

**African Vaccine Regulatory Forum (AVAREF)
Strategy and Guidance for Emergency Preparedness**

AVAREF Strategy and Guidance for Emergency Preparedness

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1.0 Definitions

Assisted Review – An approach, which may be used on a case-by-case basis to assist a single country in the review of a Clinical Trial Application (CTA), or to assist a country in processing of a CTA undergoing joint review, in the in-country level steps. The request for assistance comes from the country to WHO, and in an AVAREF Assisted Emergency Review, the request for assistance comes from the country to AVAREF Secretariat for coordination purpose.

Candidate vaccines- Any product which has gone through pre-clinical assessment and received a positive go-no-go verdict or decision and is ready to enter Phase I clinical trials.

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.

Emergency – An emergency is any public health event of national, international, or global concern.

Invited experts – Experts and representatives from better-resourced National regulatory Authorities (NRAs) and ethics committees (ECs) 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.

Joint Review- AVAREF joint review process which brings experts from the NRAs and ECs of two or more countries, together with the sponsor, investigators, 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. In response to an epidemic or pandemic situation, a timeline of 10-15 days would be appropriate for the entire joint review cycle.

Neutral partner – 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 - Countries where the clinical trial is not taking place. Representatives from the NRA and EC of a country not participating in the clinical trial may be invited to the joint review as observers. Observers do not participate in the decision-making process.

Participating countries – 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 the country's NRA and EC in consultation with the convener.

Public Health Emergencies - An outbreak of a disease declared by WHO as an emergency of international concern. It also includes any outbreak of a disease declared as national, sub-regional, or regional epidemic.

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 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. Representative of the sponsor for the joint review may include the Principal Investigators (PIs) of the different sites, experts in the clinical development of the product, experts in production and control of the investigational product, etc.

2.0 Acronyms

| | |
|---------|---|
| AAR | After Action Reviews |
| ADR | Adverse Drug Reaction |
| AEFI | Adverse Events following Immunization |
| AVAREF | African Vaccine Regulatory Forum |
| AMRH | African Medicines Regulatory Harmonization |
| CT | Clinical Trials |
| CTA | Clinical Trial Application |
| EC | Ethics Committee |
| IRB | Institutional Review Board |
| LoQ | List of Questions |
| MTA | Material Transfer Agreement |
| MOU | Memorandum of Understanding |
| NGO | Non-governmental Organization |
| NRA | National Regulatory Authority |
| PHEIC | Public Health Emergency of International Concern |
| PI | Principal Investigator |
| REC | Regional Economic Community |
| UN | United Nations |
| WHO | World Health Organization |
| WHO EUL | World Health Organization Emergency Use Listing |
| WHO TRS | World Health Organization Technical Report Series |

3.0 Background

The African Vaccine Regulatory Forum (AVAREF) created by the WHO in 2006 as an informal capacity building network aimed at improving the ethics and 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 priority public health vaccines. Critically, as the Ebola experience demonstrated, collaboration and information exchange should not end at the point of joint review of clinical protocols but should cover the entirety of the product life cycle.

With the adoption in 2016 of a revised governance structure and the expansion in scope from vaccines to medical products, the AVAREF Steering Committee developed a strategic plan to realize the potential of this new operating model. In 2017, WHO in collaboration with partners organized a tabletop exercise using MERS-CoV as an example, to test the readiness of AVAREF to address clinical trials in the face of an epidemic or pandemic. The outcome of that exercise is this current strategy and guide which has been developed to expedite reviews and clearance of clinical trial applications, and to provide oversight to ensure efficient and informative trials.

Additionally, the AVAREF Strategic plan¹ (2018-2020) aligns with the African Medicines Regulatory Harmonization (AMRH²) objectives and contains provisions to enhance emergency preparedness and capacity building for decision makers and those with technical responsibility for ethics and regulatory approval of clinical trials. This is significant because delayed decision-making in emergency situations could impede use of interventions with potential for reducing morbidity and mortality. It is assumed that each National Regulatory Authorities (NRAs) will have their own legal frameworks and national guidelines which mandate them to provide oversight for all clinical trials in their respective countries.

