African Vaccine Regulatory Forum (AVAREF)

Strategic Plan, 2018 – 2020

New Plan to Accelerate Product development and Access in Africa

September 2017

Table of Contents

1. Introduction

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. With the adoption in 2016 of a revised governance structure and the expansion in scope from vaccines only to medical products, the AVAREF Steering Committee agreed on the need to develop a strategic plan to realize the potential of the new operating model, as reflected in the revised terms of reference.

The regulatory and product development landscape in Africa has evolved substantially since the launch of AVAREF in 2006, a time when few countries had appropriate systems in place for the approval and oversight of clinical trials. The past decade has also witnessed an increase in the sophistication of trials 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. This need has been particularly acute in times of crisis.

The launch of the East Africa Community Medicines Regulatory Harmonization (EAC MRH) Project in March 2012 represented an equally important initiative predicated on the principles of regional harmonization, work-sharing and reliance, beginning with market authorization of generic medicines and now broadening to other product types, regulatory functions and geographies. It is within this context that AVAREF has developed and is implementing a strategic plan.

The strategic plan for AVAREF therefore centres on the seamless alignment of AVAREF with the AMRH initiative, with implementation of all activities within the RECs and the promotion of an end to end product lifecycle approach to regulation. The plan should also build upon the solid

experience and work output of AVAREF, including the strong collaboration, information and work-sharing by ethics committees and regulators, in accordance with their clearly defined roles and responsibilities. The progress at the level of individual countries and of the RECs will be evaluated with the WHO Global Benchmarking tool, while the overall progress of AVAREF should be monitored using the results framework with specific Key Performance Indicators (KPIs) in a simple tracking tool. This plan also takes into account the approved 60 working days for the review and decision-making on a clinical trial application.

The 2018 – 2020 AVAREF strategic plan takes account of this dynamic regulatory environment and positions AVAREF as a platform for accelerating change. With the above in mind, the strategic objectives for the renewed AVAREF should serve to:

- increase the efficiency and quality of reviews and inspections and the timeliness and transparency of regulatory decisions for all interventional trials conducted in Africa;
- promote the safety of patients;
- accelerate the AMRH process, linking all regional economic communities (RECs);
- stimulate innovation and research in Africa;
- enhance emergency preparedness on the continent, in RECs and in individual countries;
- strengthen AVAREF's capacity building role, and
- promote awareness, sustainability and monitoring of AVAREF.

This document describes the strategic directions over the short to medium term, that is, over the 2018 – 2020 timeframe.

Considerations

In setting strategic objectives for the new AVAREF network, a number of important considerations should be kept in mind, including:

- The unique role AVAREF plays as the first (and currently the only) pan-African network for the regulation of medical products in contributing to vision, mission and goal of the

African Medicines Regulatory Harmonization (AMRH) initiative – of which AVAREF plays an integral part – as well as the future African Medicines Agency (AMA);

- The demonstrated value of AVAREF in accelerating access to vaccines in times of emergency and the potential to leverage this experience to accelerate access to essential medical products in non-emergency situations;

- The need to maintain momentum in realizing expectations set with the adoption of a strengthened governance structure and a robust programme of work;

- The stated objective of promoting innovation and research in Africa for diseases disproportionately affecting Africans and for which limited or no experience in high income countries of origin exists;

- Recognition of the importance vigilance and safety monitoring play in ensuring the protection of subjects in clinical trials and ultimately the safe use of medical products, as well as the particular challenges faced in collecting and analysing adverse event data in low resource settings;

- The continued and increased need for AVAREF to serve as a platform for training and capacity-building;

- Key enablers for success, including ongoing political support, strengthening of partnerships, country and regional ownership and financial sustainability.

2. Values, Vision and Mission of AVAREF

The strategic plan is anchored on identified core values and the long-term vision and mission of AVAREF as endorsed in its Terms of Reference by all countries. The core values, vision and mission of AVAREF were carefully selected to reflect the contributions to past successes while acknowledging what failed and can be improved upon in the coming years. These elements will shape the future of AVAREF for the period of the strategic plan and beyond, and inspire other ethics committees and regulators to make their mark in the region and globally.

Core Values

Values are important and constitute the beliefs that drive behaviour and decisions. The key values of AVAREF are transparency, integrity, responsiveness, ownership, collaboration and innovativeness. These have played a role in the past and will play even greater role into the future.

