and Pharmacovigilance. The MSEC Chairperson and the Director of Clinical Trials and Pharmacovigilance are responsible for the MSEC meeting agenda.

8.7. Persuant to the Act, a clinical trial authorisation letter (certificate) shall be issued to the applicant by MCA upon approval indicating the MCA CT number. The clinical trial authorisation letter may contain conditions required by MCA with the respect to the conduct or reporting of the clinical trial.

8.8. If the clinical trial application was rejected, the applicant can appeal which shall be made in writing to the Executive Director within sixty (60) calendar days of receipt of the rejection notice, or incase of Emergency CTA which will be 21 working days.

8.9. No information given in an application shall be disclosed by the MCA to a third party except:

- MCA technical advisory support (such as MSEC)
- with the written consent of the applicant; or
- in accordance with the directive of the Governing Board of MCA; or

- for the purpose of a legal process under the Medicines and Related Products Act, 2014.

8.10. MCA shall register all clinical trial applications in a database.

8.11. An authorisation may be rejected in accordance with section 40 of the Act where the-

(a) documents submitted are incomplete and the PI or sponsor fails to submit the appropriate documents within the time frame provided by the Agency;

(b) documents submitted, including data on the investigational products, the trial protocol, investigator's brochure and the investigational medicinal product dossier, do not correspond with the scientific knowledge available and the clinical trial is considered unsuitable to provide proof of the safety and efficacy of an investigational product;

(c) the requirements stipulated under provision 73 of the Regulations are not fulfilled; and

(d) the Agency is in possession of findings which indicate that the clinical trial facility is not a conducive environment for the trial to be conducted.

8.12. The Agency may use relevant clinical trial decisions, reports or information from other regulatory authorities as the Agency may consider necessary to assess any application.

8.13. The Agency may use reliance in its decision-making process on clinical trial authorisation in the following circumstances:

- If the investigational product has already been evaluated and listed as a WHO Prequalified Product through the WHO PQ collaborative registration procedure between WHO and NMRAs;
- If the investigational product has already been evaluated and listed as a product of either the WHO collaborative registration pilot for stringently authorised products, including through the EU-M4 all Procedure or the Swiss medic's Marketing Authorization for Global Health products or the International Generic Drug Regulatory Programme (launched July, 2014);
- If the investigational product has been authorised in a clinical trial or granted marketing authorisation by a recognised NMRA (e.g. WHO Listed Authority); or
- If either the trial or the investigational product has been evaluated and judged satisfactory at a joint review meeting facilitated by the World Health Organization under the African Vaccine Regulatory Forum (AVAREF).

8.14. It is mandatory that all clinical trials shall be registered by the sponsor or PI in the Pan African Clinical Trials Registry (PACTR) Or international CT registry, like EUDRACT, clinicaltrials.gov.

9 Reporting of Adverse Events

9.1. For purposes of safety monitoring, procedures for the collection, management and reporting of suspected adverse reactions/adverse events should be put in place and summarised in the clinical trial protocol as follows:

- in the case of a serious adverse reaction (SAR) including suspected unexpected serious adverse reaction (SUSARs), not later than fisteen (15) calendar days after the sponsor became aware of the reaction;
- in the case of a SAR which was initially considered to be non-serious but which turns out to be serious, as soon as possible and in any event not later than 7 days after the sponsor became aware of the reaction being serious;
- in the case of a fatal serious adverse event, it shall be reported within seven (7) calendar days to MCA.
- Cases of non-serious ADRs, whether expected or not, would not normally be considered reportable on an expedited basis. Non-serious ADRs should be included in the Line listings and provided in an individual case safety report (ICSR), annual report and DSUR/PSUR accordingly.

9.2. The sponsor or PI of an ongoing clinical trial shall report to the Agency serious adverse events suspected to be related to the IMP by using a Serious Adverse Event Report form provided by MCA (see SAE Report Form MCA-F-501/09), which is available from the MCA website: www.mca.gm, or an equivalent.

9.3. Any serious adverse event to the investigational product shall receive immediate medical attention before reporting same to the MCA.

9.4. Fatal serious adverse events shall be reported within seven (7) calendar days to MCA whether suspected to be related to the IMP or not. They shall be followed by a formal or verbal autopsy report. Verbal autopsy shall be conducted in line with the World Health Organization guideline for verbal autopsy. The cause of death shall be classified according to current ICD guideline.