4.0 Purpose of the Strategy and Guide

The purpose of this document is to guide and assist ethics committees (ECs) and national regulatory authorities (NRAs) to plan, undertake expedited reviews and approvals of clinical trial applications, and provide oversight of trials during a pandemic or epidemic. This strategy is consistent with national emergency preparedness and response plans for public health emergencies.

It is also intended to inform and guide regulators and ethics committees of the Regional Economic Communities (RECs) in Africa and sponsors on the critical elements of emergency preparedness to ensure that ethics and regulatory decisions do not constitute barrier to access, but rather promote public health. Ultimately, the intention is to facilitate compliance of all stakeholders with the ethics and regulatory requirements of countries in the review and approval of clinical trials of medicines and vaccines as outlined in each country's regulatory frameworks.

¹ https://www.afro.who.int/sites/default/files/2018-07/2018-2020_Avaref_Strategic_Plan.pdf

² <https://apps.who.int/medicinedocs/documents/s20130en/s20130en.pdf>

This document does not replace national guidelines and processes for reviews of clinical trial applications and should be used together with the provisions of WHO's Technical Report Series on review of clinical trials, WHO Technical Report Series No 924 (Guidelines on Clinical Evaluation of Vaccines: Regulatory Expectations), together with related WHO documents^{3,4,5,6} and other related international guidelines.

5.0 Scope

In the event of epidemics, pandemics, or other health emergencies, the AVAREF platform is well positioned to facilitate clinical trials approval, accelerated product development, and access to life saving vaccines and medicines. The role of AVAREF extends beyond joint reviews, and includes engagement and provision of guidance to countries, RECs, and research consortia. This strategy and guidance will prepare the African continent to respond to epidemic and pandemic situations with concerted preparedness for expedited CTA processing needed to prevent delays in access to lifesaving medicines and vaccines.

The document recognizes the WHO Blueprint list of priority diseases, as well as other priority health threats in Africa. The scope covers all the steps of a joint review of eligible clinical trial applications, the decision making, including post- decision processes involved, as well as processes for effective communication in an emergency applicable to Phase I, Phase II and Phase III clinical trials.

6.0 Strategy for Emergency Preparedness

Many countries have developed national pandemic preparedness plans, which typically focus on in-country strategies to be applied in preparation for and during influenza pandemics. These plans should be robust enough to be applicable to other potential public health emergencies with epidemic/pandemic potential. The AVAREF Strategy and Guidance for Emergency Preparedness differs significantly in that the focus is on harmonization of the ethical and regulatory components of emergency preparedness within the continent. Implementation of these plans by testing and simulation at country level, within RECs and as a continent, is key to the success of a convergent strategy for Africa.

At the country level, the emergency preparedness plans should be developed within the context

³ The AVAREF Guideline for Joint and Assisted Reviews of Clinical Trial Applications for National Regulatory Authorities (NRAs) and Ethics Committees (ECs) <https://www.afro.who.int/publications/avaref-assembly-resolution-avaref-guideline-joint-and-assisted-reviews-clinical-trial>

⁴ WHO TRS No 1004 Annex 7 –Guideline on Regulatory Preparedness for Provision of Marketing Authorization of Human Pandemic Influenza Vaccines in Non-vaccine Producing Countries <https://apps.who.int/medicinedocs/documents/s23326en/s23326en.pdf>

⁵ WHO Emergency Use Assessment and Listing Procedure (EUAL) for candidate vaccines for use in the context of a public health emergency <https://apps.who.int/medicinedocs/documents/s21987en/s21987en.pdf>

⁶ WHO Guidelines for Safe Disposal of Unwanted Pharmaceuticals in and after Emergencies https://www.who.int/water_sanitation_health/medicalwaste/unwantpharm.pdf?ua=1

of existing legislature and national pandemic preparedness plan. The plans will then have to be tested and go through the required approval process. Country level plans should cover at least the following- ethics and regulatory instruments/pathways for expedited clinical trial application review; importation of investigational products and transfer of biological specimens during a public health emergency; appointment of focal points and establishment of clear operating procedures for working under emergency conditions including timelines, and effective emergency communication channels.

