African Vaccine Regulatory Forum

Presentation of AVAREF and its emergency joint-review process

Q&A session

1. What is the influence of the AVAREF on local registration process within the countries for example: does it help registration in Egypt should the vaccine clinical trials proven effective?
   Answer:
   This first question addresses registration of products, which is beyond clinical trial approvals. AVAREF consists of the regulators of the countries who also register products. It is true that AVAREF has been involved in registration of vaccines. For example vaccines against malaria and conjugate meningitis. The influence that regulators have on each other's decision is very important and this is what AVAREF promotes, information sharing and work sharing, which is great as products are often submitted as applications for clinical trials or for registration to individual country regulators. Having a continental platform to share knowledge and information whether for clinical trials or registration is very helpful and will significantly facilitate the work of regulators.

2. Are the official regulatory bodies of Egypt part of the AVAREF?
   Answer:
   The answer is yes. As a member state of the African Union Egypt is member of AVAREF. Egypt belongs to the WHO EMRO and as such is also a member of AVAREF, because the secretariat of AVAREF includes our regional office in EMRO. However at the local level the NRA of Egypt and the EC or IRBs have not been fully engaged in AVAREF activities. That being said, in the event of a joint review request which includes Egypt, AVAREF is able to fully support them and involve them in the process, from pre-submission to the review and final decision. As a secretariat, we are working with our colleagues in the WHO EMRO and in collaboration with AUDA NEPAD and the African Medicines Regulatory Harmonization initiative to fully bring all the countries of EMRO into all AVAREF activities.

3. How many joint-reviews have been coordinated by AVAREF?
   Answer:
   AVAREF has coordinated more than 10 joint-reviews since its creation. While the joint-review activity of the platform was still limited in the first 10 years, more and more developers are now submitting clinical trial applications though AVAREF. We have supported joint-review with very diversified scope, from 2 target countries to 15 target countries. As the process has proved its effectiveness, we want now to communicate broadly about it and to make it available to all the developers willing to conduct trials in Africa.

4. Will the recording be available? Is this emergency process in place for vaccine only or could be used for Antivirals for treatment of COVID under emergency measures?
   Answer:
   The PDF of our presentation will be sent out to all participants, since at this point, we have no plans to share the recording of the meeting, given that we did not discuss or seek consent of the sponsors to do

so. The new AVAREF Emergency review process and timelines of 10 and 15 working days applies to all products against COVID-19, vaccines, diagnostics and therapeutics..

5. Do you already have a list of documents already available for submission of a Phase III application?
Answer:
Yes. on the AVAREF Website you can find both the guidance documents on submission and the data requirements. https://www.afro.who.int/health-topics/immunization/avaref

6. What is the difference between repurposing and repositioning of drugs?
Answer:
A repurposed drug as used here refers to a drug registered for use against a condition or disease but has potential to treat COVID-19 and so it is being tested clinically against COVID-19. Examples are chloroquine, hydroxychloroquine and remdesivir, all with antiviral properties.. This is also used interchangeably with the term repositioning drugs.

7. In the event that we may only have 1 country for a clinical trial for COVID-19 product, can we use the emergency procedure and AVAREF to assist in this review?
Answer:
Yes the emergency process and timelines apply to all countries. AVAREF can assist the country using what is called an assisted review, by inviting another country (both Ethics committee and National Regulatory Authority) to participate in a joint review of the same application. This requires agreement by the CTA-recipient country. The same timelines will apply.

8. After phase 3 is completed and we enter the product approval phase, would AVAREF play a coordinating role in the licensure process?
Answer:
Yes. We support member states for joint reviews for product registration in public health emergencies as well as other situations which are outlined in the AVAREF guidelines.

9. May ask if the parallel (regulatory and ethics) review is a mandatory requirement to adhere to this process from the countries. If so, how to deal with that for the countries having sequential reviews in their national regulations as well as in their practices?
Answer:
The AVAREF Emergency Joint Review process requires parallel submission to both ethics and regulators as a way of minimizing any delays. If a country does not allow parallel submissions, they have to find a way to still meet the agreed upon timelines. The secretariat is supporting countries to switch from sequential to parallel submissions and reviews.

10. For a multi-country trial with single protocol, if few of the countries agree to while others don't, is there any way to resolve the blockage for protocol approval?
Answer:
In these cases, the Secretariat agrees to share outcomes (including queries raised and the sponsor's answers) of the review with non-participating countries to avoid duplication of work. Engaging with these countries is important, as well as ensuring that there is alignment to the timelines and processes or steps agreed upon by all. The secretariat has responsibility to follow up with all stakeholders of a joint review

until decisions are made. This is done carefully, ensuring that the decisions are made by countries without any pressure. This is part of the capacity-building function of AVAREF. Often the countries which initially do not follow the few whole process will come round to the same position as the others.

11. Is there any provision for joint inspections of clinical trial sites after CTA approval?
    Answer:
    Usually countries will conduct their own GCP inspections of trial sites. However AVAREF has conducted joint inspections for multi-country clinical trials starting with the 2006 joint inspections of the conjugate meningitis vaccine clinical trial sites. More recently a joint GCP inspection was undertaken in Ethiopia to pilot a new GCP inspection guide and checklist developed by AVAREF.

12. Do the countries allow First in Human Trials for new vaccines?
    Answer:
    Yes. One of the first vaccine candidates to be trialed for Ebola in 2015 took place in Mali and Kenya. These were first in human phase I clinical trials. The Secretariat will provide all necessary support to countries

13. What is your take in using anti-rheumatic arthritis drugs for COVID-19 based on the hyperinflammatory response in both COVID-19 and rheumatoid arthritis.?
    Answer:
    For COVID-19, all options are being assessed given the current understanding of the disease. Minimizing the inflammatory response could potentially reduce complications and lead to recovery from severe disease in COVID. Many drugs used to treat inflammatory diseases are being tried against COVID-19 too. If possible, addressing the disease early is the ideal. Obviously a vaccine which can protect against the disease will be the ultimate tool against the disease.

