Overview
Initial HIV epidemiologic studies and HIV vaccine clinical trials in Africa conducted by the International AIDS Vaccine Initiative (IAVI) and Clinical Research Center (CRC) partners faced major hurdles and lengthy ethics and regulatory review. The increased number of clinical trials taking place in Africa in addition to the complexity of trial protocols require that the local ethics review committees (ERCs) have the capacity to ensure that trials are conducted to the highest ethical standards. Regulatory capacity strengthening approaches from 2001-2010 first focused on establishing national guidelines for conducting AIDS vaccine research and targeted individual and institutional training for National Regulatory Authorities (NRAs) and ERCs.

More recently, from 2010-2016, this approach to capacity strengthening expanded to provide technical support and training for the conduct of new and complex HIV vaccine trials including ethical participation of key populations and adolescents, along with support for wider national and regional initiatives. These efforts addressed challenges related to individual country approval delays, duplication of processes and increased costs due to the lack of procedure harmonization in regional blocks. This work also included support for national and regional programs to develop policy frameworks that guide multi-country studies. IAVI and CRC regulatory strengthening projects focused on staff training, policy formulation and operational improvements.

IAVI and CRC partners conducted national and regional staff training to ensure a more effective review of HIV vaccine research submissions. Highlights include:

- Kenya AIDS Vaccine Initiative Institute of Clinical Research (KAVI-ICR) and the Kenyan National Council for Science and Technology (NCST) looked to enhance Kenyan ERC capacity and training standardization through training initiatives beginning in 2011. A National Bioethics Training manual resulted from an audit of all Kenyan ERCs and a training needs assessments that identified both knowledge and capacity gaps (http://www.ajol.info/index.php/sajbl/article/view/113692). Over 486\(^1\) staff have been trained mostly by KAVI-ICR with support from Canada Global Health Research Initiative and IAVI on a wide range of topics related to HIV vaccines, including HIV vaccine science, innovative approaches to vaccine design and delivery, clinical trial design, issues related to first-in-human trials, ethical issues in HIV vaccine trials, bioethics, Good Clinical Practices (GCP), Good Clinical and Laboratory Practices (GCLP), human rights issues related to target populations for HIV vaccines and Good Participatory Practices (GPP).
- Projet San Francisco (PSF) supported the Rwanda Ministry of Health by providing training to two potential clinical trial sites at the Kigali and Butare University Teaching Hospitals.

\(^1\) Through a collaboration with KAVI and co-sponsorship with Health Canada.
on GCP and Regulatory issues. Over 63 staff from two potential new clinical trial sites have been trained by PSF.

- IAVI in partnership with New Partnership for Africa’s Development (NEPAD) and through its Center of Excellence in Clinical Trials, the Ghana Food and Drug Administration (FDA) and University of Ghana School of Public Health, developed an experiential and practical training manual for NRA staff across Africa in 2016. A training manual pilot began at the end of 2016 and will be rolled out in 2017.

IAVI and CRC partners focused on multiple national and regional country-led advocacy initiatives to increase regulatory efficiency.

Highlights include:

- A new Rwandan policy framework for review and registration of clinical trials is under development with technical working group participation from PSF Rwanda and is also planning to expand its capacity for clinical trial with support from PSF.
- The East African Community (EAC) initiated consultative policy dialogues on harmonization of clinical trial regulations across its five countries with initial support from IAVI. IAVI supported the development of the following guidelines for the ethical conduct of HIV vaccine research:
  - National Guidelines for conducting AIDS vaccine research in Kenya and Uganda, and provided technical support in the development of the South Africa guideline
  - National Guidelines for conducting HIV and Sexual and Reproductive Health (SRH) research with adolescents in Kenya and Nigeria
  - Global guidance document for conducting HIV research with Men who have Sex with Men (MSM) and lesbian, gay, bisexual and transgender, and intersex people LGBTI (in partnership with amfAR, United Nations Development Programme (UNDP) and Johns Hopkins University.)

IAVI and CRC partners improved NRA and ERC operations to facilitate regulation of clinical trials and epidemiologic studies by supporting nationally identified capacity strengthening initiatives to strengthen operations of health research.

Key areas of focus in 2015 and 2016 included:

- Introduction of RHInnO Ethics, an electronic platform for submission and review of protocols, in Kenya and Uganda
- Support for NEPAD to develop a Training Curricula for NEPAD Centers of Excellence in collaboration with Ghana FDA and Ghana School of Public Health
- Initiation of the East Africa Harmonization of Clinical Trials Regulations.

Impact

Based on the range of interventions, IAVI and CRC partners focused on the impact to three regulatory capacity strengthening areas – changes in review timelines, increased capacity to review complex protocols/products and improved efficiency in operations.

Review timelines

Timelines are dependent on numerous factors such as the complexity of the proposed study, the capacity of regulatory and review bodies, approval policies and procedures, the quality of the submitted proposal and the efficiency of research institutions in responding to NRA/ERC queries.

Countries with sequential, rather than parallel, submission procedures had longer review times. Clinical trial review times of more than 200 days were frequently associated with amendment submissions prior to initial approval. Protocols of investigational products that required institutional biosafety committee review were associated with longer timelines that may also have influenced the overall trend.

Similarly, epidemiology studies with more invasive procedures were also associated with lengthier review. CRC partner respondents who observed reduction in timelines suggested possible factors related to shortened review timelines including more reviewers and more frequent meetings. They attributed delays to multiple protocol amendments, sequential submission processes and limited technical capacity for review of complex protocols.

