Regulatory Mapping Project
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AVAC

The recent breakthroughs in HIV prevention research have created unprecedented opportunities to curb new HIV infections, save lives and set the world on a path toward eliminating HIV transmission. Yet it is quite clear that while the tools of today can begin to bend the curve of the epidemic in the short-term, a safe, effective, affordable and context-appropriate AIDS vaccine is still urgently needed to ultimately end the epidemic.

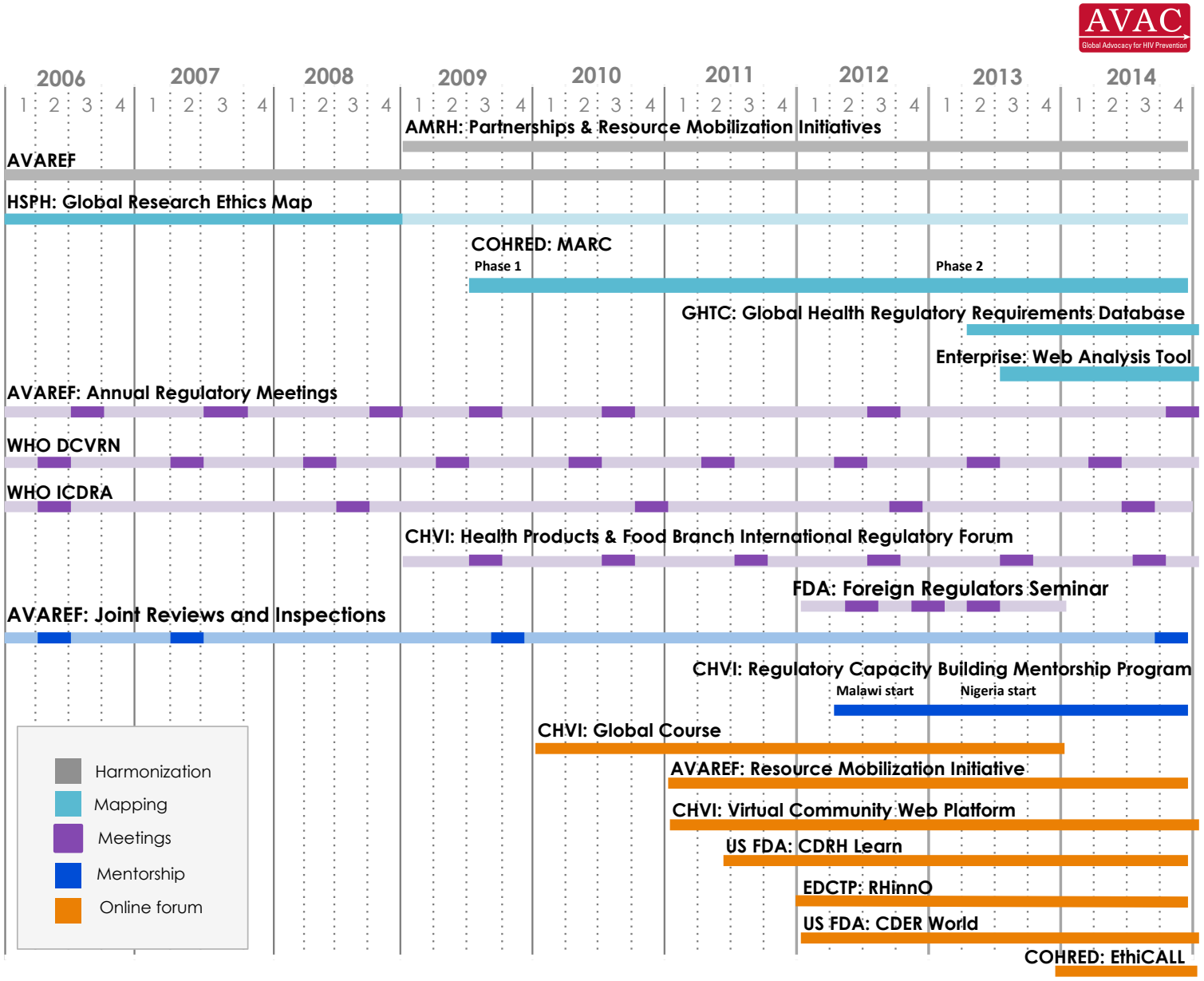
Designing and implementing large-scale clinical trials for AIDS vaccines, however, have never been more complicated or expensive – and they will likely only get more complex. Critical and urgent issues to be considered include: delays between initial efficacy results and the follow-on trials; evolving standards of prevention for participants in clinical trials; transforming broadly neutralizing antibodies into clinically feasible vaccine candidates; the possibility of gene therapy and/or passive antibody studies; establishing and enforcing good participatory practices (GPP); and strengthening national legal, ethical and regulatory bodies.