At the level of RECs, emergency preparedness involves emergency procedures for joint review of investigational products/vaccine candidates for clinical trials, data sharing, communication and conduction of simulations.

Recommendations for the minimum provisions of the emergency preparedness strategy are described below. Countries are encouraged to include other relevant details in order that the plan is functional and in line with local regulations. Care should be taken to ensure that the proposed timelines are maintained and that the procedures are transparent and straightforward.

6.1 Communication and Rapid Alert Systems between NRAs, ECs, AVAREF Secretariat and WHO

In the event of pandemics/epidemics or other health emergencies, it is essential to have strong communication mechanisms between NRAs, ethics committees, AVAREF Secretariat and WHO not only to share as fast as possible the latest information and epidemiologic data of the pandemics/epidemics, but also growing scientific knowledge on the pathogen and any potential in vitro diagnostics, therapeutics, and vaccines. To this end, the use of online platforms for efficient communication becomes very critical. Through the online platform, the members should be able to access critical regulatory updates including the use of unapproved therapeutics, circulation of counterfeit medicines, shortage of drug supplies, recent clinical developments of target medicines and vaccines, approvals of alternative therapeutics in other countries, etc.

6.2 Pathways for Emergency Ethics and Regulatory Review

Each country should develop and formalize through relevant administrative approval processes, an ethics and regulatory review pathway for emergencies. Without compromising patient safety, using the shortest realistic timelines, access to vital interventions must be prioritized and ensured. To make the emergency review pathway shorter and more efficient, ethics and regulatory reviews should be parallel/simultaneous, with close collaboration and effective communication between ethics and regulatory groups, and shorter decision-making procedures. The success of the emergency joint review process relies heavily on efficient and expedited processing of the CTA at country level. Countries need to efficiently manage the in-country steps for emergency joint reviews to reflect the urgency of the situation and to avoid any delays.

A timeline of 10 working days is suggested for processing CTAs where the product is already registered for other indications, and 15 working days for novel products. These timelines are for the entire review process from receipt of CTA to the final decision and applies to parallel submissions to both EC and NRA, with exception of clock stops.

Countries can request for technical support from AVAREF secretariat if needed, to expedite country level ethics and regulatory reviews. Such requests should be communicated to AVAREF immediately after pre-screening the application to enable facilitation and provision of technical support without undue delay. Where possible, countries are encouraged to participate in multi-national clinical trials in order to share expertise and workload and improve upon efficiency of product development.

6.3 Practical Steps for Submitting an Application

To initiate the submission process, the applicant should send an email of intention to the EC and NRA, with a copy to the AVAREF Secretariat. The EC and NRA will then set up a pre-submission meeting (via a mutually convenient medium) with the applicant and communicate the meeting outcome to AVAREF Secretariat. E-mail contacts and phone numbers for all countries will be made available on the AVAREF Website together with a list of countries with websites and portals for electronic submissions. The AVAREF CTA format⁷ should be used to prepare and submit online applications to ECs and NRAs.

6.4 Importation of Investigational Products in a Public Health Emergency

Specific permits are needed for the importation of investigational products to be used for approved clinical trials and for emergency use authorization during a public health emergency. Each country, according to its legal provision may have a different approach, or in some cases may not have one developed yet. In order that the inter country differences do not constitute an additional barrier to access to the product, it is recommended that countries within RECs develop a harmonized procedure for the importation of investigational product for use in approved clinical trials and emergency use authorization.