These core values will drive AVAREF and feature significantly in the coming years in addressing new and emerging challenges in ethics and regulatory oversight of product development. These values will determine the identity and uniqueness of AVAREF and inspire AVAREF members to meet their goal.

Vision

The vision captures an image of the future and indeed for the change desired by all in the ethics and regulatory environment of the African Region and which will translate into global product development and access. The vision for AVAREF as stated in the Terms of reference is as follows:

African population with timely access to safe and efficacious medical products of assured quality.

Getting to this state will require every effort in fully implementing the plan, reviewing performance and ploughing the lessons learnt back into the way ethics committees and regulatory authorities in the region function.

Mission Statement

A mission statement defines the purpose, reason for being who a target group is and what they do.. It is also a statement of how they wish to get to their goal bearing in mind their core values and guided by the set of principles as signposts. AVAREF's mission therefore states the purpose of the platform and gives reason for being who they are and what they do as ethics committees and regulators of the continent. It defines where AVAREF is and where they want to get to in the period of the plan. It is the goal of everyone engaged in AVAREF and states as follows:

To strengthen ethics and regulatory capacity for clinical trials, ensuring oversight of product development in the countries of the African continent.

Goal

"To build robust capacity of National Regulatory Authorities and Ethics Committees as well as Regional Economic Communities to ensure efficient, transparent, high quality and timely clinical trials, and licensing of medicines and vaccines critical to improved maternal, family and general health in Africa".

Main Guiding Principles

Guiding principles play a role in signposting the implementation of any strategic plan. These principles serve to shape the implementation of activities by AVAREF and how the RECs,

individual institutions and regulatory authorities relate to each other and with their stakeholders. These principles have been the basis of the work which has led to the success of AVAREF so far while others will further enhance the chances of delivering on the vision and goal.

The proposed guiding principles are as follows:

1. Strong Partnerships and alignment with AMRH and other initiatives

An important element of the new governance and model for AVAREF is the linkages and alignment with AMRH. The strategic plan will implement the new governance structure, with strong reliance on the participation and leadership of the RECs,. The strategic plan also envisages that the WHO AVAREF secretariat will also work very closely with NEPAD in the implementation of activities, exploiting the expertise and strengths of each organization.. The contribution of other partners, including BMGF, EDCTP, PEI, US FDA, EMA, Health Canada will continue to play a vital role in attaining the AVAREF vision, goal and strategic objectives. Partnerships should be expanded and strengthened.

2. National ownership, stewardship and leadership

The ultimate goal of AVAREF is to build strong national regulatory authorities and ethics committees to facilitate better timelines for reviews and to contribute to product development and access. National leadership and ownership is key to attaining this goal. The strategic plan therefore stresses the prioritization of ethics and regulatory systems by countries and RECs by allocating more resources to them to implement their activities. Countries and RECs should take ownership, provide good stewardship and build sustainable systems.

3. Reliance on competent work and decisions of functional ethics committees and regulatory authorities.

The participation of regulators and ethics committees from more resourced countries with longer experience and facilities is key to AVAREF. Regulators from the EMA, USFDA and Health Canada as well as experts in ethics have supported their African colleagues through AVAREF by giving advice on various aspects of their work. For example, expert consultation sessions were held in past AVAREF meetings during which regulators and ethics committee members would consult with experts, discussing products, clinical trial applications and

safety data. The new governance model will allow these experts, partners and other stakeholders to participate in SC and RCC meetings and to provide advice and suggestions into strategic decisions and recommendations of AVAREF. Regulators and ethics committee members of AVAREF will rely on the advice and decisions of competent and well-functioning ethics committees and regulators from other parts of the world, thereby minimizing duplication of efforts and putting their scarce resources to better use in arriving at their own decisions. With time ethics committees and regulators of AVAREF should rely more on each other's decisions and advice, to minimize duplication and to move closer to harmonization.

4. Upholding confidentiality

The success of AVAREF will continue to depend on the concept of work and information sharing since its inception. Through this principle, regulators from the EMA, Health Canada and USFDA have been willing to share information with African regulators through AVAREF and similarly AVAREF has shared information in confidence with regulators form outside the region. Sponsors have also shared product information under confidentiality agreement in joint reviews with target countries, confident that their product information will not be divulged to third parties without their consent. The strategic plan will be implemented by AVAREF, based on this guiding principle.