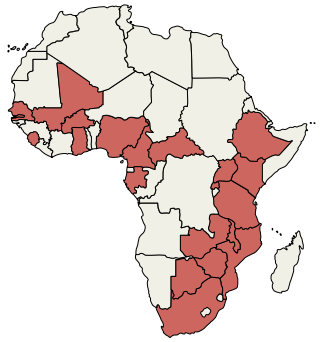
To address the last point, and as part of AVAC's policy and advocacy work supported via a USAID-funded, IAVI sub-award, AVAC undertook a desk review of various regulatory strengthening activities currently underway or planned, especially in Africa. AVAC supplemented this review by interviews with key informants related to activities intended to support regulatory capacity building in low and middle income countries focused upon efforts that were of potential assistance to HIV vaccine development.

As described in the table below there is a variety of efforts underway – general networking support in some cases, while others offer more specific capacity building, mentorship and/or mapping.

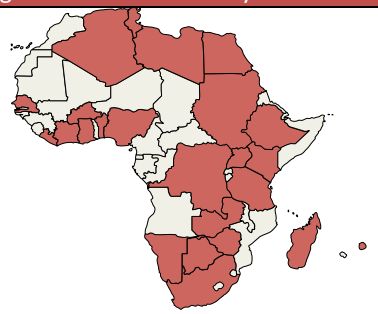
Snapshot of activities

	Harmonization	Mapping		Meeting		Mentorship		Online forum	
		Ethics	Process	Networking	Training	Joint inspection	Capacity building	Networking	Training
AMRH	●								
AVAREF	●			●		●		●	
CHVI					●		●	●	●
COHRED		●						●	
EDCTP							●	●	●
FDA					●		●		●
GHTC		●	●						
Global Enterprise			●						
Harvard SPH		●							
WHO			●	●					


AVAC
Global Advocacy for HIV Prevention
2006
2007
2008
2009
2010
2011
2012
2013
2014
1 2 3 4
AMRH: Partnerships & Resource Mobilization Initiatives
AVAREF
HSPH: Global Research Ethics Map
COHRED: MARC
Phase 1
Phase 2
GHTC: Global Health Regulatory Requirements Database
Enterprise: Web Analysis Tool
AVAREF: Annual Regulatory Meetings
WHO DCVRN
WHO ICDRA
CHVI: Health Products & Food Branch International Regulatory Forum
FDA: Foreign Regulators Seminar
AVAREF: Joint Reviews and Inspections
CHVI: Regulatory Capacity Building Mentorship Program
Malawi start
Nigeria start
CHVI: Global Course
AVAREF: Resource Mobilization Initiative
CHVI: Virtual Community Web Platform
US FDA: CDRH Learn
EDCTP: RHinnO
US FDA: CDER World
COHRED: EthiCALL
Harmonization
Mapping
Meetings
Mentorship
Online forum

Project/Organization	Effort	Details	Map
African Medicines Regulatory Harmonization Programme (AMRH) aims to harmonize regulatory processes and minimizing time to register medicines without compromising quality and safety.			
Partnership & Resource Mobilization Initiative	Harmonization	Partnerships[1] established to provide technical assistance with documentation and assessment/inspection and regulatory decision-making. The goal is to have 5 to 6 African Regional Economic Communities (REC) across the continent of Africa. Partnerships work together to increase technical support, mobilize political and financial resources and promote inter-REC communication.	
African Vaccine Regulatory Forum (AVAREF) aims to support African National Regulatory Authorities (NRAs) in gaining expertise in clinical trial and vaccine review and evaluation.			
AVAREF mission	Harmonization	AVAREF's core purpose is to harmonize efforts across sub-Saharan Africa.	
Annual Meeting	Meeting: Networking	Meeting intended to encourage dialogue between sectors, discuss concerns and ultimately inform decisions for approval, monitoring or evaluation of vaccines for clinical trials. Member states, World Health Organization representatives and those involved in vaccine research and development attend the Annual Meeting. Recent meeting in November 2014 shifted focus to Ebola.	
Joint Reviews and Inspections	Mentorship: Joint Inspection	Facilitated by the WHO, regulators from multiple NRAs (those targeted for same trial) convene for a joint review. Regulators meet and formulate a single list of questions and concerns to sponsors. The process aims to foster collaboration and simplify the review process for multi-site protocols.[2] Technical assistance and funding provided by regulatory experts appointed by the WHO.	
Resource Mobilization Initiative[3] *Under Development*	Online forum: Networking	This online forum provides a tool for members to discuss concerns, access information and training resources, and provide and receive guidance from expert peers. A task team[4] was established in 2010.	