The procedure for importation of each investigational product should address administrative details, product labeling, how the product should be used, quantities being imported, in-country responsible authority, responsibility for adverse events (AEs), monitoring, and all other relevant details as agreed upon by the countries.

6.5 Exchange and Transfer of Biological Specimens during Public Health Emergencies

⁷ https://www.afro.who.int/sites/default/files/2019-09/2-Avaref_Clinical_trial_application_form_11Sept2019.pdf

An effective response to a public health emergency can depend on the ability to move biological material and data from one place to another to advance research into the cause and appropriate medical countermeasures. The movement of such specimens and any associated data must be as simple and as transparent as possible and must protect the interests of the population sampled.

Improved awareness of the value of specimens and data has led to increased demand for this protection, also enshrined in the Material Transfer Agreement (MTA) contracts. These agreements govern the transfer of research materials between two organizations (or countries) and define the rights of the provider and the recipient to the utilization of the materials as well as to publication rights. Biological specimens, such as reagents, plasma, serum, cell lines, and microorganisms are the most frequently transferred materials.

Lessons from the Ebola epidemic in West Africa and the Zika-related public health emergency revealed that lack of time and capacity to effectively negotiate limited the possibility of setting up favorable MTAs. It is therefore important to build the necessary capacity and establish the needed processes in advance of public health emergencies.

Key aspects of MTAs include ownership and custodianship, incentives for sharing specimens, as well as intellectual property. An agreement in principle about what biological specimens can be exchanged and transferred, to which organizations, and for which purpose, and development of the related documents and procedures as well as identification of decision makers in the process must be done by each country's Ethics Committee, in agreement with their applicable national agencies who will ultimately issue the related permits.

AVAREF secretariat is available to offer technical guidance for this process. The final decision and responsibility will rest with individual countries regarding whether to permit transfer of biological specimens or not.

6.6 Appointment of Focal Points for Ethics Committees and NRAs in Public Health Emergencies

The appointment and empowerment of country specific ethics and regulatory focal points for clinical trials is an important aspect of emergency preparedness. The ethics and regulatory focal points will have the responsibility of being accessible at pre-agreed times for communications with AVAREF Secretariat during the period of the emergency.

For the focal points to be effective, country specific legal and administrative authorization needs to be carefully addressed so that they can function as expected. These may differ from country to country and may not be immediately apparent.

The ethics and regulatory focal points responsible for clinical trials in a specific country should have clearly established links with their counterparts to facilitate parallel review of CTAs. They should also have coordination mechanisms with other focal points in the REC for multi-site trials involving other countries and facilitated by AVAREF secretariat.

The responsibilities of the focal points, in addition to being available without exception during the pre-determined period include:

- Serving as linkage within each country to facilitate parallel review of CTAs, and coordinating with other focal points in the REC for multi-site trials involving other countries;
- Responding on behalf of the NRA or EC to clinical trial sites for any requests;
- Information sharing with AVAREF contact point regarding progress of CTA applications and in-country post approval steps;
- Responding to AVAREF contact point requests for consultations, verifications, or on other matters which may arise;
- Serve as recipient and disseminator for information received from AVAREF contact point for agreed audience and purpose;
- Encourage as much as possible adherence to processing timelines.

6.7 Communication during a Public Health Emergency

Communication for preparedness during public health emergencies must be carefully planned, implemented, and properly integrated with other existing emergency management activities and operations. Communicating effectively through the media during public health emergencies requires an effective strategy; identifying trained, well informed, and approved senior single/focal spokespersons to represent the health organization, as well as providing clear, factual messages, which will address current public concerns. Though emergencies are unpredictable, it is clearly a key responsibility of public health professionals, even in an advisory role, to establish effective media communication strategies which can be planned, tested and approved in advance, contributing greatly to and furthering public health objectives by informing and calming the public, reducing misinformation, directing focus onto critical issues, and helping to minimize the impact of adverse socio-economic and political repercussions. Therefore, ECs and NRAs must put in place effective media communication incorporating these elements.