9.5. In line with the Regulations stipulated in part XI, section 80 (b) fatal events should be reported preliminary within 72 hours which can be an informal notification, while a detailed report must be submitted within seven (7) calendar days.

9.6. Any adverse events that are relevant with respect to nature or frequency shall be reported to MCA within specified timelines with progress reports.

9.7. The sponsor or PI is required to submit follow-up information as soon as it becomes available. Additional information may include copies of diagnostic test results, laboratory reports, or medical record progress notes. All additional information should be clearly marked as update information and should include the Protocol Number and Participant Number.

9.8. MCA shall ensure to record and evaluate all reports on suspected serious adverse reactions to an IP which are brought to its attention.

10 Notifications and Clinical Trial Reports

Notifications

10.1. A notification of arrival and receipt confirmation of imported products stating the name(s) of product(s), batch numbers or code numbers and quantities received should be sent immediately by scanned email and then delivered in hard copy to MCA within (5) five working days.

10.2. The sponsor or PI shall notify the MCA of the start of the trial within 15 working days; the start of the trial is the date when the first act of recruitment of a

potential participant was performed (e.g. date of the first contact with potential trial participants).

10.3. If the trial does not start within six (6) months of issuance of the authorisation letter or at the date as stipulated by the applicant, the sponsor or PI shall inform MCA of the planned date of commencement.

10.4. The sponsor or PI shall inform the MCA of early termination or suspension of a clinical trial by using form MCA-F-501/15 or equivalent immediately and at the latest within 15 days after the trial is halted clearly explain the reasons, and describe follow-up measures, if any, taken for safety reasons.

10.5. The sponsor or PI shall notify MCA within 90 days of the end of a clinical trial by using form MCA-F-501/15 or equivalent; the end of the clinical trial shall be defined in the clinical trial protocol (e.g. last participant last visit or database lock).

Reports

10.6. The sponsor or PI shall provide progress reports on the clinical trial including safety data at least annually or as stipulated in the clinical trial authorisation letter to MCA starting from the date of issuance of the clinical trial authorisation letter by using the Clinical Trial Progress Report form (MCA-F-501/07). The report form is available from the MCA website: www.mca.gm.

10.7. A simplified annual safety report is acceptable for low intervention clinical trial and clinical trials with authorised IMPs.

10.8. The sponsor shall provide to the Agency and the Ethics Committee once a year for ongoing clinical trials in The Gambia a Development Safety Update Report (DSUR) for IMPs under development as per International Council for Harmonisation (ICH) format.
Note: The International Council for Harmonisation (ICH) has published 'model DSURs' taking account of the differing knowledge about a medicine, depending on whether the sponsor holds the marketing authorisation or not.

10.9. The start of the annual period for the DSUR is the date of the sponsor's first authorisation to conduct a clinical trial with the IMP(s) concerned in any country worldwide.

10.10. The sponsor or PI shall submit a clincial trial summary report to MCA within one year of the end of the clinical trial by using the Clinical Trial Summary Report form (MCA-F-501/10) or equivalent.

11 Clinical Trial Files and Archiving

11.1. The PI shall keep an Investigator Site File (ISF) and the sponsor a Trial Master File (TMF) containing the essential documents relating to the clinical trial as indicated in the ICH E6 GCP guideline, which allow verification of the conduct of the clinical trial and the quality of the data generated, taking into account all characteristics of the clinical trial.

11.2. The files shall be readily available, and directly accessible upon request, to the MCA.

11.3. The sponsor and the PI shall archive the contents of the TMF and ISF, respectively, for at least 10 years for marketed products and 25 years for unauthorised IPs after the end of the clinical trial.

11.4. All original and latest approved versions of Clinical Trial protocols, Investigator's Brochure, Informed Consent, Ethics Committee favourable opinion, summary of amendments, and final Clinical Trial report including summary of safety reports shall be recorded, filed and archived by the Clinical Trials and Pharmacovigilance Directorate of the MCA for at least five (5) years.

11.5. Stored files shall be accessed only by duly authorized MCA staff and shall be stored and disposed thereafter in a manner as may be provided by existing laws, regulations and rules. Disposal of files shall be in coordination with the Records Section of the MCA and would be in accordance with national guidelines, laws and rules.

Definitions

Interpretations and abbreviations contained in the MCA Glossary can be found on the MCA website: www.mca.gm.