[1] Current list of partnerships can be found at http://amrh.org/donate/partnership-and-resource-mobilisation
[2] Candidate malaria and meningococcal-A conjugate vaccines have been reviewed to date.
[3] Previously referred to as the Database of Experts
[4] Members: Tanzania, Ethiopia, Ghana, Nigeria, Uganda, Cameroon, Gabon and Senegal

Project/Organization	Effort	Details	Map
Canadian HIV Vaccine Initiative (CHVI) responds to the articulated need for coordinating global efforts to advance the production of HIV vaccines.			
Health Products & Food Branch International Regulatory Forum	Meeting: Training	Designed to support growth and training of foreign NRAs, the four-day training from the leaders in Canadian regulation of biologic drugs and therapies. Attendees included members from AVAREF, PMPB of Malawi, PANDRH- Vaccine Working Group, and DCVRN.	The last meeting attracted over 100 participants representing over 40 nations
Regulatory Capacity Building Mentorship Program	Mentorship: Capacity Building	Selected NRAs are offered close mentoring to identify and ameliorate gaps in clinical trial regulation. The program is tailored to the partnered NRA and tailors the mentorship to the cultural and political climate of the nation. Malawi's PMPB was the first recipient and Nigeria's NAFDAC was included in March 2014. A regional approach is being adopted to maximize efforts in the context of existing funding constraints.[5] Total funding to date is $4 million CAD with $800,000 CAD planned funding in 2014-2015	
Virtual Community Web Platform	Online Forum: Networking & Training	The online database and forum to allows NRAs and ethical committees to exchange information. This tool is intended to encourage discussion and communication concerning clinical trials. The Regulatory Capacity Training Resource Library houses documents and files used in training programs for developing NRAs, increasing accessibility of resources.	
Global Course	Online forum: Training	Training course on regulatory legislation to support NRAs.	
Council on Health Research for Development (COHRED) is an international, non-profit organization with the goal of strengthening research for health systems.			
Mapping African Research Ethics Review Capacity (MARC): PHASE I	Mapping: Ethics	To document and map research ethics committees in sub-Saharan Africa. Drug regulatory committees and capacity building efforts are also examined.[6] The interactive map captures the capacity of NRAs to ethically review health research in countries where EDCTP operates. Partner: South African Research Training Initiative (SARETI) through the University of Kwazulu-Natal (UKZN). To date, 173 RECs have been mapped across 37 sub-Saharan African countries.	

[5] Participants from Ghana, Kenya, Uganda, and Tanzania attended workshops as these authorities have an equivalent level of expertise to that of NAFDAC.
[6] Funded by EDCTP and US NIH Fogarty