5. Efficiency

Efficiency has been the hallmark of the past successes of AVAREF, built on the earlier informal network and the initial enthusiasm and willingness of the ethics committees and regulators to implement recommendations. The new governance structure will help ensure that the efficiency of the AVAREF process and in turn the efficiency of regulators and ethics committees in conducting their functions continues to improve.

6. Sustainability

Sustainability is defined as an ability to be maintained at a certain level without complete dependence on external resources. Sustainable financing is a critical component of every plan. AVAREF was established through an initial project funding from obtained by the WHO from the EDCTP and other partners. Subsequently with funding from the Canadian HIV Vaccine Initiative and the BMGF it has been maintained with a small secretariat at WHO. This has effectively been sufficient to ensure that meetings are convened, guidelines and

tools developed endorsed and disseminated and progress is tracked. This funding model has limitations, most importantly that it is not sustainable in the longer term and does not promote country commitment and ownership. A sustainability plan is required to ensure that dependence on partner support is kept to a minimum and national ownership is demonstrated through funding. A companion sustainability plan is thus important for the attainment of the strategic objectives outlined. The plan aims at transitioning funding for participation in meetings to countries and RECs, hosting meetings in agencies and national institutions to reduce costs, reduction in face-to-face meetings of the SC and TCC meetings to a minimum, reliance on virtual meetings of WG meetings where possible with teleconferences and video conferencing, exploitation of gatherings to which regulators and ethics committees have been earmarked to attend to convene AVAREF statutory bodies and expanding the funding base through fees for joint reviews, more partner participation. The RECs will increasingly play more significant role in domesticating all tools and monitoring their own progress with minimum involvement of the secretariat. The plan will have clear timelines for shifting the funding responsibility from donors to the RECs and the countries. This will ensure better sustainability and less involvement of the WHO secretariat except in setting the norms and standards, evaluating competencies of other training institutions such as RCORES, providing training, supporting joint reviews and disseminating information and guidelines.

Strategic Objectives

Under the goal of the strategic plan, strategic objectives have been defined. The strategic objectives are (1) to improve the efficiency of reviews, inspections and timelines for regulatory and ethics decisions for better outcomes and access to priority medical products; (2) Promote the safety of patients and products; (3) Accelerate the alignment with the AMRH initiative; (4) Stimulate innovation in ethics and regulatory work in Africa to improve access; (5) Enhance emergency preparedness (6) Strengthen AVAREF's capacity building role; (7) Promote awareness, build sustainability and institute monitoring and evaluation of the implementation of the strategic plan of AVAREF;

Under each objective the strategies to be employed and the critical activities are defined.

3. Strategic Directions

The strategic directions define the recommended activities to be addressed within the period of the plan.

Strategic Direction 1: Improve the efficiency of reviews, inspections and timelines for regulatory and ethics decisions for better outcomes and access to priority medical products

AVAREF was created with the goal of addressing gaps in the ethics and regulatory oversight of clinical trials conducted in sub-Saharan Africa, gaps which have caused unnecessary delays in the review and approval of clinical trials and access to new vaccines. This remains the primary focus of AVAREF, but now with an expansion in remit to cover medical products. This has meant building capacity and promoting changes designed to improve the quality, timeliness, transparency and predictability of reviews, all essential elements of good regulatory and good review practices. Experience has shown that this must also consider the end to end regulatory process, with inefficiencies relating to administrative matters, the sequential processing of ethics and regulatory approvals and the inflexibilities of regulatory frameworks in times of public health crisis recognized as equally important factors contributing to the overall problem.

AVAREF will continue to target key areas of the regulatory and ethics process as part of an overall strategy to improve regulatory outcomes as measured through performance indicators that include the following:

- percentage of RECs and Member States establishing, publicizing, tracking and reporting review times;
- percentage of African countries meeting (internationally competitive) AVAREF review target for 90% of clinical trial application (CTA) review decisions;
- percentage of RECs and Member States that have implemented good review and submission management practices and quality management systems to improve the quality of regulatory and ethics review;
- common application requirements, format and procedures for CTAs, consistent with international norms;

- quality-based procedures for accreditation of ethics committees implemented in RECs and Member States;
- percentage of RECs and Member States that have established fully coordinated NRA and EC review processes.