The definitions provided below apply to the terms used in this guideline. They may have different meanings in other contexts and documents.

The interpretation of terms provided in the Act and Regulations apply, unless further defined in this guideline.

Applicant
Sponsor or sponsor 's representative, principal investigator (PI), or sponsor-investigator.

Assent
The trial participant who is a minor aged between 12 and 17 years agrees to participate in the clinical trial; it is required in addition to the consent of the legal guardian of the trial participant.

Auxiliary medicine or Non-Investigational Medicinal Product (NIMP)
Medicines used in the context of a clinical trial (but not as investigational medicinal products), such as medicines used for background treatment to ensure that adequate medical care is provided for the participants, challenge agents, rescue/escape medication, or used to assess end-points in a clinical trial.

Concomitant Medication
Medication unrelated to the design of the clinical trial, and which is permitted or not permitted before and/or during the trial and their time restrictions.

Indemnity
Provision of legal and financial coverage for the investigator or the institution against claims arising from the clinical trial, except for claims that arise from malpractice and/or negligence.

Informed Consent
A process by which an adult participant competent to make the decision voluntarily confirms his or her willingness to participate in a particular research study, after having been informed of all aspects of the study that are relevant to the participant's decision to participate

Investigational Product (IP)
Any product used in a clinical trial including medicine, herbal medicine, homeopathic medicine~~s~~, food and food/dietary or nutritional supplements, medical device, diagnostics, cosmetics and any other related product.

Investigational Medicinal Product (IMP)
A medicine or placebo being tested or used as a reference in a clinical trial, including a product with a marketing authorisation 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.

Legal Guardian
A person who is the guardian of a child (aged <18 years) by virtue of the provision the Children's Act 2005 or a person lawfully appointed to be guardian of the child by Deed or Will or by an order of a court of competent jurisdiction or by operation of law.

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

Adverse Drug Reaction (ADR)
Adverse drug reactions, as established by regional regulations, guidance, and practices, concern noxious and unintended responses to a medicinal product. 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 (refer to the ICH E2A guideline). A reaction, in contrast to an event, is characterized by the fact that a causal relationship between the drug and the occurrence is suspected. For regulatory reporting purposes, if an event is spontaneously reported, even if the relationship is unknown or unstated, it meets the definition of an adverse drug reaction.

Serious AE/ADR
In accordance with the ICH E2A guideline, a serious adverse event or reaction is any untoward medical occurrence that at any dose:

- results in death,
- is life-threatening (NOTE: The term "life-threatening" in the definition of "serious" refers to an event/reaction in which the patient was at risk of death at the time of the event/reaction; it does not refer to an event/ reaction which hypothetically might have caused death if it were more severe),
- requires inpatient hospitalisation or results in prolongation of existing hospitalisation,
- results in persistent or significant disability/incapacity,
- is a congenital anomaly/birth defect,
- is a medically important event or reaction.

Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious such as important medical events that might not be immediately life-threatening or result in death or hospitalisation but might jeopardise the patient or might require intervention to prevent one of the other outcomes listed in the definition above (e.g., intensive treatment in an emergency room or at home for allergic bronchospasm, convulsions that do not result in hospitalization, development of drug dependency, etc).

Non-serious AE
An event or reaction that is nonserious (does not meet any of the criteria for seriousness).

Adverse Event Following Immunization (AEFI)
An Adverse Event Following Immunization (AEFI) is defined as any untoward medical occurrence which follows immunization. An AEFI does not necessarily have a causal relationship with the usage of the vaccine.

Unexpected ADR
An ADR whose nature, severity, specificity, or outcome is not consistent with the term or description used in the local/regional product labelling (e.g. Package Leaflet (PL) or Summary of Product Characteristics (SmPC)) should be considered unexpected. When a Marketing Authorisation Holder (MAH) is uncertain whether an ADR is expected or unexpected, the ADR should be treated as unexpected.

An expected ADR with a fatal outcome should be considered unexpected unless the local/regional product labelling specifically states that the ADR might be associated with a fatal outcome.

Suspected Adverse Drug Reaction (SADR)
A noxious and unintended response to any dose of a drug or biologic product for which there is a reasonable possibility that the product caused the response. In this definition, the phrase "a reasonable possibility" means that the relationship cannot be ruled out (ICH E2A).