14. We have a drug that has completed Phase 2 in another indication. We now have significant in-vitro data. Wold you see us doing a multi country study or limit the study to 1 or 2 countries to reduce complexity?
    Answer:
    The first practical step is to engage AVAREF and begun discussions with regulators from countries targeted in the trial. Complexity can be managed by the Secretariat drawing from the available resources. However, the Secretariat is confident in their ability to provide adequate support

15. Can this procedure be used for other therapeutic areas in addition to COVID-19?
    Answer:
    Yes, it is possible. There are criteria for emergency and expedited reviews. These criteria can be found in the AVAREF guidelines.

16. Why did you not consider doing the trial in one of the countries with high number of COVID-19 cases such as Egypt, Sudan, South Africa or Nigeria? (To Nathalie of DNDi)
    Answer:
    We did: Sudan is part of the study, and we are also investigating Nigeria.

17. Is there a potential opportunity to initiate clinical trial in Africa? And what are the possible funding opportunities available for Covid-19 vaccine?
    Answer:
    AVAREF does not fund clinical trials. However, there are many WHO partners who fund clinical trials and are involved in funding COVID-related clinical trials. The Solidarity clinical trials are supported by WHO and partners.

18. Do the regulatory authorities allow vaccine trials if we would like to do study in HIV positive individuals?
    Answer:
    Yes. However, the final decisions are made by regulators and ethics committees in each country. AVAREF facilitates meetings for regulators to provide scientific advice to sponsors. This is an opportunity to find out what regulators will allow.

19. What's the role of WHO? Does it facilitate WHO PQ as well by connecting AVAREF countries' NRAs with WHO PQ teams?
    Answer:
    WHO PQ consistently engages with AVAREF and will continue to do so in the COVID pandemic. This includes creating a roadmap to address issues in the African region (and the rest of the world). Discussions on this document will include input from AVAREF. A roadmap for registration and rollout of vaccines against Ebola has been developed and another addressing COVID vaccines is being developed.

20. Any priority on funding clinical trials on herbal medicines?
    Answer:
    Herbal medicines are not excluded. The immediate focus is to address clinical trials for priority diseases in the continent. Trials of traditional medicines against COVID-19 are occurring in Africa and are welcome in future. All treatments addressing COVID-19 are of primary importance for AVAREF.

21. Has AVAREF assisted facilitating the trials of any therapeutic devices for the treatment of COVID-19?
    Answer:
    Yes, the presentation by Nathalie of DNDi was of an emergency joint review of therapeutics against COVID-19. There were also joint reviews of a treatment for eumycetoma and also for visceral leishmaniasis organized by AVAREF.

22. Different from Ebola, coronavirus pandemic is affecting ALSO Africa and not JUST Africa, so the question is if AVAREF plans or is taking already this extraordinary momentum to work with other organizations (e.g. EMA, FDA) in the global research efforts against covid-19?
    Answer:
    Yes, we do work with WHO HQ, EMA and USFDA by inviting them to participate in joint assessments. NRAs from AVAREF also work jointly with EMA and PQ in some reviews.

23. Is there any idea to share the best practices and lessons learned by AVAREF to help other regions to establish something similar?
    Answer:
    Definitely, colleagues in WHO HQ who are also part of the AVAREF secretariat, and are also mandated to address all WHO regions globally are sharing AVAREF best practices with other regions. For example the

RSS Team in Geneva organized a meeting for the Americas and invited AVAREF to present to regulators of that region. The meeting was very successful and many ideas from AVAREF were shared with regulators in the Americas.

24. Apart from facilitating submissions and approvals, does AVAREF also identify sites and provide CRO services?
    Answer:
    Regarding the question on CRO services, we do not provide CRO service or identify sites. But we can certainly provide suggestions through AVAREF members if necessary.

25. What is the current coverage of African countries by AVAREF? Are there plans to expand this?
    Answer:
    All 55 member states of the African Union are member states of AVAREF. Thus, the whole continent is covered. The engagement initially began with 19 members and subsequently grew to 23 countries all in the WHO African region before finally covering all countries on the continent. Collaboration with WHO EMRO region will improve contributions of North African countries to the AVAREF platform

26. How is AVAREF supporting community preparedness for clinical trials?
    Answer:
    The AVAREF platform ensures regulators and ethics committees are able to comprehensively address all issues of a clinical trial application. These can include issues on community engagement and issues specific to certain communities and populations. Such issues have been addressed in past CTAs joint reviews (for example Ebola) and AVAREF is committed to providing countries with the required support and advice. AVAREF is also in partnership with the Bill & Melinda Gates Foundation (BMGF) to further address this component and to improve clinical trial outcomes.

27. Why has DNDi included hydroxychloroquine in the study given the WHO recommendations on HCQ? (For Nathalie of DNDi)
    Answer:
    Past studies on HCQ, specifically the Solidarity trial, assessed the efficacy of HCQ in hospitalized and more severe patients. There is no solid evidence on whether HCQ can bring benefit in early treatment and mild cases of COVID-19, which is what the DNDi study focuses on and seeks to address. HCQ is still the standard of care in many countries on the continent, so evidence is needed to support the use of this treatment.

28. Does AVAREF charge a fee for services provided during joint-reviews?
    Answer:
    No, AVAREF does not charge fees for their services, but the ethics committees and regulatory authorities have fees for clinical trial application reviews.