This work will be accelerated through the new governance structure already created and a stronger RECs-based approach being instituted designed to facilitate harmonization and implementation across RECs. The implementation of the annual workplan of AVAREF will be aim at attaining the above indicators and objectives. To successfully implement the objectives, a mapping exercise will be required to take stock of and address gaps in guidelines, tools and in work undertaken to date, including with respect to guidelines and procedures.

Strategic Direction 2:   Promote the safety of patients and products

Although access to medical products in LMICs is been improving steadily, there is only limited capacity to monitor the safety of these products in the post-approval phase in LMICs, and even less capacity for regulatory oversight of clinical trials. Indeed safety data from clinical trials conducted elsewhere before efficacy trials in Africa is often not available to African regulators. Safety evaluation is a central component in all stages of the drug development lifecycle, and plays a strong role in the 'end to end' product management process.

With the expansion of AVAREF in scope of products and the growing need to strengthen pharmacovigilance globally and in LMICs in particular, AVAREF will promote the capacity of countries to collect, evaluate, report and take appropriate actions related to adverse events for all products. As the Ebola experience has demonstrated, collaboration and information exchange should not end at the point of joint review of clinical protocols.   Such collaboration would allow for the better identification of potential signals that might not otherwise be seen from trials in individual countries.

AVAREF will specifically be used to

- adapt and socialise international pharmacovigilance standards, templates and best practices to the African setting, ensuring the standards are meaningful and 'fit for purpose';

- build and improve regulatory capacity to implement the Global Vaccine Safety Initiative and other international standards in the continent, WHO Collaborating Centres and partnerships with relevant organizations such as Council for International Organizations of Medical Sciences (CIOMS), European and Developing Countries Clinical Trials Partnership (EDCTP), Health Canada, USFDA and EMA etc.;

- guide processes for establishing common requirements and databases for information sharing on adverse events (AEs), as well as standardized e-reporting of AEs on a common African platform;

- build upon work already initiated on the establishment and use of a public registry for clinical trials which fulfils the WHO clinical trials registry platform requirements, notably the Pan African Clinical Trial Registry (PACTR) and reporting of outcomes as recommended by WHO. ;

- promote collaborative approaches to GCP and pharmacovigilance inspections, and

- promote the establishment of independent data safety monitoring boards.

Strategic Direction 3: Accelerate the alignment with the AMRH initiative

AVAREF will take full advantage of its status as the first pan-African regulatory platform to accelerate the alignment with AMRH. The timing is right to exert a leadership role given a new governance structure composed of heads of agencies from the relevant RECs and the enhanced alignment with NEPAD. In this regard, AVAREF represents the embodiment of the AMRH goal of moving from country to regional to a pan-African approach. As acknowledged at the extraordinary AVAREF meeting in Addis Abba in June 2016, AVAREF is also well positioned to serve as the precursor to the African Medicines Agency (AMA) in terms of operating model (Appendix 1).

AVAREF will promote

- an end to end product/regulatory approach, with AVAREF covering the upstream space and serving as a model for a similar pan-African model for post-market surveillance (PMS) and vigilance. This will also elucidate the interface between AVAREF and the RECs (as initiated by the AVAREF working group on Linkages and Alignment with the AMRH Initiative) and explore the expanded use of the platform, for example, based on the RTS,S malaria vaccine clinical trials to product registration experience.
- the adoption and domestication by RECs of the products of AVAREF, rather than to develop their own. The RECs will contribute to the development of guidelines, templates, procedures, etc. that then serve as pan-African standards;
- the expansion of linkages of AVAREF with other networks such as DCVMN, ICH and DIA.

Strategic Direction 4: Stimulate innovation in ethics and regulatory work in Africa to improve access.

Regulatory authorities are on the critical path to innovation and access to safe and effective medical products. Therefore, the degree to which regulators fulfil their mandates in an effective, efficient and transparent manner has a direct impact on innovation, access and public health. Increasingly, regulatory authorities must consider more modern and responsive models of regulation that consider resource constraints, increasingly complex technologies, globalization and public expectations. Such models require innovative pathways for ethics and regulatory approvals and oversight. These innovations will be based on the guiding principles of work-sharing, reliance and recognition of the work of competent and functional ethics committees and regulators while focusing resources on critical regulatory functions that cannot be undertaken by others.

