

**African Vaccine Regulatory Forum (AVAREF)**

**Guideline for joint and assisted reviews of clinical trial applications**

GUIDELINE FOR JOINT AND ASSISTED REVIEWS OF CLINICAL TRIAL APPLICATIONS

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## GUIDELINE FOR JOINT AND ASSISTED REVIEWS OF CLINICAL TRIAL APPLICATIONS

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## **Executive summary**

Joint reviews by multiple National Regulatory Authorities (NRAs) and Ethics Committees (ECs) are increasingly being used as a platform for accelerating review of clinical trial applications (CTAs).

The value proposition of joint reviews lies in the:

1. Scientific and ethical robustness of the collaborative review and hence the protection of human research participants<sup>1</sup>
2. Overall amount of time saved in undertaking reviews
3. Knowledge and experience sharing among regulators as well as ECs
4. Opportunity to establish mechanisms for information sharing once the trials begin
5. Use of standardized formats

This document provides guidance to NRAs, ECs, trial sponsors and their investigators on a joint review model for submission and review of CTAs in Africa.

The document addresses the criteria for triggering a joint review using the AVAREF platform, the key participants and their respective roles, as well as the steps and expected outcomes from the joint review process.

AVAREF countries are encouraged to incorporate this joint review model and guideline into their review process as a means of fulfilling regulatory requirements.

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<sup>1</sup> This term is used as defined in ICH E6R2 Section 1.57: an individual who participates in a clinical trial, either as a recipient of the investigational medical product(s) or as a control.

## 1.0 Background

The past decade has witnessed an increase in the sophistication of biomedical research and the number of products being tested for diseases endemic to Africa for which no prior knowledge and evidence base exists in high income countries. While providing opportunities for enhancing expertise and earlier access to novel therapies, these trends have also underscored the need for a regulatory platform for promoting human resource capacity, best practices, common technical requirements and the efficiency and transparency of the regulatory process. The growing complexity of biomedical research calls for increased cooperation between partners, including funders, sponsors, researchers, product developers, regulators and the ethics community.

The African Vaccine Regulatory Forum (AVAREF), initially created by the WHO in 2006 as an informal capacity building platform aimed at improving the regulatory oversight of interventional clinical trials being conducted in Africa, has demonstrated its value in strengthening regulatory and ethics reviews, promoting harmonized standards and approaches and accelerating the review of vaccines of high public health value – most recently in relation to vaccines against Ebola.

Clinical trials are carefully conducted experiments in humans with the aim of testing products for safety, efficacy and immunogenicity (in the case of vaccines). Applications for clinical trials are usually submitted to National Regulatory Authorities (NRAs) and Ethics Committees (ECs) for approval and authorization before the importation and use of new investigational drugs. The trials are then monitored until completed and the data is submitted for the authorization and registration of the final product in the countries of intended marketing.

Sometimes clinical trials are planned in more than one country and at several sites in these countries for the same product. For such a multicenter, multi-country clinical trial, clinical trial applications (CTAs) will have to be submitted to individual NRAs and ECs, often in different formats as defined by each country. Reviews will then be conducted individually and at different times before final outcomes are communicated individually to the sponsor. Furthermore, many of the questions submitted by countries will be similar in nature. To optimize the review of multi-country clinical trial applications, promote harmonization of regulatory requirements, practice and processes across countries, as well as build capacity for more efficient oversight, WHO introduced the concept of joint reviews in 2006.

Joint reviews are intended to enhance the quality of the reviews of an application submitted to multiple countries, optimize review timelines for such applications, serve as a platform to allow regulators and ECs to exchange and validate their findings with peers and also act as a capacity-building tool. Joint reviews enable NRAs and ECs to collectively prepare a consolidated list of questions for the sponsor and to discuss directly with manufacturer/sponsor the candidate product, trial design, safety and other aspects of the proposed trial.

## 2.0 Purpose

This guideline has been developed by AVAREF to provide a model of joint scientific and ethical review of CTAs by NRAs and ECs. This model may also be applied to the review of unconventional regulatory pathways at different stages of the product lifecycle.

This guideline is intended to assist Regional Economic Communities (RECs), individual countries and sponsors in how to plan, organize, and conduct joint reviews of applications for medical products.

This guideline is not intended to replace but rather facilitate compliance with the regulatory requirements of countries in the review, approval and authorization of medical products clinical trials as outlined in each country's legislation. AVAREF countries are encouraged to consider this joint review model into their review process as a means of fulfilling regulatory requirements. This guideline should be used together with WHO's Technical Report Series on review of clinical trials (WHO Technical Report Series No 924 - Guidelines on Clinical Evaluation of Vaccines: Regulatory Expectations) and other international guidelines for the review of CTAs by ECs/institutional review boards (IRBs) and NRAs. It is also expected that AVAREF will serve to promote convergence of CTA technical requirements and processes.

This guideline is subject to amendment as further experience is gained with the joint review process.

## 3.0 Scope

This guideline covers all aspects of the joint review of a qualifying medical product<sup>2</sup> using the AVAREF platform, specifically:

1. Conditions or requirements for joint/assisted reviews, including criteria for triggering a review
2. Key participants as well as their roles and responsibilities in the review process
3. The steps and timelines in the review process, from pre-submission meeting to the conclusion of the joint review exercise
4. Expected outcomes from the joint review process
5. Post-review steps leading to the commencement of the clinical trial<sup>3</sup>

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<sup>2</sup> For the purpose of this document a medical product includes a medicine, vaccine or other biological product, and an in-vitro diagnostic.

<sup>3</sup> This normally includes GCP inspections, post-review administrative steps, and import authorization of investigational medical products.

