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**STATUS OF REVIEWS, AUTHORIZATIONS AND OVERSIGHT
FOR CLINICAL TRIALS IN THE WHO AFRICAN REGION**

Technical Document

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BACKGROUND

1. Clinical trials are important for evaluating the safety and efficacy of new products prior to wider human utilization. A number of new vaccines and treatments against meningitis, rotavirus diarrhoea, pneumonia, malaria and HIV have been tested during clinical trials in the Region. In 2014, during the largest ever outbreak of Ebola virus disease (EVD), clinical trials of candidate vaccines against EVD were conducted in the Region, resulting in a safe and highly effective vaccine.¹ Achieving universal health coverage requires overcoming inequities in access to health interventions, and this, in part entails clinical trials of new or existing medicinal products, particularly those meant for poor populations.

2. Clinical trials are conducted in three phases: phases 1 and 2 assess safety, potency and dose; phase 3 demonstrates efficacy in support of licensure or marketing. After licensure, phase 4 studies measure effectiveness in implementation. The target populations for trials should present sufficiently high disease burdens to permit estimation of efficacy from a reasonable number of subjects, within a short time frame and at reasonable cost. These sites should therefore be adequately resourced and compliant with Good Clinical Practices (GCP) standards.

3. Before commencement, a clinical trial application is submitted to an ethics committee (EC) or Institutional Review Board (IRB) and a National Regulatory Authority (NRA) in a country for review. Upon approval, an import permit is issued by the NRA to the sponsor of the trial for the importation and use of the new investigational product. Additionally, a trial site visit is undertaken to assess compliance with GCP standards. Also, details of the trial should be registered in a publicly available and searchable clinical trial registry.

4. In supporting Member States to conduct clinical trials in the WHO African Region, WHO in 2004 published guidelines for clinical study of traditional medicines in the African Region. Since 2006, through the African Vaccine Regulatory Forum (AVAREF), National Regulatory Authorities (NRAs) and ethics committees (ECs) of Member States have been supported to review, authorize and provide oversight of clinical trials in the WHO African Region.

5. With the recognition of the contribution of health research to the development of innovative health interventions, strategic decisions and commitments have been undertaken, urging Member States to strengthen health research, including clinical trials.² Furthermore, the Regional Strategy on Regulation of Medical Products in the African Region, 2016–2025,³ calls for close collaboration with regional and international platforms, such as AVAREF, for review of clinical trial applications and to reduce the current lengthy timelines for review and authorizations of applications. Additionally, AVAREF promotes harmonization, best practices, information and work sharing among Member States to improve efficiency in the processing of clinical trial applications. AVAREF has been re-structured with a new governance model and strong representation by the regional economic communities (RECs). It also is aligned with the African Medicines Regulatory Harmonization initiative of the African Union. WHO and the New Partnership for Africa's Development (NEPAD)

¹ Henao-Restrepo A.M et al. 2015. Efficacy and effectiveness of an rVSV-vectored vaccine expressing Ebola surface glycoprotein: interim results from the Guinea ring vaccination cluster-randomised trial. *Lancet* 386(99596):857-66.

² Global Ministerial Forum on Research for Health. The Bamako Call to Action on research for health, strengthening, research for health, development and equity, Bamako The Global Ministerial Forum on Research for Health; 2008.

³ Regional Strategy on Regulation of medical products in the African Region, 2016–2025. World Health Organization Regional Committee for Africa AFR/RC66/13.

Agency of the AUC are working closely together to effectively provide common support to NRAs of Member States.

6. There is a rise in clinical trial numbers in the Region, resulting from the global interest in developing products for diseases that disproportionately affect the Region, including those of pandemic potential such as EVD. However, review and authorization timelines are still too long, while oversight of trials remains inadequate. This paper therefore reviews the status of clinical trials, identifies the challenges and proposes actions that can be taken by Member States and partners to improve timelines for authorizations and enhance oversight of clinical trials in the Region.

ISSUES AND CHALLENGES

7. **Inadequate preparedness for rapid initiation of clinical trials, especially in emergencies:** Several clinical trials in Member States have led to the development of health products. However, most countries are often unprepared and lack the human, technical and financial resources to undertake clinical trials, especially during disease outbreaks. During disease outbreaks, all resources and efforts are directed towards disease surveillance, contact-tracing, case management and infection control, in an effort to stop the transmission.

8. **Insufficient country ownership and resources for clinical trials:** Most priority products are identified and the clinical trials are designed, funded and led by investigators from outside the African Region. Some of the trials do not address urgently needed health products for local, national or regional priority diseases and conditions. As a result, clinical trial results are not translated into policies to guide national or regional public health needs. In addition, clinical trial sites are under-resourced and still lack the full capacity to conduct trials which meet international standards. Most sites depend solely on external resources, with little local funding for human resources, infrastructure as well as access to healthcare for the local population.

9. **Lack of harmonized procedures for ethics and regulatory review and oversight:** The legislative framework for oversight of clinical trials is lacking or weak in most countries. There is lack of clarity of the roles of ethics and regulatory functions, often leading to duplication of efforts and undue delays in processes. Member States have multiple submission formats for clinical trial application requirements and variable timelines for the review and authorizations of clinical trials. Good Clinical Practice inspections and monitoring of the safety of participants are generally weak in most Member States.