Lack of adequate preparation for emergency situations could result in poor communication and lead to public perception of incompetence, insensitivity, or lack of transparency. This guide should be used by countries and RECs in conjunction with the WHO handbook on Effective Media Communication during Public Health Emergencies⁸ which describes tried and tested effective communication strategies for developing relevant communication plans.

6.8 Emergency Joint Review Procedure

A guideline already exists for joint reviews. Eligibility criteria of a candidate vaccine/medicine for the emergency procedure is same as for the joint review procedure and includes the

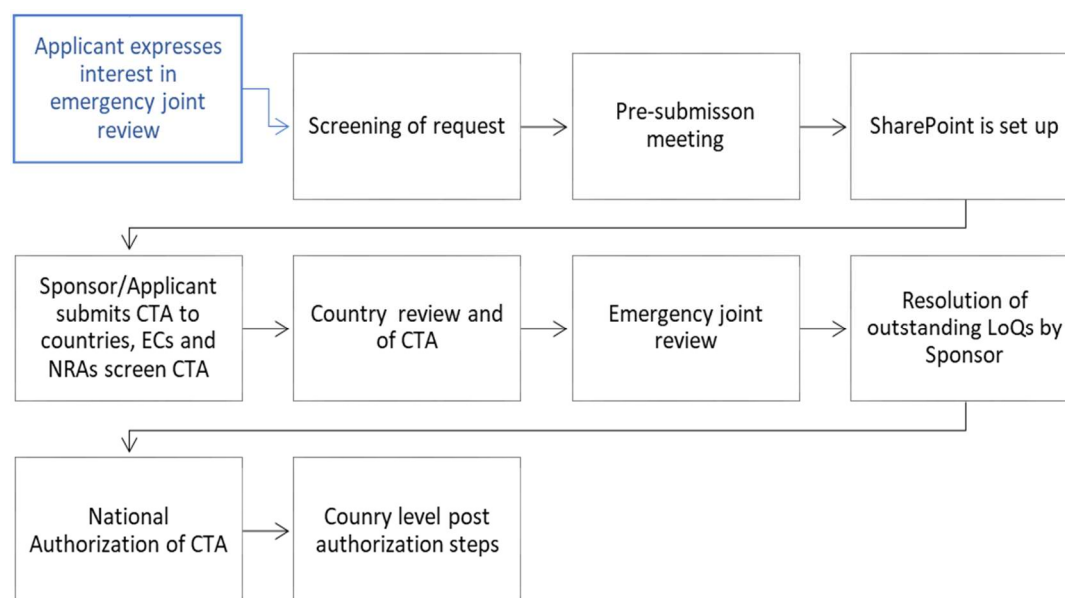
⁸ https://apps.who.int/iris/bitstream/handle/10665/43511/WHO_CDS_2005.31_eng.pdf?sequence=1

following: that the product addresses a disease of national, sub-regional, or regional emergency, for which the Director General of the World Health Organization has declared a Public Health Emergency of International Concern (PHEIC).

6.8.1 Process Steps and Timelines for Emergency Joint Review

The process steps for emergency joint reviews are shown in Figure 1.

Figure 1 Process Steps for Emergency Joint Review



The emergency joint review process is initiated when the applicant submits an expression of interest to the AVAREF Secretariat. The email addresses are provided in Table 1. The applicant receives an acknowledgement of submission from AVAREF Secretariat.

Step 1 - Screening of Request

The request is screened against eligibility criteria by the AVAREF Secretariat and the AVAREF Technical Coordinating Committee (TCC).

Step 2 - Pre-submission meeting

AVAREF Secretariat convenes a virtual pre-submission meeting 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 an emergency joint review in accordance with the provisions of this guideline. Applicant is made aware of all administrative requirements which will apply at country level. A date and other details for the joint review meeting are also set in a closed session. Representatives of ECs and NRAs attending the pre-submission meeting will have the authority to decide on their participation in the emergency joint review and commit to nominate reviewers. The sponsor

provides a waiver agreement to share existing information about the application.