Suspected, Unexpected, Serious Adverse (Drug) Reaction (SUSAR)
An adverse event that occurs in a clinical trial participant, which is assessed by the sponsor and or study investigator as being unexpected, serious and as having a reasonable possibility of a causal relationship with the study drug. Reports of these reactions are subject to expedited submission to health authorities.

Expected ADR
As opposed to "unexpected," an event that is noted in the Investigator's Brochure or labelling (PL or SmPC). Reports which add significant information on specificity or severity of a known, already documented serious ADR constitute unexpected events.

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  - E2C: _R2_Step4 Periodic Benefit -Risk Evaluation Report (PBRER)
  - E2D: _Guideline Post approval safety data management- Definitions and standards for expedited reporting
  - E2E: _Guideline Pharmacovigilance Planning
  - E2F: _Step_4 Development Safety Update Report
  - E2: Clinical Safety Data Management
  - E3: Structure and Content of Clinical Study Reports
  - E4: Dose-Response Information to Support Drug Registration
  - E5: Ethnic Factors in the Acceptability of Foreign Clinical Data
  - E6: Good Clinical Practice: Consolidated Guideline
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  - E9: Statistical Principles for Clinical Trials
  - E10: Choice of Control Group in Clinical Trials
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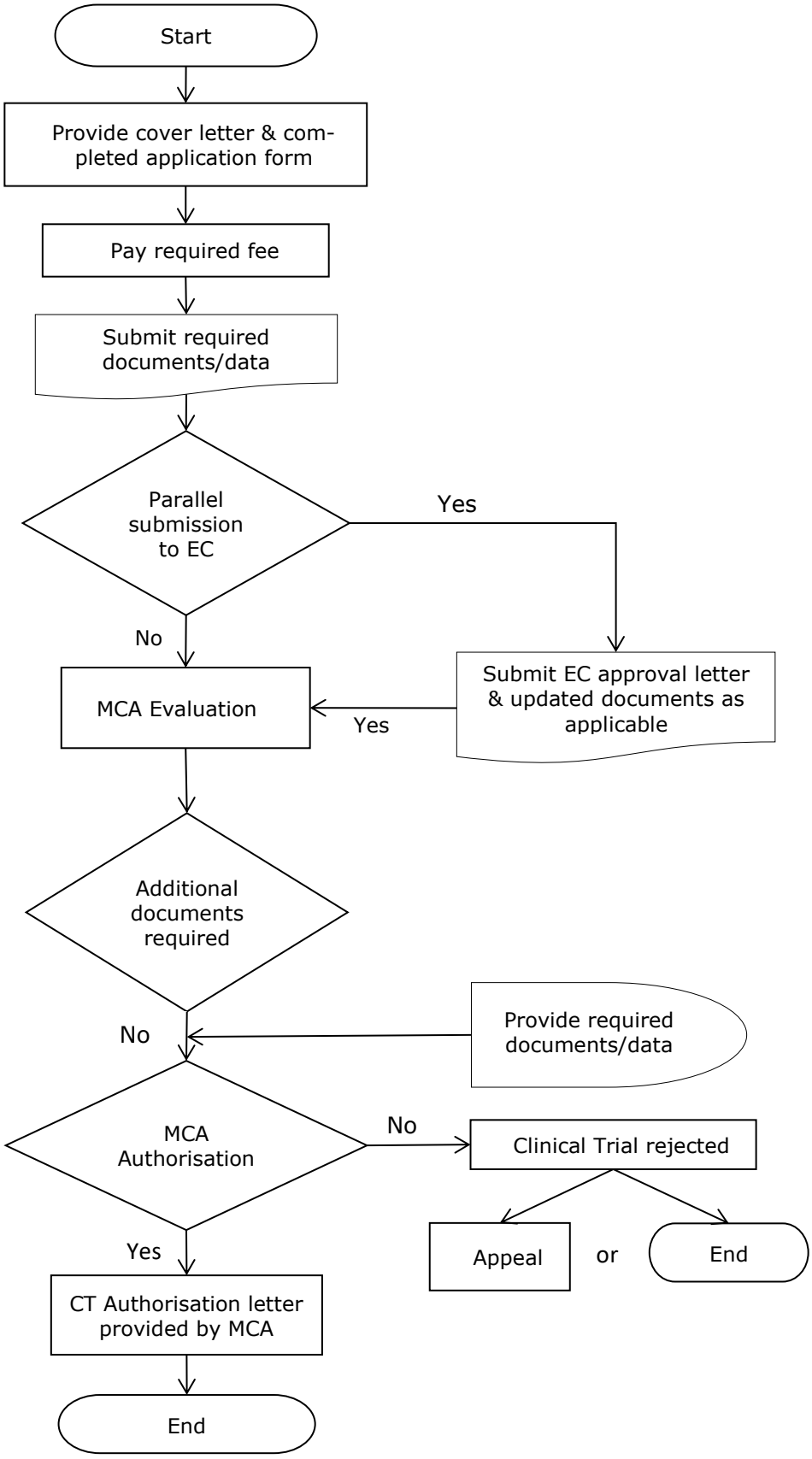
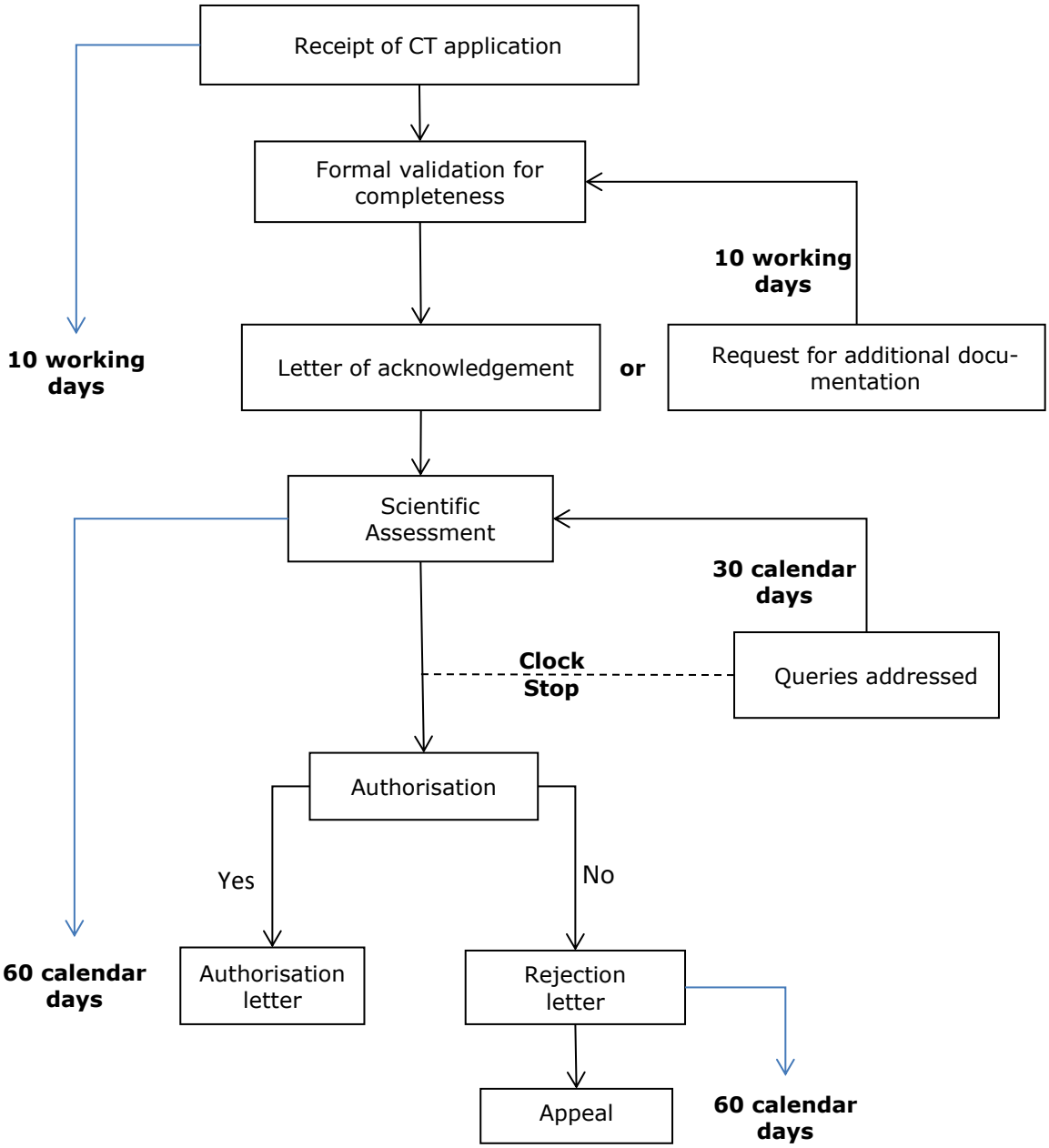
Flow Chart 1: Application for a Clinical Trial