Project/Organization	Effort	Details	Map
Mapping African Research Ethics Review Capacity (MARC): PHASE II	Mapping: Ethics	Aims to intervene and ameliorate ethical review bottlenecks. Active training and strengthening information management system will be rolled out to increase efficiency.[7]	
ETHICall	Online Forum: Networking	ETHICall is a tool that is part of the "RHinnO 2.0" repertoire.[8] It is a discussion forum developed to facilitate communication between ethics committees and NRAs. It was developed to coordinate multi-center review processes.	
Health Research Web (HRWeb)	Online Forum: Networking	The REC data collected by the MARC project is housed online at HRWeb. The web-based platform provides a broader context with data on financing, civil society and governance/policy. HRWeb provides a platform to bridge MARC findings with other relevant data, not just dissemination of REC data.	
European & Developing Countries Clinical Trials Partnership (EDCTP) is a network of developing countries and the European Union. This network promotes the conduction of clinical trials and development of treatments against HIV/AIDS, TB and malaria.			
Coordination & Support Call for Proposals ***Under Development***	Mentorship: Training	African nations are invited to submit proposals for support in training to promote good practices. The proposal timelines should span 24 to 36 months with only 5 to 10 grants expected for approval. The aim is to build capacity of staff through individualized, long-term training.	
Research for Health and Innovation Organizer (RHinnO) Ethics	Online forum: Networking	An online ethics review tool. The software's aim is to decrease the turnaround of the research ethics review process. RHinnO offers application management, tracking and increased communication between ethic committees and researchers. Notably, the platform is designed to operate in low bandwidth connections.[9]	Has been used by over 50 RECs across African countries such as Malawi, Mozambique Nigeria, Senegal and Swaziland
Training and Resources in Research Ethics Evaluation (TRREE)	Online Forum: Training	Basic, free online training in ethics and health research regulation.[10] The training module was developed for the South African RAs so despite the presence of universal concepts, some in-country, context-specific material is included.	

[7] Funded by Pfizer

[8] EthiXPERT also part of "RHinno 2.0" is in the pipeline and designed to keep up-to-date with research ethics developments globally.

[9] Feature integrates RHinnO with HRWeb

[10] Module developed by Nivedhna Singh (UKZN's MEPI program), Dr. Ann Strode (UKZN) and Dr. Joanna Bourke-Martignoni (University of Neuchâtel, Switzerland)

Project/Organization	Effort	Details	Map
Food and Drug Administration (United States) supports and sponsors several initiatives to accelerate regulatory strengthening. Several programs are aimed to increase communication, skills and knowledge to build capacity.			
Center for Biologics Evaluation and Research (CBER): Foreign Regulators Seminar	Meeting: Training	Training sessions offered through this 5-day meeting explore CBER's oversight of scientific research, regulation and general procedures. Technical components of the seminar equip participants with foundational skills in monitoring, quality review, licensing and post marketing.	
The Office of International Programs - Clinical Trials Regulatory Capacity Building in sub-Saharan Africa	Mentorship: Capacity Building	Partnering with the Southern Africa Development Committee (SADC), the FDA delivers capacity strengthening workshops, with a focus on good clinical practices and monitoring of clinical trials, to over a dozen nations. Training is delivered in the host nation allowing for direct evaluation of needs and gaps.	The latest four-day workshop was hosted in Zambia (2012) with previous hosts including, South Africa and Botswana.
CDRH Learn	Online Forum: Training	Online training modules that were initially developed for internal use have been published on for training foreign regulators and manufacturers. The educational tool includes interactive modules and is offered in English, Mandarin and Spanish.	
CDER World	Online Forum: Training	This collection information about how CDER carries out its mission, adapts to new legislative initiatives, and initiates directions in regulatory science to improve public health. More modules are being developed.	
Global Health Technology Coalition (GHTC) is a network of NGOs committed to promoting the need for medicines and technology in resource-poor settings. Funded by the Bill & Melinda Gates Foundation, the GHTC focuses on improving global health and regulatory pathways.			
Global Health Regulatory Requirements Database	Mapping: Ethics	The database is a tool provided by the GHTC, containing information concerning regulatory requirements for several nations in Africa, Asia and Latin America (Argentina & Brazil). Pathways to conduct clinical trials and marketing of products can be accessed.	
GHTC Publications	Mapping: Process	GHTC produces documents highlighting examining emerging issues in the regulation of biologics. Examples include documents such as,	

Project/Organization	Effort	Details	Map
		"WHO Product Decisions - A Navigation Guide for Product Developers, Vaccines" and "The African Vaccine Regulatory Forum – An Introductory Guide for Product Developers".	
Global HIV Vaccine Enterprise consists of several independent organizations[11] whose mission is to accelerate the development of an HIV vaccine. The Enterprise supports this mission through coordinating strategic plans, mobilizing funding and encouraging information sharing and collaboration.			
Web-based Analysis Tool	Mapping: Process	Developed a web tool to help researchers most efficiently move their candidate vaccines into first-in-human trials as an adjunct to regulatory capacity strengthening. The tool is currently online. The tool is intended to introduce researchers, funders and advocates, with the processes, costs and timelines involved in the first phase of product development.	
Harvard School of Public Health (HSPH)			
Global Research Ethics Map	Mapping: Ethics	A database of nations and their corresponding ethical guidelines for clinical research.[12] Each country profile includes essential information for conducting studies on human subjects in that region. HSPH also includes commentary regarding possible changes in regulatory guidelines so researchers can plan accordingly.	
World Health Organization			
Regional Meetings	Mapping: Process	WHO in partnership with IPM have convened a series of regional meetings in East and Southern Africa and India with representatives of NRAs to review progress in microbicide R&D and to discuss regulatory mechanisms for reviewing clinical trial applications and registration of new microbicide products. Regulators from the SADC emphasized that they do make autonomous marketing authorizations based on the epidemiology and risk-benefit profile in their respective populations, independent of FDA and EMEA decisions.	