Step 3 – Setting up a SharePoint

On the same day as the pre-submission meeting, a SharePoint is set up by WHO and AVAREF Secretariat and made accessible to the Sponsor and all NRAs and ECs/IRBs for target countries.

Step 4 - Submission to countries and screening by ECs and NRAs

The sponsor submits the applications to ECs and NRAs as agreed during the pre-submission meeting and fulfills all administrative requirements (including payment of fees as applicable). The goal is to have parallel submissions in all countries. Information on the product and proposed trial must be identical, as attested to in writing by the sponsor prior to all participants.

Step 5 - Country review of the CTA

Once the application has passed the screening/validation step, the NRA and EC in each participating country review the CTA and upload a list of questions onto the SharePoint which has been set up for this purpose. Supporting agencies and invited experts may also do the same. Comments will be accessible to all joint review participants, and the sponsor.

Step 6 - Emergency joint review

AVAREF Secretariat convenes the joint review meeting at the agreed upon date and location, the meeting may be virtual or physical. Depending on the anticipated complexity of the review, 1-2 working days will be allotted for the review. AVAREF Secretariat 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 normal joint review format:

Opening session (all participants):

AVAREF's role:

To brief on the joint review process

To introduce the objectives of the meeting, format, agenda and expected outcomes

To confirm no conflict of interest on the part of participants

To 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.

During the emergency joint review session, participants (with exception of sponsor/applicant) 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.

In the emergency joint review closing session, 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 7 - Resolution of outstanding list of questions (LoQ)

In the event that the emergency joint review session results in outstanding questions, the sponsor submits the responses to each country as soon as possible, after the session. Participants in the emergency joint review will review and communicate virtually (via WebEx or teleconference) to ensure consistency and reach consensus on resolution of the questions which were 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. The process will continue until all participating countries agree that the questions have been satisfactorily resolved.

Step 8 - National authorization of CTA

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

Step 9 - Post-authorization steps

Post-authorization steps required for the start of the clinical trial to begin should be adapted if necessary to reflect the urgent need, without compromising legal requirements or ethical and regulatory responsibility, 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.

The AVAREF Joint Review Guideline⁹ describes the expected timelines for various steps of the joint review and expedited joint review process, however the timelines are still considered to be too long for use in emergency joint reviews during a pandemic situation. In addition, the unpredictability of the duration of post authorization steps constitutes a further challenge in emergency situations.

For the emergency joint review process to be meaningful, it should be conducted within an overall timeline of 10 working days for processing of CTAs where the product is already registered for other indication(s), and 15 working days for novel products. These timelines are for the entire process from receipt of CTA to the final decision at country level, with exception of clock stops, including both ethics and regulatory review.

Without better control over in-country steps, the purpose of carrying out an emergency review is lost. For the post-authorization process, countries are strongly encouraged to set the shortest and realistic timelines achievable for each of the steps, which should be tested during simulations of country level emergency plans, in addition to all other steps as described in Table 1.

⁹ <https://www.afro.who.int/publications/avaref-assembly-resolution-avaref-guideline-joint-and-assisted-reviews-clinical-trial>

Table 1 Timelines for the Emergency Joint Review Process

| Step | Description | Target Timeline (working days) | Responsibility |
|------|---|--------------------------------|--|
| 1 | Screening of requests for a joint review | 1-2 | AVAREF Secretariat ¹⁰ |
| 2 | Pre-submission meeting ¹¹ | 1 | AVAREF Secretariat ¹² |
| 3 | A SharePoint platform accessible to Sponsor and all NRAs and ECs/IRBs for target countries is set up with immediate needed access | Same day | WHO and AVAREF Secretariat |
| 4 | a) Submission to NRAs and ECs by Sponsor b) Screening by the NRAs and ECs | Same day | a) Sponsor b) NRAs c) ECs |
| 5 | Country review of the CTA | 2-3 | NRAs and ECs ¹³ |
| 6 | Joint review | 1-2 | AVAREF Secretariat, NRAs and ECs ¹⁴ |
| 7 | Resolution of pending LoQ | 2 | Sponsors ¹⁵ |
| 8 | National authorization of CT | 1 | NRAs and ECs |
| 9 | Post-authorization steps | 1-3 | Country dependent |