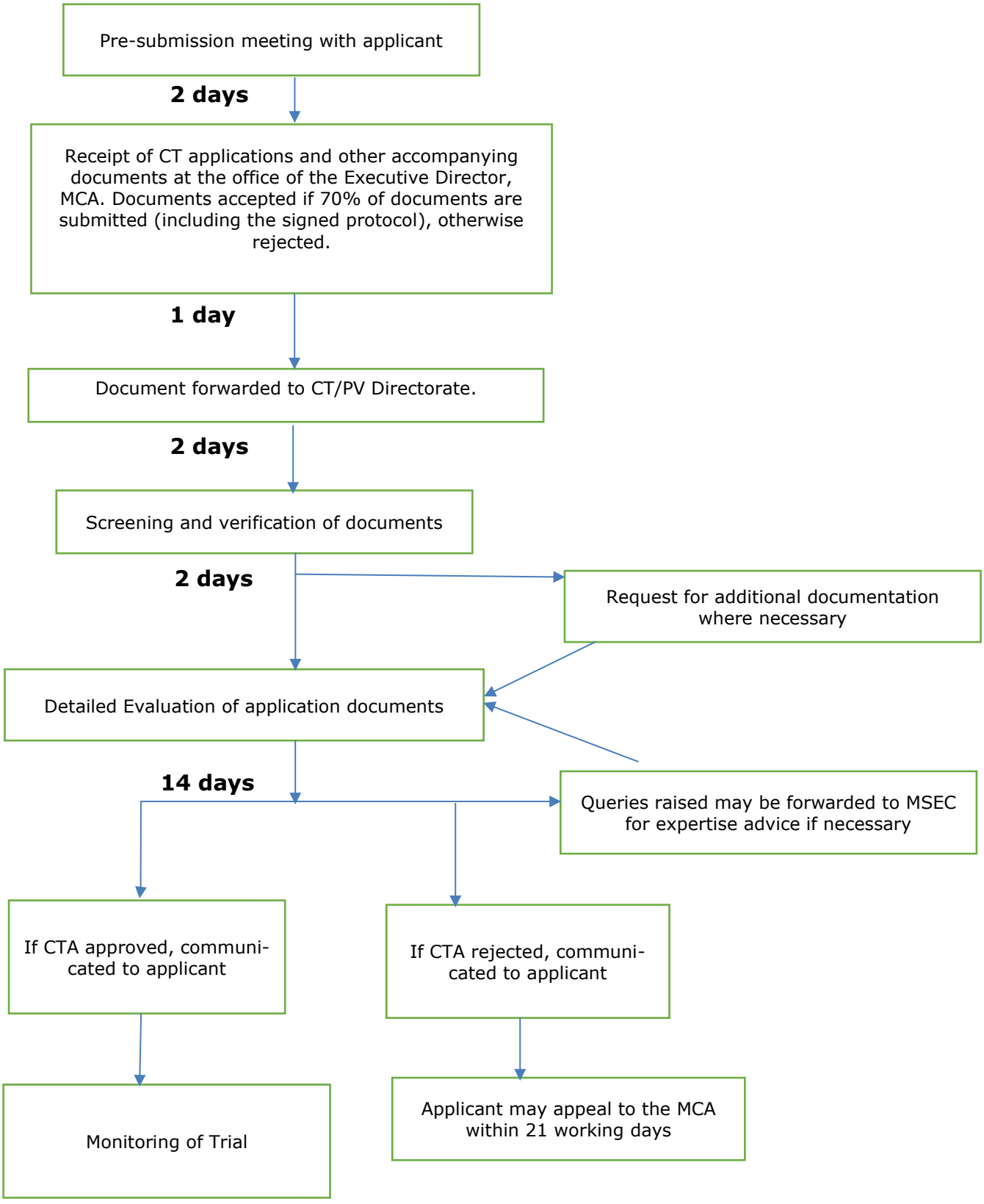


Flow Chart 2: Timelines for Clinical Trial Applications

(except IPs containing genetically modified organism)



Flow Chart 3: Timelines for Emergency Clinical Trial Application



Appendix 1: Substantial and Non-Substantial Amendments

1. Substantial Amendments

A substantial amendment refers to any change that has a significant impact on the safety of clinical trial participants, the scientificity of the trial as well as the reliability of trial data.