[11] Enterprise stakeholders can be found at http://www.vaccineenterprise.org/content/enterprise-stakeholders.
[12] Mapping is limited to nations aligned with the HSPH's research priorities.

Project/Organization	Effort	Details	Map
Developing Country Vaccine Regulators' Network (DCVRN)	Meeting: Networking	DCVRN focuses its capacity building activities to countries evaluating vaccine clinical trials. Information is exchanged between foreign regulators and experts (from developed regions) on vaccine development, monitoring clinical trials, evaluation of data and dossiers and surveillance of products. Recent discussions have been around harmonization of trial evaluation. AVAREF has been used as a reference in developing the new model for DCVRN.	Other member nations: Brazil, Cuba, India, Indonesia, Iran, China, Republic of Korea and Thailand
International Conference of Drug Regulatory Authorities (ICDRA)	Meeting: Networking	Member states meet every two years to brainstorm ways to strengthen collaboration and promote information exchange. The meeting aims to provide consensus among NRAs on drug development, quality and safety. The recent meeting provided recommendations on how to leverage resources to provide practical experience and knowledge for capacity building.	

Summary

Our review found mostly activities described above that relate to general regulatory strengthening, and are not specific to AIDS vaccines. This results, unsurprisingly, from the fact that a relatively few number of countries are hosting AIDS vaccine clinical trials, and none are reviewing AIDS vaccines for licensure. Moreover, it became clear that while there are some major issues and challenges that AIDS vaccine clinical trials might face, most key informants interviewed expressed the opinion that regulators would most likely deal with these issues on a case-by-case basis and only when an actual protocol was under review. Few regulators, and especially those with limited capacity and/or resources, are able or interested in talking about hypothetical situations about proposed trial designs, products in development or levels of efficacy required for approval. Hence, the focus on most projects is on broad-based capacity strengthening that is not disease, intervention or product specific. This work should, in theory, support the eventual review and approval of AIDS vaccine clinical trials and, eventually, a licensed AIDS vaccine.

As a result, we do not see an immediate need for an active AIDS vaccine-specific role or project in this area, although there are certain key efforts that should be monitored and supported where possible. The African Vaccine Regulatory Forum and the Canadian HIV Vaccine Initiative which are engaged in a mentorship and information sharing could form a basis for regulatory dialogue, strengthening and capacity building in response to an AIDS vaccine trial and/or candidate submitted for future review. In addition, given the HVTN's plans for two major efficacy trials in South Africa (and possibly Southern Africa), it will be important to monitor their progress generally and regulatory aspects specifically. This will be especially important since they are planning both a major licensure study with ALVAC and a protein boost as well as very large efficacy trial that will explore a range of DNA and pox-protein combinations. The size, complexity and range of products in these two trial programs will require significant dialogue with the current South African Medicine Controls Council. AVAC hopes that this review provides a useful tool for a strategic conversation about what activities listed above might be supported and/or monitored; and/or what existing activities or partnerships.

Founded in 1995, AVAC is an international, non-profit organization that uses education, policy analysis, advocacy and community mobilization to accelerate the ethical development and global delivery of biomedical HIV prevention options as part of a comprehensive response to the pandemic. AVAC is based in the US, and focuses on issues and priorities in countries where prevention research and implementation are ongoing. Specifically, we seek to deliver proven HIV prevention tools for immediate impact; demonstrate and roll out new HIV prevention options; and develop long-term solutions needed to end the epidemic. More information at www.avac.org.

Please do send any questions or updates about this report to AVAC's Policy Director, Kevin Fisher, at kevin@avac.org.

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