10. **Weak governance and lack of transparency:** There is weak governance and the processes for the submission, review and authorization of clinical trials lack clarity and transparency in some Member States. As a result, sponsors of clinical trials often seek approvals for their clinical trial applications from multiple sources.

11. **Limited biobanking capacity, infringement of intellectual property rights and data usage:** Most Member States lack the facilities for storage of biological materials collected during clinical trials. For example, most of the biological materials collected during the clinical trials of medicines and vaccines against EVD in Guinea, Liberia and Sierra Leone were shipped to different countries outside the African Region. Under these circumstances, biological samples of potential benefit are transported for storage outside the continent, out of the reach of African countries, and often without

a signed Material Transfer Agreement (MTA) on the use of the samples as well as sharing of potential benefits which may arise.

12. Slow implementation of activities required to facilitate regulatory reviews of applications:

Member States are not fully implementing guidelines, strategies and plans in support of clinical trial reviews and authorizations. Recommendations from AVAREF meetings are not fully implemented and benchmarking data about timelines, required for monitoring progress of clinical trial reviews and authorizations by NRAs and ECs of Member States, are often not available. Consequently, timelines for clinical trial reviews are too long, affecting product development.

PROPOSED ACTIONS

Member States should:

13. Ensure preparedness and availability of resources for rapid initiation of clinical trials in general and especially during emergencies:

Plans should be developed by Member States, sites and facilities for clinical trials and target populations identified and their capacities strengthened in readiness to undertake clinical trials. Member States are also urged to include in their emergency response plans, a blueprint for triggering a response by ECs, NRAs, investigators and laboratories to support clinical trials of products which can be used to address disease outbreaks. The ethics and regulatory planning could be done within the context of the Regional Economic Communities (RECs) and should be consistent with the African Medicines Regulatory Harmonization initiative and AVAREF.

14. Take ownership of, and provide resources for clinical trials:

Member States should fully implement global and regional actions, resolutions and recommendations, including the Bamako Call to Action and the Framework for Implementation of the Algiers Declaration, mapping health product needs, and setting national priorities for research questions to be answered through clinical trials. Member States should invest in product development by allocating more resources to clinical trial sites. Investments in ECs and NRAs and effective management of trial sites will permit development and implementation of new and more effective health products to address national priorities. Member States should also promote technology transfer from better-resourced countries through mentorships, staff attachments and training. They should engage in networks such as the NEPAD/AU African Medicines Regulatory Harmonization initiative of the Regional Economic Communities (RECs).

15. Improve governance and transparency:

ECs and NRAs should ensure compulsory registration of all clinical trials in the Region prior to authorization in the publicly available and searchable, Pan-African Clinical Trial Registry or any WHO-primary registry.⁴ This will ensure that clinical trial reviews and authorization processes are transparent and will eliminate the shopping for approvals from one site to another. In order to provide full transparency on the results of clinical trials and enable evidence-based decision-making, all clinical trials should be reported in a timely manner consistent with the WHO position⁵ on public disclosure of results from clinical trials.

16. Provide biobanking facilities, adhere to intellectual property rights and fair use of materials and data:

Member States should include signed MTA for the storage, use and sharing of benefits of biological materials obtained from clinical trials, as part of protocol review requirements.

⁴ www.who.int/ictrp/last accessed 17 March 2017.

⁵ www.who.int/ictrp/results/reporting/last accessed 17 March 2017.

Member States should also ensure that data emanating from clinical trials are made available to the populations where the trials took place and that benefits are shared with study participants and communities, consistent with international principles of ethics.

WHO and partners should:

17. Accelerate the implementation of activities to reduce review timelines: WHO and partners should continue to support Member States to ensure that guidelines, strategies and recommendations are adequately implemented. WHO and partners should provide support to ECs and NRAs of Member States to reduce timelines for clinical trial reviews and authorizations as well as adequate oversight. WHO should mobilize additional resources to support Member States through AVAREF, facilitate joint activities and monitor the progress of Member States in reviewing applications for clinical trials and providing adequate oversight.

18. Benchmarking to identify needs of NRAs and ECs and provide training to strengthen capacity: Through AVAREF and the use of the WHO NRA Benchmarking tool, WHO should undertake needs assessment of the NRAs to identify major gaps. Provide training through AVAREF and the WHO Global Learning Opportunities (WHO GLO) and other opportunities for Member States to strengthen their capacity for reviews and regulatory oversight of clinical trials.

19. Promote harmonized procedures and guidelines by ECs and NRAs: AVAREF has been re-structured and now covers all the Member States and all the RECs of the Region and is in alignment with the African Medicines Regulatory Harmonization Initiative.⁶ Through AVAREF, capacity for clinical trials is being strengthened and harmonization of procedures and processes promoted, while timelines for review and authorizations are being optimized. Member States should take advantage of the re-structured AVAREF platform to strengthen their ethics and regulatory capacity by adopting strategies and guidelines developed for AVAREF and to improve their timelines for review and authorization of clinical trials.

20. The Regional Committee is invited to consider and endorse the actions proposed.

⁶ Akanmori B.D, et al. 2016. New development of medicines for priority diseases in Africa. Lancet. 2016; 388(10049):1053-4.