For confirmatory clinical trials, examples of possible substantive changes that require special attention and evaluation are as follows:

(a) Change of primary objective;

(b) Change of primary endpoint or secondary endpoint which has a significant impact on the safety or scientificity of the trial;

(c) Change the measurement method or evaluation standard for the primary endpoint or important secondary endpoint;

(d) Change of inclusion or exclusion criteria, such as significant change to the characteristics of the participant population, if these changes are likely to have a significant impact on the scientificity and safety of the trial;

(e) Change dosage of administration;

(f) Change of treatment schedule, such as dosing time, dosing interval, treatment duration, etc.;

(g) Change, addition or deletion of control group/comparator (including placebo);

(h) Change of a diagnostic/therapeutic monitoring method or procedure which is likely to have a significant impact on the safety or scientificity of the trial;

(i) Change of a backbone therapy which is likely to have a significant impact on the safety or scientific value of the trial;

(j) Reduction of safety measures or the number of visits, or shortening of the duration of follow-up;

(k) Change the definition of trial termination, trial suspension criteria and trial termination criteria (including the termination of individual participant trial and of entire clinical trial);

(l) Change bias control methods, such as randomization methods, blinding settings, etc.;

(m) Change the statistical analysis method and analysis plan for the primary or important secondary endpoint;

(n) Revoke the data security monitoring committee/data monitoring committee/independent data monitoring committee;

(o) Others.

*For **clinical pharmacology research and exploratory clinical trials**, the nature, purpose, design and confirmatory trials are quite different, and the dosage and dosage regimen are in the process of exploratory research. Therefore, at this clinical trial stage, the assessment of substantial changes focuses more on the **changes that significantly affect the participant's safety.***

2. Non-substantial Amendments

A non-substantial amendment refers to any change that will not cause any significant impact on the safety of clinical trial participants, the scientificity of the trial, or the reliability of the trial data.

Examples of other common non-substantial amendments are as follows:

(a) Typographical errors;

(b) Minor adjustments to the wording, to clarify the ambiguous content in the protocol;

(c) Appropriate adjustments to the format or content of documentation used for recording trial data;

(d) Changes to exploratory endpoints or their detection methods;

(e) An increase in safety measures or the number of visits for preventive purposes rather than emergency risk control (except for invasive examination);

(f) Change of the contact person, contact information, etc. of related parties;

Appendix 2: Severity of AE/ADR

- **Mild:** Awareness of signs or symptoms, but easily tolerated and are of minor irritant type causing no loss of time from normal activities. Symptoms do not require therapy or a medical evaluation; signs and symptoms are transient.
- **Moderate:** Events introduce a low level of inconvenience or concern to the participant and may interfere with daily activities, but are usually improved by simple therapeutic measures; moderate experiences may cause some interference with functioning.
- **Severe:** Events interrupt the participant's normal daily activities and generally require systemic drug therapy or other treatment; they are usually incapacitating.

Explanatory note: Severity is not synonymous with seriousness. A severe rash is not likely to be an SAE. Likewise, a severe headache is not necessarily an SAE. However, mild chest pain may result in a day's hospitalization and thus is an SAE.

Appendix 3: Reporting requirements from Sponsor/MAH to MCA and ECs

Type of Event/Reaction	Form of Reporting	When to Report
Serious ADR	SAE Report Form (MCA-F-501/09)	As soon as possible, but not later than 15 calendar days
Fatal SAE	SAE Report Form (MCA-F-501/09)	As soon as possible, but not later than 7 calendar days
AE/ADR	Line listing (MCA-F-501/14)	Annually
IB, ICF Updates	Submission of IB, ICF	Annually with the annual safety report, or as required
Annual safety report	Annual Progress Report (MCA-F-501/07)	Annually
Protocol Deviations	With amendment, if applicable (MCA-F-501/08)	As applicble, if necessary to eliminate an immediate hazard to trial partici-pants as soon as possible, but not later than 72 hours
CT early termination	Letter	As soon as possible, but not later than in 15 calendar days.
End of Trial notification	Notification of the End of a Clini-cal Trial (MCA-F-501/15)	Within 15 days in case of early termination, 90 days after completion
Clinical Study Report	Clinical Trial Summary Report (MCA-F-501/10)	Within 12 months upon completion.