## 4.0 Definitions

**Joint review** – The AVAREF joint review process brings experts from the NRAs and ECs of two or more countries, together with the sponsor, as well as external experts that serve to guide and support the NRAs and ECs of the target countries of the CTAs to review a common CTA submitted by a sponsor. Countries may also be invited as observers to benefit from the knowledge and experience of other regulators and ECs towards building their capacity.

**Assisted review** – The same approach may be used on a case by case basis to assist a single country in the review of a CTA that complies with the criteria under Section 6.

Hereinafter, joint and assisted reviews will be referred to as ‘joint review,’ unless otherwise indicated.

### **Review participants:**

**Convener** – Neutral entity responsible for organizing the joint review and for ensuring the agreed upon process is respected. The convener will liaise with all prospective participants and as such will seek endorsement for the joint review process. The convener will facilitate but not chair the face-to face meeting. For the initial pilot phase of the joint review process, the WHO will serve as the convener. This would not preclude working in partnership with the secretariats of regional regulatory networks to organize a joint review when the majority of target countries are members of a regional network.

**Invited experts** – Experts and representatives from more experienced NRAs and ethics committees from the region and/or country of manufacture of the product or from well-established NRAs outside the region who act in an advisory capacity. This could include disease-specific experts, statisticians or individuals with relevant expertise.

**Neutral partner** – a Product Development Partner (PDP), Non-governmental Organization (NGO) or another non-profit organization that 1) supports the development of a medical product without specific commercial interests in the proposed trial that would constitute a real or perceived conflict of interest and 2) who is also willing to support the regulatory oversight of the clinical trials in target countries. The neutral partner should play a key role in advocating for a joint review facilitated by WHO.

**Observer countries** - NRAs and ECs from countries not involved in the proposed trial who may be invited to the joint review as observers to learn and in anticipation of additional trials of the product in these countries. The convener will select countries based on the need for capacity building. Observers do not participate in the decision-making process.

**Sponsor** – Entity that takes responsibility for the clinical trial. In some cases it may be one organization, while in other cases it might be more than one. Sponsor and manufacturer may also be different companies or organizations. The sponsor will designate persons to participate

in the joint review to ensure that all foreseeable questions presented by the review group can be promptly responded to, ideally during the joint review meeting. They may include the Principal Investigators (PIs) of the different sites, company experts in the clinical development of the product, company experts in production and control of the investigational product, etc.

**Target countries** – The EC and NRA representatives of the countries where the clinical trials will take place. The decision on which regulators and ethics committee members and how many representatives will participate will be determined by each institution in consultation with the convener.

## 5.0 Pre-requisites for joint review

The following are important pre-requisites for the successful conduct of joint reviews:

- A waiver agreement obtained from the sponsors to share existing information about the application
- Consensus among the countries involved to undertake the review of the application together and to use a common report as a basis for their national decision to authorize a trial
- A neutral convener to ensure that the clinical trial applications go through a rigorous, unbiased regulatory review<sup>4</sup>
- Focal persons for the NRA and EC in each participating country to ensure continuity in communications regarding the entire process
- Reviewers nominated by the heads of agencies with the authority to act on behalf of their respective agencies
- All applicable fees should be paid in advance
- Experts from supporting agencies who share their knowledge and experience but do not have decision-making roles or responsibilities

## 6.0 Criteria for joint review

To be considered for joint review, a candidate medical product of high public health value to countries on the African continent will be considered based on one or more of the following criteria:

- Addresses a neglected tropical disease or other highly prevalent and serious disease (e.g., non-communicable disease - NCD) on the continent
- Addresses an unmet medical need or a significant improvement over available intervention
- Involves a novel technology

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<sup>4</sup> This could also involve a neutral partner who will support the review through negotiations with the sponsor.



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- Product that addresses a disease for which the Director General of the World Health Organization has declared a Public Health Emergency of International Concern (PHEIC)
- Responds to request from one or more countries for assistance

Other criteria may be considered based on the needs of the countries.

Furthermore, there must be a candidate medical product which is ready to go into clinical trial. The clinical trial could be multicenter involving more than one country or on a case by case basis involve one country.

Finally, all participants in the joint review must agree to respect the provisions of this guideline and the specific agreement reached for the candidate product and trial in terms of roles, responsibilities, process, and timelines.

### **7.0 Joint review process**

The steps in the joint review process are described below. The overall model is illustrated in Figure 1.

The proposal to initiate a joint review using AVAREF may come from:

- A sponsor
- A PDP
- An AVAREF member-state
- WHO or other international organization, for example, in the case of public health emergencies

