HIV Vaccine Clinical trials in Africa - Regulatory Considerations

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Why regulatory Capacity for vaccine trials?

- Vaccine R&D - On the rise in the African Region.
  - phase 3 (1), phases1 & 2 (several) cf 15 years ago – phase 3 (0), phase 2 (few), phase 1(0).

- Top 3 WHO disease priorities for new vaccines – malaria, HIV, and tuberculosis

- Malaria hospitalizations >100x higher cf other vaccine preventable diseases

- SAGE April 2013: “Malaria Vaccine Development remains a global public health imperative”

- 34 million living with HIV, 3.1 million <15 years
Advancing the findings of RV144 in a clade C region of the world (*P5 partnership)

**Prime:** ALVAC vCP1521  
**Boost:** ALVAC vCP1521 plus VAXGEN env protein (B/E)  
**Schedule:** 0, 1, 3, 6 months; 16,000 volunteers; 1:1 vaccine: placebo; follow-up for 3 years

*Pox-Protein Public-Private Partnership (P5)*
<table>
<thead>
<tr>
<th>Vaccine Candidate</th>
<th>Countries</th>
<th>Phase</th>
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<tbody>
<tr>
<td>HIV Vaccines</td>
<td>Uganda, Rwanda, Zambia</td>
<td>I/ II</td>
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<tr>
<td>Phase I/II plasmid DNA-MVA prime-boost HIV-1 vaccine candidate</td>
<td>Tanzania</td>
<td>I/II</td>
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<td>HIV-1, MVA HIVA</td>
<td>The Gambia</td>
<td>I/II</td>
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<tr>
<td>HIV-1 MVA HIVA</td>
<td>Kenya</td>
<td>I/II</td>
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<tr>
<td>Cape Town</td>
<td>South Africa</td>
<td>I/II</td>
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<tr>
<td>HIV-MAG, Human IL-12 pDNA, followed or before Ad35-GRIN/ENV HIV</td>
<td>Uganda</td>
<td>I</td>
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<tr>
<td>Penvax DNA (ENV &amp; GAG) IM biojector 2000 or collectra IM electroporation device followed by MVA-CMDR (HIV-1) CM 235 ENV/CM240 GAG/POL</td>
<td>Tanzania</td>
<td>I</td>
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### Status of NRAs of AVAREF countries targeted for vaccine clinical trials