6.8.2 Roles and Responsibilities

There are clear roles and responsibilities for each party to the joint review. These are summarized in Table 2.

¹⁰ Sponsors are invited to contact the AVAREF Secretariat to express their interest at akanmorib@who.int or maigad@who.int

¹¹ Pre-submission meeting is conducted virtually, all aspects of actual submission should be agreed on.

¹² Key decision makers from NRA and EC should attend the pre-submission meetings and be involved in the entire expedited review process, there must be agreement on expectations, role and responsibilities.

¹³ This should be done by the most efficient means possible as agreed on in the pre-submission meeting.

¹⁴ The virtual review should be attended by key decision makers from NRAs and ECs as during the technical review, agreements and decisions on timelines will have to be made.

¹⁵ The channels for submission of LoQs are agreed on during the joint review meeting.

Table 2 Summary of Roles and Responsibilities for each Party to the Joint Review

| Role/Responsibility | SPONSOR | NRA | EC/IRB | AVAREF | WHO | MOH | NEC |
|--|--|---|---|--|----------------------------|----------------------------|--|
| Initiation of requests for joint review | | Notify WHO and AVAREF | Notify WHO and AVAREF Notify NRA and NEC | | | | |
| Pre-Submission | | | | Notify All Stakeholders | | | |
| Processing and National Review | Submit Application | Screen and schedule review | Screen and schedule review | | | | |
| Joint Review | Submit Queries Address Additional Queries | Review Queries | Review Queries | Schedule Review Provide Experts | Manage Platform | | Review Queries |
| Decision and Approvals | | Give Approval | Give Approval | | | | Give Approval |
| Post-Approval Authorization and Import Permit | Import IND | Give Final Approval Issue Certificate of Importation | | | | | |
| Monitoring of Safety | Sign MOU Review AEs Make decisions | Sign MOU Review AEs Make decisions | Sign MOU Review AEs | Sign MOU Review AEs | Sign MOU Review AEs | Sign MOU Review AEs | Sign MOU Review AEs Make decisions |

6.8.3 Post-Approval Authorizations

There are in-country steps to be taken after the joint review and final decision has been made. These should be made clear to the applicant/sponsor during the pre-submission meeting. Sponsor letter(s) authorizing the clinical trial must be signed and delivered to the Sponsor within a fixed time (48 hours or as agreed) and the WHO and AVAREF secretariat must be duly notified and provided with a copy of signed approval authorization letter(s). Additionally, where a National Importation Permit for the investigational product/candidate vaccine is required, this should be provided within 5 days of the clinical trial approval.

6.8.4 Safety Monitoring

The countries involved in the joint review shall sign an MOU that allows them to mutually view all safety data. They will jointly analyze all adverse events (AEs) and use the outcome for decision making as part of their oversight function of clinical trials.

7.0 Listing of Candidate Vaccines in Public Health Emergencies using the WHO ‘Emergency Use Listing’ (EUL) Procedure

The 2014 Ebola epidemic demonstrated the need for a WHO Emergency Use Listing procedure (EUL)¹⁶ for candidate vaccines for use in public health emergency contexts. The purpose of the procedure is to provide guidance to interested UN procurement agencies and NRAs on acceptability of use of candidate vaccines in a public health emergency, based on available quality, safety, and efficacy data. The EUL procedure for candidate vaccines is primarily aimed at manufacturers of these vaccines in public health emergency contexts. Participation of manufacturers in the procedure is voluntary. The EUL is not equivalent to licensure, approval or a WHO pre-qualification, and should not be considered as such.