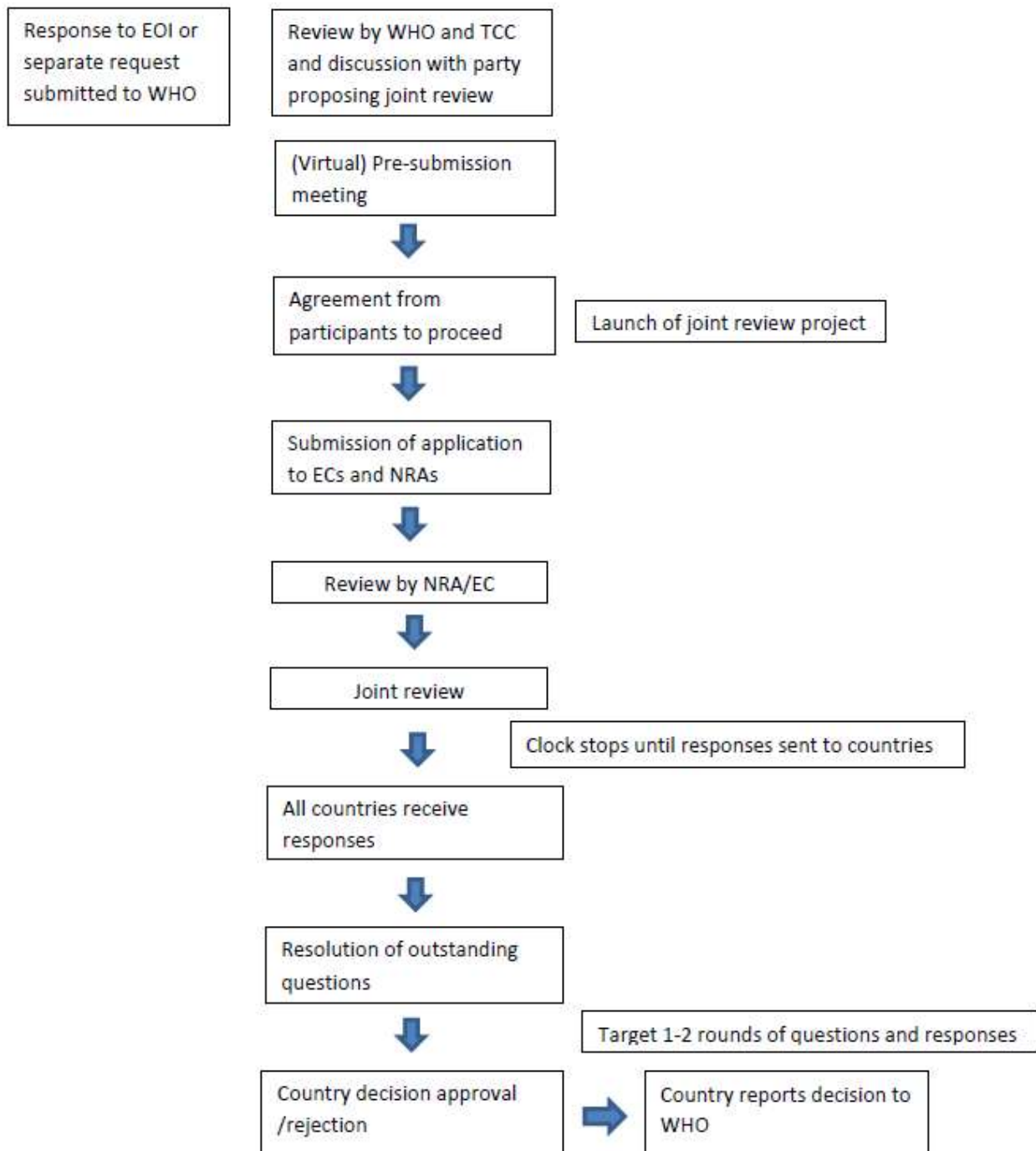
Regardless of who requests the joint review, the same process is set in motion. Requests should be placed with the convener (WHO).

It is envisaged that a proactive approach to the conduct of joint reviews will be established, including online Expressions of Interest and the development of a medical product pipeline platform that tracks candidate products of interest.

Funding models to support the joint review process are being explored. At the current time, no fees are associated with the joint review beyond those required by participating regulatory authorities and ECs as part of their administrative process.

## 7.1 Process steps

Figure 1 Flowchart



***Step 1- Screening of requests***

Requests to utilize the AVAREF joint review process will be screened against criteria by the AVAREF's Secretariat and the AVAREF Technical Coordinating Committee (TCC).

***Step 2 - Pre-submission meeting***

Convened by the WHO in discussion with the sponsor, target countries and the neutral partner (when involved). The objective is to present the product, the clinical trial plan, and proposed timelines. A decision is made on whether to proceed with a joint review in accordance with the provisions of this guideline. A date and location for the face to face meeting is also set.

Representatives of ECs and NRAs attending the pre-submission meeting will have the authority to decide on their participation in the joint review and commit to nominate reviewers. The sponsor provides a waiver agreement to share existing information about the application.

***Step 3 - Submission to countries***

The sponsor will submit the applications to ECs and NRAs as agreed during the pre-submission meeting. The goal is to have parallel submissions in all countries. In some countries, the PI submits the protocol to the EC and NRA. However, in the context of this document, the sponsor is considered the entity responsible for the clinical trial.

The CTAs submitted to the target countries are not considered valid until they have been screened for completeness and all administrative requirements are fulfilled (including the payment of fees, where relevant). Information on the product and proposed trial must be identical, as attested to in writing by the sponsor prior to all participants.

Opportunities for central electronic filing of non-administrative information and subsequent access by the countries will be explored.

***Step 4 – Country review of the CTA***

Once the application has passed the screening/validation step, the NRA and EC in each participating country will upload a list of questions onto the WHO joint review platform. Supporting agencies and invited experts may also do the same. Comments will be accessible to all joint review participants, including the sponsor.

***Step 5 – Joint review***

The WHO will convene the joint review meeting at the agreed upon date and location. Depending on the anticipated complexity of the review, 2-3 working days will be allotted for the review. WHO will circulate an agenda for the meeting following a standard format for the organization of such meetings.

The structure of the meeting will generally respect the following format:

Opening session (all participants):

WHO's role:

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- Brief summary of joint review project and process
- Objectives of the meeting, format, agenda and expected outcomes
- Confirmation that no conflict of interest on the part of participants
- Elect chair(s) for the meeting and lead(s) for drafting report

### Sponsor's role:

To introduce the product, clinical development plan, clinical trial, and rationale for the protocol. Clarifications: responses to questions raised by countries to which the application was submitted.

*Joint review session* (only country representatives, observers, experts, WHO, and neutral partner):

Participants will agree on time slots to discuss specific sections of the application and will develop a list of questions to be submitted to the sponsor at the end of each day. Time in the first portion of the next day will be allocated for responses and discussion with the sponsor.

*Closing session* (all participants):

The questions and answers sessions will continue until all questions are either completely resolved or agreement is reached on a list of outstanding questions to be addressed by the sponsor.

The review report will be finalized and signed by the Chair(s), countries and sponsor.