<table>
<thead>
<tr>
<th>Country</th>
<th>Regulatory Authority</th>
<th>Ethics Committee</th>
<th>Activities/responsibilities</th>
<th>WHO Support</th>
</tr>
</thead>
<tbody>
<tr>
<td>Botswana</td>
<td>Drug Regulatory Unit, Health Research Unit (HRU) <strong>Bill introduced in parliament to create autonomous NRA</strong></td>
<td>Independent NEC - ethics and scientific reviews</td>
<td>Director of Health Services authorizes and inspects Clinical Trials. Authorizes importation and use of IND</td>
<td>Clear submission requirements in place AVAREF Formats of CTA submissions</td>
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<tr>
<td>Burkina Faso</td>
<td>National Drug Regulatory Authority Decree regulating clinical trials adopted in May 2010.</td>
<td>Independent NEC</td>
<td>Part of Min of Health and under DG, Pharmacy, Medicines &amp; Laboratories</td>
<td>Same as above</td>
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<tr>
<td>Gabon</td>
<td>Department of Pharmacy and Laboratories (DPL) as defacto NRA</td>
<td>National Bioethics Committee established in 2009.</td>
<td>All CTs approved by competent Ethics Committees and the DPL</td>
<td>Same as above</td>
</tr>
<tr>
<td>The Gambia</td>
<td>Medicine Act established Medicines Board (Director of Medical Services, Chief Pharmacist and medical practitioners) as defacto NRA</td>
<td>No NEC. Several IRBs</td>
<td>Medicines Board advises on the use, importation and registration of medicinal products Medicines Board also authorizes importation and release of investigational batches for clinical trials</td>
<td>Same as above</td>
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<tr>
<td>Ghana</td>
<td>Food and Drugs Board (FDB) established by Food and Drugs Law 1992, PNDCL 305B</td>
<td>NEC plus several IRBs</td>
<td>FDB regulates clinical trials, including authorization and inspections</td>
<td>Utilizes expertise of scientists from academic institutions for reviews of clinical trial applications</td>
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<td>Kenya</td>
<td>Pharmacy and Poisons Board (PPB) is the NRA. New legislation creating Food &amp; Drugs Board</td>
<td>No NEC, but several IRBs. Leading are KEMRI and Kenyatta National Hospital</td>
<td>Regulation of clinical trials by PPB</td>
<td>Online submissions. Utilize academic experts. Otherwise same as above.</td>
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<tr>
<td>Malawi</td>
<td>Pharmacy, Medicines and Poisons Board</td>
<td>NEC</td>
<td>Clinical Trial Review Committee (set up on as need basis by Poisons Board) responsible for regulatory review and approval of clinical trials involving medicinal products</td>
<td>Same as above</td>
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<tr>
<td>Mali</td>
<td>DPL of MOH</td>
<td>NEC</td>
<td>Active clinical research, but lacks capacity to regulate clinical trials</td>
<td>Same as above</td>
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<td>Mozambique</td>
<td>Pharmaceutical Department regulates drugs and drug registration. New law establishing NRA</td>
<td>NEC</td>
<td>WHO Fellowship for attachment to ANVISA of Brazil</td>
<td>Use Portuguese</td>
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<td>Nigeria</td>
<td>National Agency for Food and Drug Administration and Control (NAFDAC)</td>
<td>NEC, and several IRBs</td>
<td>NAFDAC regulates clinical trials</td>
<td>Same as above</td>
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<tr>
<td>Senegal</td>
<td>DPL is defacto NRA</td>
<td>CNERS (Comite National de Recherche Scientifique) performs scientific and ethics reviews (NEC+), and several IRBs</td>
<td>DPL authorizes use of clinical batches. New law established CNERS. Roles of CNERS and NRA sufficiently clarified</td>
<td>Same as above</td>
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<td>South Africa</td>
<td>New regulatory authority, the South African Health Products Regulatory Authority (SAHPRA)</td>
<td>Several IRBs</td>
<td>Parallel submission to IRBs and SAHPRA but approval by both</td>
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<tr>
<td>Tanzania</td>
<td>Tanzania Food and Drugs Authority (TFDA) regulates quality, safety &amp; efficacy of food, drugs, biologicals, medical devices and cosmetics</td>
<td>Defacto NEC</td>
<td>TFDA regulates clinical trials, including authorization and inspections</td>
<td>utilizes expertise of scientists from academic institutions for reviews of clinical trial applications</td>
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<tr>
<td>Uganda</td>
<td>National Drug Authority (NDA) New legislation creating Food &amp; Drugs Board</td>
<td>NEC, plus several IRBs accredited by NEC</td>
<td>Parallel submission to IRBs (and later NEC) and NDA but approval by both</td>
<td>Same as above</td>
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<tr>
<td>Zambia</td>
<td>Pharmaceutical Regulatory Authority (PRA)</td>
<td>NEC, plus IRBs</td>
<td>PRA Regulates clinical trials,</td>
<td>Uses Clinical Trial Application regulatory procedures developed by AVAREF as well as those under SADC Harmonisation</td>
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Pathways for Submissions & Reviews of CTAs

Sponsor

1. EC/IRB Review & Approval
2. Joint EC & NRA Review African Vaccine Regulatory Forum (AVAREF)

1. NRA Review & Authorization
Processing of CTA

CTA Submitted

- Screening Validation
  - Deficient/Rejected
  - Accepted for Review

- Safety & Efficacy
  - Deficient/Rejected
  - Approved

- Quality
  - Review Completed
HIV Vaccines
Regulatory Considerations (1)