In instances where, given the morbidity and/or mortality of the disease, and where there is a shortfall of treatment and/or prevention options, and there is reasonable potential benefit, the community may be willing to tolerate less certainty about the efficacy and safety of products. It is paramount to determine the minimal level of information needed prior to making a product available under a time-limited EUL, while further data are being gathered and evaluated.

The inclusion of a product in the EUL list should not compromise the conduct and completion of clinical trials. It should be noted that it is the sole prerogative of WHO Member States whether to allow the emergency use of a candidate vaccine in their country. There may be situations where the only options available are EUL listed candidate vaccines. Ethics and regulatory emergency review procedures at country level and AVAREF facilitated emergency joint review procedures should include provisions for review and approval of EUL listed products.

8.0 Testing the Plan- Simulation

Simulation exercises and After-Action Reviews (AAR) represent the functional assessment of capacities and play a key role in identifying the strengths and gaps in the development and implementation of preparedness and enhancing capacity for response measures before an actual emergency occurs. A simulation exercise is a form of practice, training, monitoring or evaluation of capabilities involving the description or simulation of an emergency, to which a described or simulated response is made.

¹⁶ <https://apps.who.int/medicinedocs/documents/s21987en/s21987en.pdf>

These exercises enable people to practice their roles and functions and can help to develop, assess, and test functional capabilities of emergency systems, procedures, and mechanisms to respond to the target situation, in this case, public health emergencies.

The WHO Simulation Exercise Manual¹⁷ provides an overview of the different simulation exercise tools and guidelines developed and used by WHO. This guide should be applied with these tools in the testing of all aspects of the CT emergency preparedness plans at the three levels described in this document, in-country preparedness, harmonization of country preparedness at the level of RECs, and also to test the response plan at the level of the continent.

9.0 Capacity Building- Preparing for Public Health Emergencies

It is expected that during the development and testing of emergency preparedness plans, key deficiencies and gaps will be identified. Training of decision makers and technical members of ethics committees and regulatory authorities in areas which are recognized as being relevant to processing of CTAs within the context of access to medicines, vaccines and ancillary products in public health emergencies is an important step in capacity building targeted at emergency preparedness.

The focus of training is to strengthen the capacity of the AVAREF network, NRAs and ECs to review and authorize clinical trials using a parallel review system of CTAs by NRAs and ECs, while at the same time promoting collaboration between the NRAs and EC, improving communication channels and skills, streamlining related processes and providing opportunity to test decision making structures, which will improve efficiency in routine and emergency reviews.

Decision on what type of training will be suitable to meet a specific training need should be made taking into consideration the immediate and long-term value of the training in routine reviews and emergency or expedited reviews, practicality of organization, technical expertise required, ease of reproducibility, and logistical prudence. Wherever possible a training of trainers' approach should be used with the aim of expanding the pool of experts within the continent. AVAREF secretariat will maintain a database of experts within the continent. The experts will be called on to assist in training and participate in reviews and expedited reviews.

¹⁷ <https://www.who.int/ihr/publications/WHO-WHE-CPI-2017.10/en/>

References

1. *AVAREF Guideline for Joint and Assisted Reviews of Clinical Trial Applications for National Regulatory Authorities (NRAs) and Ethics Committees (ECs)*
2. *WHO TRS No. 924-Guidelines on Clinical Evaluation of Vaccines: Regulatory Expectations*
3. *WHO TRS No. 1004 Annex 7-Guideline on Regulatory Preparedness for Provision of Marketing Authorization of Human Pandemic Influenza Vaccine in Non-vaccine Producing Countries*
4. *WHO Emergency Use Listing procedure (EUL)*
5. *WHO Guidelines for Safe Disposal of Unwanted Pharmaceuticals in and after Emergencies*
6. *WHO Simulation Exercise Manual*