### ***Step 6 – Resolution of outstanding list of questions (LoQ)***

In the event that the joint review session results in outstanding questions, the sponsor submits pending responses to each country. Participants in the joint review will review and communicate virtually (via WebEx or teleconference) to ensure consistency and reach consensus on resolution of the questions jointly presented to the sponsor. Should they agree that the questions were not satisfactorily responded to, the sponsor will be requested to provide additional information (clock stop). The process will continue until all participating countries agree that the questions have been satisfactorily resolved.

### ***Step 7 – National authorization of CTA***

After the joint review as described above has been completed, each EC and NRA will proceed according to their national procedure to issue the decision to authorize or not to authorize the clinical trial. NRAs and ECs of participating countries will inform WHO about their decision. In the event trials are not authorized, the NRA and/or EC commit to report to WHO the reasons for non-authorization.

### ***Step 8 – Post-authorization steps***

Efficiency gains achieved in the joint review of a CTA could be negated by lengthy post-authorization steps required for the start of the trial to begin, including the authorization to import investigational products. Countries are encouraged to coordinate and streamline these steps to allow for the timely and near simultaneous commencement of trials in the respective countries. Table 1 and Table 2 give the timelines for the joint review process and for the

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expedited joint review process.

*Table 1 Timelines for the joint review process*

Step	Description	Target Timeline (working days)	Responsibility
1	Screening of requests for a joint review <sup>5</sup>	5	AVAREF Secretariat
2	Pre-submission meeting	1	AVAREF Secretariat
3	a) Submission to NRA and EC by Sponsor b) Screening by the NRA* and EC	5	a) Sponsor b) NRAs c) ECs
4	Country review of the CTA	20	NRAs and ECs
5	Joint review	2-3	NRAs and ECs <sup>6</sup>
6	Resolution of pending LoQ	10	NRAs and ECs
7	National authorization of CTA	10	NRAs and ECs
8	Post-authorization steps		Country dependent <sup>7</sup>

*Table 2 Timelines for the expedited joint review process*

Step	Description	Target Timeline (working days)	Responsibility
1	Screening of requests for a joint review <sup>8</sup>	3	AVAREF Secretariat
2	Pre-submission meeting	1	AVAREF Secretariat
3	a) Submission to NRA by Sponsor b) Screening by the NRA*	3	d) Sponsor e) NRAs f) ECs
4	Country review of the CTA	13	NRAs and ECs
5	Joint review	2-3	NRAs and ECs <sup>9</sup>
6	Resolution of pending LoQ	5	NRAs and ECs
7	National authorization of CTA	3	NRAs and ECs
8	Post-authorization steps		Country dependent <sup>10</sup>

<sup>5</sup> Day 0 begins once screening completed, confirming compliance with national requirements.

<sup>6</sup> Organized by the convener.

<sup>7</sup> Target countries should make their best efforts to ensure minimal delay in completing post-authorization steps required for the start of the trial to begin, including the authorization to import investigational medical products.

<sup>8</sup> Day 0 begins once screening is completed; therefore, confirming compliance with national requirements.

<sup>9</sup> Organized by the convener.

<sup>10</sup> Target countries should make best efforts to ensure minimal delay in completing post-authorization steps required for the start of the trial to begin, including the authorization to import investigational products.

## **8.0 Post-approval collaboration by participating countries**

The cooperation among participating NRAs and ECs is expected to extend beyond the approval of the clinical trial. The results of GCP inspections and any significant and serious observations from the safety monitoring or any other activity related to the oversight of the trials in all sites should be shared by the NRAs and ECs that authorized the trial.

## **9.0 Amendments**

In addition, if the approved protocols are amended by the sponsor, participants will communicate and discuss whether the magnitude of the amendments warrant a joint review, in which case, WHO will facilitate such activity.

## **10.0 Implementation of joint review**

The joint review model described in this guideline will be launched as a pilot for a period of two years. Refinements will be made based on experience gained.

## **ANNEXES**

A Roles and Responsibilities of Participants for WHO AVAREF Joint and Assisted Reviews of Clinical Trial Application Meetings

B Confidentiality agreement and declaration of conflict of interest

C Prioritization of clinical trial applications for joint reviews

D Release and importation of investigational medical products

## Annex A

# **Roles and responsibilities of participants for WHO AVAREF joint and assisted reviews of clinical trial application meetings**

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## **Introduction**

The meeting will proceed according to the Guideline for Joint and Assisted Reviews of Clinical Trial Applications and in line with the agreed upon agenda provided and which has been developed in consultation with the sponsor and the participating ethics committees and regulators. The roles and responsibilities of each category of participants have been outlined as follows:

### **Convener (WHO AVAREF secretariat)**

The WHO AVAREF Secretariat will facilitate the joint review and be present in the room but will not participate directly in any of the discussions regarding the protocol under review. The WHO secretariat will however respond to any request for advice or guidance by the National Regulatory Authorities (NRAs) or Ethics Committees (ECs) of its Member States involved in the joint review. The secretariat will also distribute all documents required.

The secretariat will provide a secure electronic platform for the exchange of information as part of the review process.

### **Observer countries**

A joint review may have observers participating in the meeting as part of capacity building with agreement of sponsor(s). The observers are there to learn about the process and have no direct involvement in the review. They will not contribute directly to the discussions and outcomes of the review. They may however ask questions to enable them understand the process and issues being discussed.

### **Ethics committees and national regulatory authorities of trial countries**

The ECs and NRAs will elect a chairperson as well as two rapporteurs from among themselves for the proceedings. The chairperson shall preside over the meeting. The ECs and NRAs of the target countries will review the protocol submitted by the sponsor, and will raise any queries (if any) to the sponsor for response. Timelines shall be set for the sponsor to respond to the queries raised.