AVAREF is well-positioned to change the situation of divergent requirements, prolonged timelines for clearance of applications and dossiers and lack of transparency, by contributing to human resource development, a more responsive and competitive regulatory environment. Such models will ultimately, lead to greater and more timely access to new

medical products. This is particularly important given the increasing number of candidate products for diseases endemic to Africa.

Against this backdrop, AVAREF will play a leading role in promoting research and innovation by

- introducing a product development platform that would track products of high public value, allowing sponsors and product developers to engage regulators and ethics committees early on, promoting better knowledge and planning that could result in the triggering of the AVAREF joint review mechanism. This should in fact, become the 'business as usual' model for priority medical products, leveraging the knowledge and experience gained from emergency situations. This would also require promoting awareness and the value of such a mechanism and could involve issuing expressions of interest; [1]
- exploring the development of a 'scientific advice' type service for sponsors/product developers, and
- improving the quality, transparency, predictability and timeliness of regulatory activities and the value of regulatory decisions.

Strategic Direction 5:   Enhance emergency preparedness

AVAREF proved its value as a platform to support regulatory authorities, ethics committees and sponsors in the Ebola crisis, as universally recognized across the public health emergency product development community. This community and countries will expect to use the AVAREF platform to accelerate product development in the event of future pandemics/epidemics or other health emergencies. The impact and influence of AVAREF will extend beyond the conduct of joint reviews, but cascade down to RECs, research consortia and individual countries with regard to ensuring emergency preparedness.

AVAREF will therefore be used as a platform to engage RECs to ensure that

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[1] Criteria for candidate products of high public health value to Africa would include:
  o addresses a neglected tropical disease or other highly prevalent and serious disease
  o addresses an unmet medical need or a significant improvement over available treatment
  o involves a novel technology
  o addresses a disease for which the Director General of the WHO has declared a Public Health Emergency of International Concern (PHEIC).

- regulators and ethics committees have emergency preparedness plans in place, which have been duly tested, including with respect to ethics and regulatory instruments/pathways for expedited review;
- import regulations are not a barrier for entry of investigational products during a public health emergency;
- business continuity plans are in place, focal points appointed and clear operating procedures established for working under emergency conditions, and
- sufficient communication capacity and skills exist.

AVAREF, working with the WHO, would also be used to promote an understanding and use of WHO relevant guidelines and tools, including

- WHO guidelines for approval of pandemic influenza vaccines by non-vaccine producing countries;
- Emergency Use and Assessment Listing (EUAL) process for IVDs and vaccines in a future public health emergency of international concern, which will identify appropriate products for use by countries in emergency situations.

Work in this area will be informed by the WHO R&D Blueprint and other supportive initiatives, including the Coalition for Epidemic Product Innovation (CEPI), both of which recognize the critical role of ethics and regulatory networks in accelerating access to priority products in times of public health emergencies.

Strategic Direction 6:   Strengthen AVAREF's capacity building role

Capacity building has been a core function of AVAREF since its inception. The need for this role to continue is clear, particularly in light of the increasing complexity of products being tested in Africa and the shorter timelines for development of products especially in emergencies. Training will take many forms, including hands on experience through joint reviews and twinning, with the support of well-established regulatory authorities. Going forward, this important area of work will be guided by a training strategy that defines the steering role to be played by AVAREF and the actual execution of authoritative training through partnerships with trusted institutions, including the WHO, academic institutions with relevant expertise, other training networks, such as EDCTP and the West African Task Force For the Control of Emerging and Re-emerging Infectious diseases, selected better

endowed regulatory authorities and training organizations. Training will be based on defined competencies and shall identify the target audience, including both technical and decision-makers. Increasingly, this should also involve a blend of in class, case studies/problem solving and mock exercises and e-Learning modules. Formal training in leadership will be essential to bring about effective partnerships, collaboration, work-sharing, engagement and communication to enable Africa to gain timely access to high-quality, safe and effective medicines and vaccines. Through this training AVAREF members will recognize further what they stand for and aim to deliver consistently. Training style and follow-up are also critical to learning and application of acquired skills in the work environment. Audit of courses and institutions and evaluation of learning outcomes, will also form part of such a strategy. AVAREF will work with training institutions in Africa and internationally to develop appropriate modules and to identify training resources, to support training.

The growing pool of country expertise will be recorded and updated by the AVAREF secretariat.