On average, 48 epidemiologic studies and 21 clinical trial submissions to both ethics committees and regulatory authorities between 2001 and 2015 took 70 days to receive full clinical trial approval in Rwanda (126 days including approval from an affiliated US university Institutional Review Board (IRB), 183 days in Uganda and 212 days in Kenya. On average, it took 59 days for epidemiologic study approval in Rwanda, 90 in Zambia and 94 in Uganda (UVRI). In Kenya, it took on average 111 days for approval in Coast and 213 days in Nairobi.

These timelines to approval seem significantly shorter when compared with the AIDS Clinical Trials Group Survey (Ndebele et al., 2014) that found approval timelines in Africa, Asia, South America and the Caribbean to be an average of 17.84 months and ranged from 3 - 37 months. However, these timelines are relatively longer compared to a study of review timelines of tuberculosis vaccine trials in South Africa that ranged from 60 to 122 days (Geldenhuys et al., 2012). They also remain longer in comparison to approval timelines for clinical trials of vaccines and other products in the USA and the European Union that are estimated at 15 - 45 days.
and 43 - 75 days respectively (Chester et al., 2006; Heerspink et al., 2008; Mallick et al., 2009; Salman et al., 2007).

**Increased capacity to review complex protocols and products**

IAVI’s support of the first ever Phase I HIV vaccine trials in Kenya, Rwanda and Zambia were fundamental to building both regulatory capacity in HIV vaccine trial review as well as the trial products. Seventeen IAVI-supported HIV vaccine clinical trials have now been conducted in Kenya, Rwanda, Zambia, Uganda and South Africa. The use of novel vectors and technologies, first-in-human trials and having multiple trials of a similar product or type of regimen reviewed by the same ethics and regulatory committees has helped build capacity in specific and important areas. Some examples include:

- DNA protein vaccines – numerous trials in Kenya and Uganda have built solid understanding of the technical, safety and biosafety issues around DNA protein vaccines
- Prime-boost vaccination regimens with two different vaccine components enhanced understanding of both technologies and evaluating supporting preclinical, manufacturing, safety data for testing two different investigational products in the same trial (e.g. DNA+MVA trials in Kenya)
- Novel vectors such as non-replicating low sero-prevalence adenoviral vectors – the series of IAVI-sponsored trials that used Ad35 and Ad26 led to a solid knowledge base in those countries on these vectors that are also being studied TB
- Also for Ebola, malaria and other diseases new vaccine delivery technologies and methods such as electroporation and mucosal delivery (mucosal/intranasal delivery) have built understanding of the technical, biological and safety issues of these methods in Rwanda, Uganda and Kenya.

In 2013, IAVI sponsored a Sendai Vector Phase I study in Rwanda and Kenya, the first replicating viral vector study conducted in Africa. While the timeline for regulatory and ethics review resembled other Phase I studies conducted around the same time (233 days/Kenya; 88 days/Rwanda), the nature of the product and complexity of the study makes these approvals significant. Willingness to approve the Sendai study speaks to an overall increased willingness, among some African regulators, to participate in cutting-edge research and review first-in-Africa and first-in-human studies for implementation in their countries.

This work is important, as IAVI and partners consider African participation in early-stage experimental medicine studies and novel products, such as AAV. Also noted is an increased willingness to support work with key populations. Data shows longer timelines for early observational studies in key populations, such as MSM in Kenya. However, both experience and policy guidelines have increased the comfort level of regulatory and ethical bodies to approve research with these key groups.

**Improved operations efficiency**

African Research Ethics Committees (REC)s face substantial challenges, including limited financial and human resources,
insufficient training, inadequate standard operational procedures and lack of modernized information management technologies. One-hundred-and-sixty-nine RECs are operational in 37 African countries with great variability in skills, membership, resources and capacity. A majority of RECs (93%) in Africa use a complex paper-based review system (Ndebele et al., 2014).

IAVI in collaboration with Council on Health Research for Development (COHRED) and EDCTP supported the integration of an electronic system, RHInnO Ethics, for managing the entire cycles of ethical review research process at 25 RECs in eight African countries. RHInnO Ethics has the capacity to reduce the review timeline by 12 months and improve data security and communications between researchers and ethics review boards.

IAVI and COHRED queried all 25 RECs that implemented the RHINNO Ethics. The majority of respondents (93%) reported a reduction in administrative costs and workload, improved quality of reviews, submissions, data security and confidentiality. All respondents highlighted the platform’s capabilities and potential to contribute to the standardization and harmonization of the ethics review process. Respondents who used RHINNO Ethics for more than two years (20%) reported a trend towards reduced review timelines. Other survey results of note include:

**Conclusion**

African research partners consistently state the need to strengthen national regulatory and research facilities. This need is echoed in national frameworks and strategies related to HIV/AIDS and health research. While IAVI/partner commitment to health research capacity building has remained consistent, more recently it has focused on nationally- and regionally- defined research- and regulatory-strengthening initiatives to increase country ownership and commitment to health research. Moving forward, IAVI and its partners remain committed to supporting locally defined and country-owned plans to strengthen regulatory and ethics bodies. This work will continue to improve their capacity to effectively review HIV vaccine research submissions, ensure adequate national and regional policy frameworks to effectively and efficiently review HIV vaccine research submissions, and support nationally and regionally defined regulatory/ethics strengthening initiatives. Such investments advance HIV vaccine research and development while strengthening local health research overall.

**Areas of Low Impact (<60% of respondents)**
- Easier review of multicenter trials
- Prompt receipt of notifications
- Reduced review time

**Areas of Medium Impact (60-80% of respondents)**
- Reduced workload for REC administrators
- Prompt receipt of notifications
- Reduced REC administrative costs

**Areas of High Impact (80-100% of respondents)**
- Improved protocol submission
- Improved protocol distribution
- Improved platform accessibility
- Improved communication between the REC and researchers
- Improved data confidentiality and security
- Increased adherence to international ethics review standards
- Improved standardization and harmonization of the ethics review process

**References**


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