## **Invited experts**

Experts from the ECs and NRAs of other countries invited to the meeting may ask questions and contribute their expert advice to the ECs and NRAs of countries hosting the study. The expertise may be regional, African or International. At the request of participating countries or regional economic communities (RECs), WHO will identify appropriate experts and appoint them to play this role.

They can also raise any relevant queries on the submission. Their observations remain advisory to the participating ECs and NRAs.

## **Sponsor(s)**

The sponsors will be invited to participate in the meeting whenever there is a need. They will present the protocol, provide answers to queries raised at the meeting as required. They may be required to provide some responses to queries in writing to the NRAs and ECs. They will also respond to queries posted on the platform.

They will endorse the actions and timelines as agreed at the end of the joint review.

## **Investigators**

Investigators will be invited to the meeting whenever there is a need. They will address any queries specific to trial sites as required. They will also present a brief on the characteristics of the trial sites.

They will endorse the actions and timelines as agreed at the end of the joint review.

## **Funding**

To avoid a conflict of interest due to financial relationship, the funding for the joint or assisted review does not come from the sponsor or sponsor related entity. Funding will come from countries, the RECs, and supplemented by public foundations, and partners.



Annex B

## **Confidentiality agreement and declaration of conflict of interest**

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### **Provisions for participants in WHO African Vaccine Regulatory Forum (AVAREF) joint/assisted reviews to assess applications for clinical trials by Ethics Committees and National Regulatory Authorities**

In the course of participating in this review as observer or discharging your duties as an expert adviser under this Agreement, you will have access to certain information, which is proprietary to WHO or to the manufacturer(s) of the medicine (s), vaccine(s) or diagnostic(s), which is the subject of the clinical trial application request submitted to the relevant Ethics Committees (ECs) and National Regulatory Authorities (NRAs). You undertake to treat such information (hereinafter referred to as “the Information”) as confidential and proprietary to WHO or the aforesaid manufacturer(s). In this connection, you agree:

- (a) not to use the Information for any other purpose than discharging your obligations under this Agreement; and
- (b) not to disclose or provide the Information to any person who is not bound by similar obligations of confidentiality and non-use as contained herein.

However, you will not be bound by any obligations of confidentiality and non-use to the extent that you are clearly able to demonstrate that any part of the Information:

- (i) was known to you prior to any disclosure by WHO and/or the manufacturer(s); or
- (ii) was in the public domain at the time of disclosure by WHO and/or the manufacturer(s); or
- (iii) has become part of the public domain through no fault of your own; or
- (iv) has become available to you from a third party not in breach of any legal obligations of confidentiality to WHO and/or the manufacturer(s).

You also undertake not to communicate the deliberations and findings of the joint review of the clinical trial application, as well as any resulting recommendations and/or decisions of the ECs and NRAs, “received the submissions” to any third party, except as explicitly agreed by sponsor.

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You will discharge your responsibilities hereunder exclusively in your capacity as an expert adviser to WHO. By signing this Agreement, you furthermore confirm that you have no financial interest and/or other relationship with a party, which:

- (i) may have a vested commercial interest in obtaining access to any part of the Information referred to above; and/or
- (ii) may have a vested interest in the outcome of the review, in which you will participate, including but not limited to parties, such as the manufacturer(s) of the candidate product that is (are) to be tested in the clinical trial(s) or manufacturers of competing candidates.

In this regard, it should be noted that the manufacturer(s) of the candidate product or sponsors of the clinical trial under review have the right to object to your participation in the joint review especially when there is conflict of interest. If such objection cannot be resolved in consultation with the manufacturer(s) or trial sponsors, WHO shall be entitled to terminate this Agreement or cancel participation by you hereunder.

I hereby agree to the conditions and provisions contained in this document.

Signed:

Title of Joint Review:

Signature: \_\_\_\_\_

Name (typewritten): \_\_\_\_\_

Institute: \_\_\_\_\_

Place: \_\_\_\_\_

Date: \_\_\_\_\_

## Annex C

## Prioritization of clinical trial applications for joint reviews

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This annex to the “Guideline for Joint and Assisted Reviews of Clinical Trial Applications” aims to define criteria for the prioritization of clinical trial applications for joint review. The prioritization of clinical trial applications is based on several **factors**:

### A. Severity of the disease:

1. *Public health emergencies or any other situations upon request by the RECs or member countries*

In emergency situations, and provided that there is no licensed medical product, AVAREF will consider any potential product under development that has robust pre-clinical data a priority for joint reviews.

2. *Normal circumstances (excluding emergencies)*

Clinical trial applications for joint reviews shall be considered based on the following:

#### i. Disease scenarios

##### a) Disease scenarios involving pathogenicity

- Diseases causing high mortality
- Diseases causing high morbidity
- Diseases with associated severe complications
- Diseases with severe sequela

##### b) Disease scenarios involving transmissibility

- Diseases with effective human-to-human airborne transmission
- Diseases with effective human-to-human sexual transmission
- Diseases with effective foodborne transmission
- Diseases with a common intermediate host
- Diseases with a common vector
- Diseases with a common reservoir, eg bats

##### c) Diseases with unusual patterns

- Localized – even endemic- diseases beginning to spread
- Diseases rapidly spreading
- Diseases spreading to new areas, eg Lassa fever, MERS-CoV
- Diseases demonstrating novel resistance to common countermeasures

##### d) Diseases causing disruption, eg Ebola virus

- Diseases perceived by the general public to pose a particular risk
- Diseases causing civil disruption
- Diseases causing economic disruption

##### e) Countermeasures

- There are none or insufficient effective countermeasures
- Countermeasures are too expensive, complicated, or unavailable for wide scale use
- There is increasing resistance to available countermeasures

**f) Other scenarios**

- Diseases causing high animal morbidity or mortality, eg zoonotic diseases, H1N1

**ii. Availability of reliable data**

- a. Pre-clinical safety/efficacy and proof of concept data
  - a. Vaccines:
    - i. immunogenicity data
    - ii. passive protection in challenge
  - b. Others (biologics, NCE, gene therapy):
    - i. protection or cure in challenge
- b. First-in human safety; and immunogenicity data (vaccines)
- c. Dose finding and proof of concept (S/E)
- d. Efficacy data for late phase trials, or proving immunobridging (correlate of protection)
- e. Commitment to continue the clinical development of the candidate product

**The prioritization criteria are based on:**

1. Human transmission
2. Medical countermeasures
3. Severity or case fatality rate
4. Joint human-animal interface
5. Public health context of the affected area
6. Potential societal impacts
7. Evolutionary potential
8. Other factors

It is recognized that not all the criteria are equally critical; therefore, they have to be weighed individually.