Strategic Direction 7: Promote awareness; build sustainability and institute monitoring and evaluation of the implementation of the strategic plan of AVAREF

Advocacy and communication are key enablers in promoting awareness and support for AVAREF and the increasingly important role it will play in improving the regulatory and product development environment in Africa. The AVAREF Steering Committee endorsed a robust communications strategy at the September 2016 meeting in Kigali. The full implementation of this strategy by all members and bodies of AVAREF will contribute to its success. This includes the Steering Committee, experts, secretariat, RECs, partners and in particular the NEPAD agency. Every opportunity should be taken to promote the 'AVAREF brand'. Continuing political support from member countries and RECs is in turn essential to the financial viability of AVAREF.

The effectiveness of communication and advocacy measures should be monitored and adjusted, as required.

As noted, the longer term viability of AVAREF is contingent on sufficient and stable funding. Funding must be a priority of AVAREF. Appendix 2 presents considerations and recommendations for funding.

Monitoring refers to the periodic observation of the implementation process with a view to establishing the level of compliance with laid down rules and protocol. This process gives room for periodic revision of plans and resources, especially where the plans and protocol appear unrealistic and challenges noticed/ Evaluation on the other hand refers to the end line assessment of the plan and protocol to ascertain their cost effectiveness and benefits.

Both monitoring and evaluation (M&E) constitute a critical segment of efficient research enterprise. This SFRI thus dedicates this section in the presentation of steps for monitoring and evaluating research projects. The first step here is to develop an M&E plan. The M&E plan specifies how the project will measure its achievements. It documents the stakeholders' consensus on the project, thereby fostering transparency and accountability; serves as a record in the institutional memory; tracks progress against set plans; checks for compliance with established standards; identifies trends and patterns in the programme; and helps to adapt strategies and inform decisions for project management.

Finally, a monitoring and evaluation function will form an integral part of the AVAREF governance role to ensure objectives are being achieved. As with training and communication activities, this will be based on a monitoring and evaluation plan, with the definition of key performance indicators capable of measuring meaningful change. Indicators will be consistent with those adopted by AMRH.

Framework for monitoring and evaluation

Fundamentally an M&E plan requires knowledge of what the strategic plan seeks to achieve and how this will happen, what the specific objectives are, what the major indicators of success are and how they will be measured, and how this information will be collected and analysed. The responsibilities for the project should be assigned to the executors, i.e. ethics committees and NRAs of countries and the RECs and clear targets set, with reporting systems defined and the pathway for dissemination and utilization of the results agreed. In this light, a strategic implementation framework has been developed for AVAREF and endorsed by partners and is being implemented. This follows a simple logic framework. The

framework monitors activities under each strategic objective and has key performance indicators for tracking progress of countries, RECs and the whole continent.

The secretariat will collect data, analyse and present it to the SC for their review and endorsement. The information will be disseminated to all RECs and countries to guide implementation of their activities.   The table of KPIs is presented.

Table of performance indicators

Strategic Objective	Activities	Indicators	Data sources
Objective 1 Improve the efficiency of reviews, inspections and timelines	Joint reviews and inspections across RECs	Number and quality of joint reviews and inspections	Reports, manuscripts
	Harmonized guidelines developed and used	Number of countries using common Guidelines	Reports, GCP Guidelines
Objective 2. Promote the safety of patients and products	Implement Global Vaccine Safety Initiative (GVSI) blueprint	Countries and RECs which have developed common terminology and requirements (including timelines)	National guidelines available Functional National Expert committee
		countries, who have reported minimum of 10 AEFIs per 100,000 surviving infants	WUENIC Country Data
		countries with electronic databases	Country Data
Strategic objective 3: Alignment with the AMRH initiative	Domestication of guidelines by RECs, meetings and joint activities with DCVMN, DCVRN, DIA ICH	RECs which have used AVAREF joint review model for licensure of medical products or review of CTs	Country/RECs data, NEPAD Reports