- New and complex candidates, platforms, and study designs
- New vectors – Non-human primate vectors e.g. ChAd3
- Lack of reliable correlates of protection
  - Submit CTAs without these, and use study to identify?
- Pre-submission discussions of trial designs, target countries timelines often lacking
- Lack of common/ harmonized guidelines and procedures to facilitate multi-country trials
- Inadequately-resourced and weak NRA capacity for regulatory oversight of clinical trials in Africa – Timelines for clearance of CTAs often very long, > 6 months
HIV Vaccines
Regulatory Considerations (2)

- Consider smaller and adaptive designs due to cost
- New target populations – Adolescents
- Protection given to participants and implications on ascertainment of efficacy.
  - Based on urgent public health needs licensure of a new vaccine can be issued before phase III trials have been completed.
  - Likewise, technical difficulty/impossibility to perform phase III trials (and their high price tag!), some manufacturers may contemplate to request a licensure based on preliminary read-outs, e.g.
    - Licensure based on a non-validated immune correlate of protection (US)
    - Licensure based on demonstration of efficacy in appropriate animal models (US)
    - Licensure based on the results of an interim analysis of a pivotal trial
    - "Conditional licensure" based on the results of "Proof-of-Concept" (PhIIb ToC) trials
HIV Vaccines
Regulatory Considerations (3)

- Timing of analysis plan
  - Preliminary to understand what is happening in vaccinees
  - No correlates at beginning, so plan not complete

- Hypothesis-generating vs. hypothesis-testing

- Strength of statistical plan (power, false discovery rate, multiplicity – multiple time points, multiple assays that may be redundant or correlate to each other)

- How does sponsor intend to use identified correlates to bridge?

- What does sponsor plan for bridging, if correlates of protection are not identified or don’t hold up to hypothesis testing?
HIV Vaccines
Immune Correlates Considerations

- New & improved assays will emerge between when the protocol was written & when the efficacy study is complete & the samples are ready to be analyzed (~5 years)

- Is analysis plan prospective? (may be written after study is complete, but BEFORE samples are analyzed) – acceptable to regulators?

- Does analysis plan prioritize assays to minimize false discovery rate?

- Are the assays validated or exploratory, research assays?

- Will assays be performed blinded or unblinded?
The Opportunities

- WHO-HQ RSS & AFRO capacity building efforts through networking - African Vaccine Regulatory Forum (AVAREF)
- Annual AVAREF meetings for pre-submission discussions
- Harmonization under EAC AMRH (later ECOWAS, other RECs)
- Commitment and technical support of competent NRAs (USFDA, Health Canada, EMA)
- Willingness of African NRAs and ECs to collaborate
- Financial support of global partners – BMGF, EDCTP, PATH/MVI, Canadian CIDA (CHIV Initiative).
Questions for Regulators to Consider

- A sponsor submits a CTA for an efficacy protocol, but does not propose an immune correlates analysis?

- How will you expect a sponsor to bridge efficacy established against a clade in another region to those circulating in your country/region, without a validated immune correlate of protection?

- Sponsor submits a CTA for efficacy study proposing immune correlates analysis. Propose a dozen immunological assays and a plan to analyze all, to identify a correlate.

- Sponsor submits CTA, but wants to delay initiation of consistency lot studies and other bridging studies until after completion and analysis of the efficacy study, hoping to identify correlates upon which to bridge. Is this plan acceptable? (this could delay licensure)

- A sponsor has completed efficacy trial in adults and wants to bridge to an adolescent population, but has not identified an immune correlate of protection. Proposes a non-inferiority bridging study design. Is this plan acceptable to you?
Discussion Points

- Additional guidelines for HIV vaccines vs existing ones?
- Training specific for HIV vaccine clinical regulation?
- Adoption of AVAREF tools for submissions, reviews and GCP inspections?
- Role of regulators in MOUs for bio-banking and sample tracking?
- Role of regulators from US, Canada and Europe?
- Joint Reviews
Acknowledgement

- Bill & Melinda Gates Foundation
- EDCTP
- Canadian CIDA & CHVI
Thank you!