**Co-factors for prioritization include:**

1. Human transmission
  - a) There is evidence of human to human transmission
  - b) There is widespread human to human transmission, eg airborne agents
  - c) There is more than one route of human to human transmission
  - d) The disease frequently involves infectivity before the onset of symptoms
  - e) The pathogen is able to remain infectious for a prolonged period in an infected individual when convalescent or apparently recovered
  - f) There is evidence of super-spreading events
  - g) The disease is likely to be amplified in a healthcare setting
2. Medical countermeasures; specifically for registered medical products commercially available, or advanced candidates; eg undergoing late phase clinical trials, or other available treatments
  - a) Unavailability of diagnostics effective and suitable for use in the field, or in a clinic or local healthcare setting
  - b) Effective diagnostics are available but they are only suitable for use in specialized facilities
  - c) There are no effective vaccines, human or animal, or prophylactics
  - d) There are no effective vaccines, human or animal, or prophylactics suitable for use in resource limited settings
  - e) There are no effective drugs or therapies

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- f) There are no effective drugs or therapies appropriate for use in resource limited settings
  - g) The outbreak cannot be controlled with common public health measures including contact tracing, isolation of infected patients, social distancing, closure of public events, schooling, and/or changes to cultural practices, eg burial rights, vector control, strict management of livestock movement, etc
3. Severity or case fatality rate
    - a) The disease causes high mortality
    - b) The disease frequently causes high morbidity including severe complications or sequelae
  4. Joint human-animal interface
    - a) The role of animals (including arthropods) in the transmission of the disease to people is well characterized
    - b) The transmission routes from animals (including arthropods) to humans are likely to result in high levels of human infections
    - c) The pathogen is capable of infecting multiple animal species
    - d) The animal species transmitting the disease are widely distributed and abundant
    - e) Arthropoda are responsible for transmitting the disease and are widely distributed
  5. Public health context of the affected area
    - a) The disease requires targeted surveillance, eg it is unlikely to be detected by routine surveillance but might be detected by active or sentinel surveillance
    - b) Disease control requires specialist interventions including highly skilled personnel, equipment: isolation units, respirators, personal protective equipment, etc, and infection control measures
  6. Potential societal impacts
    - a) The disease has a disproportionate impact on special populations such as pregnant women, children, immunocompromised patients, etc
    - b) The disease can cause major social disruption
    - c) The disease can cause major fear
    - d) The disease can result in major economic impact
    - e) The disease can result in major disruptions to healthcare delivery
  7. Evolutionary potential
    - a) There is evidence of rapid pathogen evolution, eg resistance, vector switch
    - b) There is a trend towards increasing severity of the disease
    - c) There is a trend towards increasing transmissibility of the pathogen
  8. Other factors
    - a) The geographic range of the pathogen has changed
    - b) The pathogen shares relevant epidemiological and/or genotypic characteristics with agents that have caused important epidemics
    - c) The natural disease does not result in robust protective immunity
    - d) The disease carries a high risk of occupational exposure for those involved in a response, eg culling, vets, undertakers, lab workers, first responders, healthcare workers, etc
    - e) The pathogen is an agent likely to cause deliberate outbreaks

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Scoring matrix of prioritization for AVAREF joint review CTA cases				
Note: This scoring applies to assess the severity of public health emergency				
No.	Criteria to assess	Sub-criteria	Questionnaire	Score (1/3/5)
1	Normal circumstances (excluding emergencies)	Disease scenarios involving pathogenicity	Diseases causing high mortality	
			Diseases causing high morbidity	
			Diseases with associated severe complications	
			Diseases with severe sequela	
		Disease scenarios involving transmissibility	Diseases with effective human-to-human airborne transmission	
			Diseases with effective human-to-human sexual transmission	
			Diseases with effective foodborne transmission	
			Diseases with a common intermediate host	
			Diseases with a common vector	
			Diseases with a common reservoir e.g. bats	
		Diseases with unusual patterns	Localized – even endemic- diseases beginning to spread	
			Diseases rapidly spreading	
			Diseases spreading to new areas, eg Lassa fever, MERS-CoV	
			Diseases demonstrating novel resistance to common medical treatments	
		Diseases causing disruption, eg Ebola virus	Diseases perceived by the general public to pose a particular risk	
			Diseases causing civil disruption	
			Diseases causing economic disruption	
		Countermeasures	There are none or insufficient effective countermeasures	
			Countermeasures are too expensive, complicated, or unavailable for wide scale use	
			There is increasing resistance to available countermeasures	
		Other scenarios	Diseases causing severe high animal morbidity or mortality, eg zoonotic diseases, H1N1	
2	Availability of reliable data	Pre-clinical safety/efficacy and proof of concept data	Vaccines: immunogenicity data	
			Vaccines: passive protection in challenge	
			Other medical products (biologics, NCE, gene therapy): protection or cure in challenge	
		First-in human safety; and immunogenicity data (vaccines)		
		Dose finding and proof of concept (S/E)		
		Efficacy data for late phase trials, or proving immuno-bridging (correlate of protection)		
		Commitment to continue the clinical development of the candidate product		
Total score				