		RECs adopted or adapted for use the AVAREF, guidelines, templates, procedures, etc. or timelines or standards; Number of countries that have domesticated the AVAREF CTA guidelines
Strategic objective 4: Stimulate innovation in ethics and regulatory work	AVAREF scientific advice provided to Product Development Partnerships (PDPs)/sponsors	Products/technologies in clinical trials in which AVAREF scientific advice contributed to the trial design
Strategic objective 5: Enhanced emergency preparedness by RECs/countries	Development of preparedness plans Table top exercises on emergency preparedness WHO guidelines for approval of pandemic influenza vaccines	RECs/countries with plans RECs and countries which have domesticated the guidance from AVAREF table top simulation RECs which have adapted Emergency Use and Assessment Listing (EUAL) Activities conducted in

		collaboration with the WHO R&D Blueprint, Coalition for Epidemic Product Innovation (CEPI)	
Strategic objective 6: Strengthen AVAREF's capacity building role	Develop capacity building plan	Availability and implementation of capacity building plan	Plan available and implemented
		Joint capacity building activities with EDCTP, West African Consortium on clinical research (WAC), West African Task Force for Emergency Response (WATER), etc.	
		Updated pool of experts in RECs/countries	
Strategic objective 7: Promote awareness, build sustainability and institute monitoring and evaluation	Publish Newsletter Update website Publish manuscripts	Number of peer review journal articles published annually or presentations made at international meetings with results of AVAREF work.	Newsletters Journal publications
		Midterm review conducted.	Midterm review report published within 3 months of review

Key AVAREF Performance Indicators to be reported by countries on a quarterly basis

No	Indicator
1	# of countries that have domesticated the AVAREF CTA guidelines
2	# of countries using a parallel review process
3	# of joint/assisted review conducted
4	median review timelines for joint/assisted review completed in the quarter
5	# of countries that completed CTA review and reported in the quarter
6	median review timelines for CTA reviews through national pathways (from 5 above)
7	# of vaccine candidates in the AVAREF pipeline
8	# of drug candidates in the AVAREF pipeline
9	# of countries that have domesticated AVAREF emergency preparedness
10	# of REC secretariats engaged through face to face visits or phone calls

Notes:

3 Name of sponsor and candidate

5 List countries and numbers in each

9 List countries

4. Priority Activities under each strategic direction.

a) Optimization of timelines for clearance of clinical trial applications.

Competitive timelines for the review and authorization of clinical trials, agreed by AVAREF will be published and tracked periodically to ensure that progress made is duly documented. All guidelines for review of clinical trial applications will include the agreed timelines for reviews.

b) Joint/Assisted Reviews to expedite clinical trials and product registration

AVAREF will include in its annual workplan the number of joint/assisted reviews to be conducted and sponsors will be encouraged to submit their products via a portal to be established for accepting applications for these reviews.

c) Development and implementation of guidelines and tools to facilitate procedures and processes across all RECs

Guidelines for joint and assisted reviews will be developed and implemented by all RECs and countries. These will be piloted by RECs and and revised appropriately to meet their needs.

    d) Sustainable financing

A sustainability plan will be developed and implemented by countries and RECs and monitored by AVAREF. The implementation of the plan will be monitored by the secretariat and SC to ensure that AVAREF become sustainable.

    e) Leadership Training

The values, vision and mission of AVAREF can only be implemented if the leadership wholly endorses and implements its goals. Leadership training, consistent with the values of AVAREF will be implemented. The leadership training will engender strengthening of behaviours and skills related to effective collaboration and joint decision-making.

    f) Influencing global ethics and regulatory policies and practices to promote product development and access

AVAREF has a global influence and will continue to demonstrate this by engaging in global ethics and regulatory platforms and activities and decisions. To this end AVAREF shall participate in all global ethics and regulatory meetings, discussions and policy decisions.
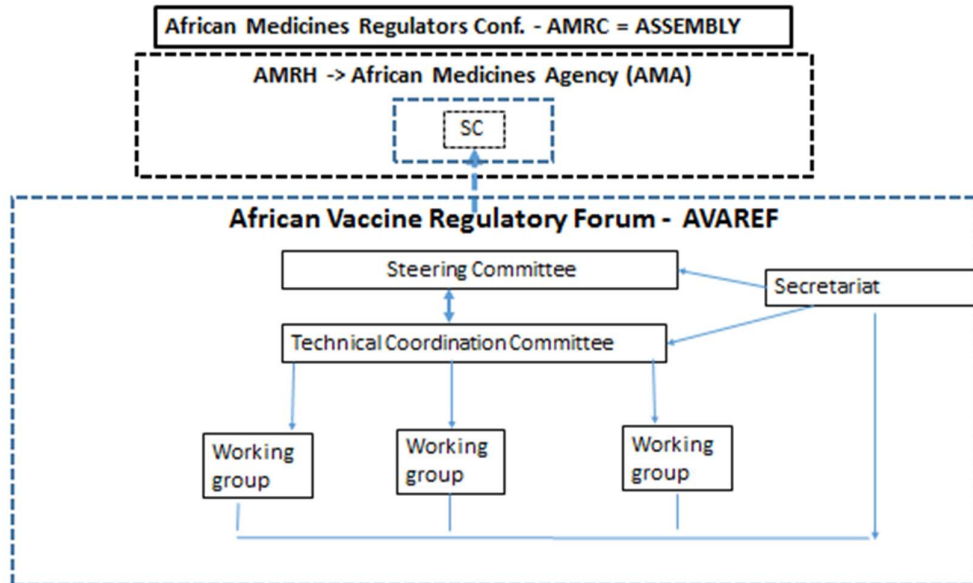
Appendix 1