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Scoring matrix of prioritization for AVAREF joint review CTA cases			
Note: This scoring applies only to non-emergency CTA cases (excludes public health emergency cases)			
No.	Prioritization Criteria	Co-factors for prioritization	Score (1/3/5)
1	Human transmission	There is evidence of human to human transmission.	
		There is widespread human to human transmission, eg airborne agents.	
		There is more than one route of human to human transmission.	
		The disease frequently involves infectivity before the onset of symptoms.	
		The pathogen is able to remain infectious for a prolonged period in an infected individual when convalescent or apparently recovered.	
		There is evidence of super spreading events.	
		The disease is likely to be amplified in a healthcare setting.	
2	Medical countermeasures	Unavailability of diagnostics effective and suitable for use in the field, or in a clinic or local healthcare setting	
		Effective diagnostics are available but they are only suitable for use in specialized facilities	
		There are no effective vaccines, human or animal, or prophylactics	
		There are no effective vaccines, human or animal, or prophylactics suitable for use in resource limited settings	
		There are no effective drugs or therapies	
		There are no effective drugs or therapies appropriate for use in resource limited settings	
		The outbreak cannot be controlled with common public health measures including contact tracing, isolation of infected patients, social distancing, closure of public events, schooling, and/or changes to cultural practices, eg burial rights, vector control, strict management of livestock movement, etc	
3	Severity or case fatality rate	The disease causes high mortality.	
		The disease frequently causes high morbidity including severe complications or sequelae.	
4	Human-animal interface	The role of animals (including arthropods) in the transmission of the disease to people is well characterized.	
		The transmission routes from animals (including arthropods) to humans are likely to result in high levels of human infections.	
		The pathogen is capable of infecting multiple animal species.	
		The animal species transmitting the disease are widely distributed and abundant.	
		Arthropoda are responsible for transmitting the disease and are widely distributed.	
5	Public health context of the affected area	The disease requires targeted surveillance, eg it is unlikely to be detected by routine surveillance but might be detected by active or sentinel surveillance	
		Disease control requires specialist interventions including highly skilled personnel, equipment: isolation units, respirators, personal protective , etc, and infection control measures	
6	Potential societal impacts	The disease has a disproportionate impact on special populations such as pregnant women, children, immunocompromised patients, etc.	
		The disease can cause major social disruption.	
		The disease can cause major fear.	
		The disease can result in major economic impact.	
7	Evolutionary potential	The disease can result in major disruptions to healthcare delivery.	
		There is evidence of rapid pathogen evolution, eg resistance, vector switch	
		There is a trend towards increasing severity of the disease.	
8	Other factors	There is a trend towards increasing transmissibility of the pathogen.	
		The geographic range of the pathogen has changed.	
		The pathogen shares relevant epidemiological and/or genotypic characteristics with agents that have caused important epidemics.	
		The natural disease does not result in robust protective immunity.	
		The disease carries a high risk of occupational exposure for those involved in a response, eg culling, vets, undertakers, lab workers, first responders, healthcare workers, etc.	
Total score		The pathogen is an agent likely to cause deliberate outbreaks.	

## Annex D

## Procedures for importation and release of investigational medical products<sup>11</sup>

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### 1. Introduction

Investigational medical products (IMP), unregistered medicines or registered products undergoing trials for indications outside of the marketing authorization may only be brought into the country after ethical approvals are in place, the clinical trial application is approved, and a letter of authorization has been issued by the national regulatory authority (NRA).

The NRA of the producing country is responsible for assuring compliance with good manufacturing practices (GMP) for the manufacture and lot release of IMPs<sup>12</sup>. The NRA has to confirm that the marketing authorization holder (MAH) has the permanent services of at least one qualified person (QP). The QP is responsible for ensuring the following:

- a) IMPs: the manufacture and control of each batch is in accordance with global GMP standards for medical products for human use, and with the product specification file; each production batch should be controlled in accordance with the information submitted in the clinical trial application
- b) Comparators produced and registered in a third country for which information on manufacturing is unavailable: verify that each production batch has undergone all relevant analyses, tests or controls necessary to confirm its quality in accordance with the clinical trial application

If the provisions lay down in (a) or (b) are followed, IMPs shall not have to undergo any further testing when imported into the country where the clinical trial is to be conducted. A batch release certification signed by the QP should be provided with the shipment.

In all cases, the QP has to certify in a register or an equivalent document that each production batch satisfies provisions (a) and (b). The register or its equivalent should be updated as operations are carried out. It shall remain at the disposal of the NRA inspectors for at least five years.

### 2. Scope

This guideline applies to all IMPs, which do not have marketing authorization in the country of intended use.

The same procedures apply to the placebo or to the comparator, if applicable.

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<sup>11</sup> Adapted from Guidelines for importation and release of investigational medicinal products, WHO, 2013.

<sup>12</sup> IMP include vaccines, biologics, and blood and blood products



Any subsequent importations of the IMP should be subject to the same procedures for the validity of the trial authorization.

### **3. Responsibilities of the sponsor**

The sponsor should not supply an IMP before obtaining all the permits from the ethics committee(s) and NRA(s).

The sponsor should ensure that the IMP is characterized appropriately according to its stage of development, manufactured according to GMP, and coded and labelled appropriately to protect the blinding, if applicable.

The sponsor is responsible for defining the IMP's acceptable storage temperatures and storage conditions, eg protection from light, storage times, reconstitution fluids and procedures, and devices for product infusion, if any.

The sponsor should:

- Ensure timely delivery of IMP(s) to the investigator(s)
- Maintain records documenting shipment, receipt, disposition, return, and destruction of the IMP
- Maintain a system to retrieve IMP(s) and document this retrieval, eg for deficient product recall, reclaim after trial completion, expired product reclaim
- Maintain a system for the disposition of unused IMPs and to document this disposition
- Ensure that the IMP(s) are stable over their period of use; the data should be available on request and for inspection purposes. The sponsor has to notify the investigators and take appropriate steps if noncompliance with the specifications becomes evident in the stability studies concomitantly with the clinical trial,
- Maintain sufficient quantities of the IMP(s) used in the trial to reconfirm specifications, should this become necessary, and to keep records of batch sample analyses and characteristics. To the extent that stability permits, samples should be retained until the analyses of the trial data are complete, or as required by the applicable regulatory requirement(s), whichever is the longest period

#### **4. Labelling and packaging**

The labelling of IMP(s) has to comply with the relevant NRA requirements. The particulars should be given in at least the official language of the country. They should appear on the outer packaging or, if there is no outer packaging, on the immediate packaging. It is expected that at least the following information will be provided:

- Clear statement to indicate that it is clinical trial material
- Product name or unique code
- Storage temperature and conditions
- Expiry date
- Sponsor's contact details

IMP(s) should be packaged so as to prevent contamination and unacceptable deterioration during transport and storage.

The IMP(s) have to be stored as specified by the sponsor and in line with good pharmacy practice and GMP, and the NRA's regulations and conditions (if applicable).

For blinded trials, the coding system for the IMP(s) should include a mechanism that allows for rapid identification in case of a medical emergency but without breaking the blind.

#### **5. Importation and release**

Shipping of the IMP(s) should be conducted according to the instructions given by or on behalf of the sponsor in the shipping order.

A pre-clearance inspection should be carried out at the port of entry by the NRA. The purpose is to verify the shipping documentation and the overall physical condition of the consignment (see 0).

Depending on the product, specific storage conditions may be essential to ensure the quality of the product, eg maintaining the cold chain for vaccines. In that case, a device to confirm that storage temperatures were not exceeded during the transportation has to be included with the shipment.

## 6. Documentation

It is expected that the documentation provided with each IMP(s) consignment will enable the NRA at the port of entry to release it to the investigator(s) responsible for conducting the clinical trial in the country.

The following should be included:

- Certificates of analysis of each IMP(s) batch
- A copy of the clinical trial approval letter or certificate from the NRA
- A copy of a valid GMP certificate issued by the NRA in the country of origin where applicable
- Lot release certificate, if applicable
- A copy of a valid WHO certificate of a pharmaceutical product issued by the competent Regulatory Authority in the country of origin, if applicable

The sponsor has to complete a cover letter, which has to be sent with each IMP(s) consignment (Appendix 1).

The checklist provided in Annex 1 could be used by the sponsor to ensure that all required documents are attached and correct. A blank document has to be submitted with the cover letter to the NRA responsible for authorizing the importation of the IMP (Appendix 2).

## 7. Definitions and abbreviations

CoA: Certificate of analysis

GMP: Good manufacturing practices

IMP: Investigational medical product

It is a pharmaceutical form of an active substance or placebo tested or used as a reference in a clinical trial, including products with a marketing authorization but used or assembled (formulated or packaged) in a way different from the authorized form, or when used for an unauthorized indication, or when used to gain further information about the authorized form.

NRA: National regulatory authority

QP: Qualified person

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

**Appendix 1**

<b>Cover letter (to be completed by the sponsor)</b>	
<b>Importation and release of investigational medical products</b>	
Fees (if applicable)	
Study title and phase of the study	
Protocol number	
Study drug	
Unique code number	
NRA approval number	
NRA reference number(s) of the comparator drug(s) (if applicable)	
NRA reference number(s) of concomitant drug(s) (if applicable)	
Sponsor	
Applicant	
Trial site(s)	
Sponsor contact person: Address Telephone number Fax number Cell number E-mail address	
Batch number(s) and expiry date: Study drug Comparator drug(s)	
Quantities	
Blinding: yes/no	
Recommended storage temperature	

## Appendix 2

### Checklist of the required documentation

*to be supplied by the sponsor for use by the NRA responsible for authorizing the IMP's importation*

<b>Importation and release of investigational medicinal products</b>			
<b>Checklist of required documentation</b>			
<b>Are the following documents attached and correct, as indicated:</b>		<b>Yes</b>	<b>No</b>
1	Copy of NRA letter of approval of clinical trial		
2	Certificate(s) of Analysis (CoA) Study drug Comparator (if applicable)		
3	Does the CoA reflect at least the following information: Product name or code Name of company / Sponsor Batch number Expiry date Date of issue Signature, qualification and title of responsible person Results of physical and analytical tests		
4	Copy of a valid certificate of manufacture issued by the competent NRA in the country of origin, if applicable		
5	WHO certificate of a pharmaceutical product issued by the competent Regulatory Authority in the country of origin, if applicable		
6	Device / Proof of maintenance of cold chain (if applicable)		
7	Labelling: <i>outer packaging, immediate container</i> Does the label clearly indicate		
7.1	that the product is clinical trial material, e.g. "For use in clinical trial only"		
7.2	Product name or unique code (if blinded) <i>Does this concur with the information on the Cover Sheet</i>		
7.3	Storage temperature <i>Does this concur with the information on the Cover Sheet</i>		
7.4	Storage conditions (e.g. protection from light)		
7.5	Batch number <i>Does this concur with the information on the Cover Sheet</i>		
7.6	Date of Manufacture		
7.7	Expiry date <i>Does this concur with the information on the Cover Sheet</i>		
<b>Importation and release of investigational medicinal products</b>			

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<b>Checklist of required documentation</b>			
<b>Are the following documents attached and correct, as indicated:</b>		<b>Yes</b>	<b>No</b>
7.8	Sponsor contact details		
	<i>Does this concur with the information on the Cover Sheet</i>		
8	Is the physical condition of the consignment acceptable?		