Figure 1. The new model and governance structure of AVAREF.

Appendix 2 – Funding Considerations

Since its establishment AVAREF was under the full financial support of the WHO with co-funding by a few donors. This funding model has significant limitations, most importantly that it is not sustainable in the longer term.

Currently several potential sources for funding exist to support the work of AVAREF:

1. Donors support. This has traditionally been the primary source of funding, however, it is contingent on the expectations of donors and can be expected to lead to "funding fatigue" – the situation when there are not enough incentives for the traditional donors to continue funding the work of the network in the lack or absence of the clear "signals" from the recipient about the practical measures to ensure the financial sustainability of the operations.

2. Development partners. A number of development partners are currently supporting AVAREF, however, most are the recipients of the financial support from traditional "cash" donors and hence are not in a position to provide substantial financial support. However, the so-called "in-kind" support in the form of technical assistance is equally important as it decreases the need for direct funding of AVAREF.

3. African Union. Discussions are underway to establish the African Medicines Agency (AMA) under the auspices the African Union (AU). The AU NEPAD Agency has proposed some innovative mechanisms which could potentially serve a basis for funding the AMA. The same model could potentially be applied to AVAREF. Two options are currently considered in this innovative financing mechanism:
    a. *Social Impact Bond (SIB)* also known as "Pay for Success Financing", is a contract with the public sector in which a commitment is made to pay for improved social outcomes that result in public sector savings;
    b. *Endowment fund* is an investment fund established by a foundation that makes consistent withdrawals from invested capital. The capital in endowment funds, often used by universities, non-profit organizations, churches and hospitals, is generally utilized for specific needs or to further a company's operating process. Endowment funds are typically funded entirely by donations that are deductible for the donors.

4. Member States. This option may include:
    a. Direct contribution of the governments of AVAREF Member States. This could be a challenge as most of the time the governments are not keen to financially support the work of their own National Medicines Regulatory Authorities (NMRAs);
    b. Participating NMRAs themselves. This is one of the most promising options in view of the transformation of the AVAREF and its alignment with the African Medicines Regulatory Harmonization (AMRH) initiative which is based on the Regional Economic Communities (RECs). Within each REC MRH project exist a number of thematic technical expert working groups, for example, on market

evaluation and registration, GMP, etc. Most RECs are also willing to establish an EWG on the authorization and control of the clinical trials. This work, especially for multicentre trials, could be delegated to AVAREF which in this case will act as a continental EWG to serve all member states, including through the joint review process. Under this model, involved NMRAs would continue to charge existing application fees but set aside a portion to cover the cost of the joint review sessions and (in the longer run) the operations of the AVAREF Secretariat. This could, however, require that AVAREF become a legal entity to allow for the transfer of funds.

5. AVAREF itself. The network could potentially be self-supported if it charges fees for various services that it offers to the member states and other customers. This possibility would need to be further elaborated and justified in terms of the added value and implications for applicants/customers. This could also involve a 'pooled' fund that would contributions from a variety of sources. As with option 4b, this might require the creation of a 'legal personality' for AVAREF.

6. Regardless of the possible funding model considered, it will be important to institute cost-savings measures, such as the rotational hosting of meetings by regulatory authorities on their premises, paperless meetings, and covering the costs of travel and accommodation costs by respective agency staff.