FIFTH MEETING OF THE
AFRICAN VACCINE REGULATORY FORUM (AVAREF)

Final Report

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Opening of Meeting

The meeting began with an address by the WHO Representative for Kenya, Dr Abdoulie Jack, who warmly welcomed all the participants to the fifth AVAREF meeting in Nairobi. He highlighted the importance of vaccines and immunization as a public health tool for the control, elimination, eradication and prevention of communicable diseases globally and especially in the African region. He further outlined the WHO strategy for research and development of vaccines, pointing out that regulation and in particular ethical and regulatory oversight of vaccine clinical trials is a critical part of this strategy. The WR acknowledged the support that WHO has been providing to countries in the area of capacity building for regulation of vaccines through the African Vaccine Regulatory Forum (AVAREF). He also said that there was evidence that this was bearing fruit as countries were doing more and more to ensure regulatory oversight of vaccines. He thanked the US Food and Drugs administration, the European Medicines Agency and Health Canada for availing the network of the expertise of their regulators. He also thanked the partners of WHO, Canadian International development Agency (CIDA), GAVI, and the Bill and Melinda Gates Foundation for their support for AVAREF. He wished all participants a very fruitful and productive meeting.

In his opening statement, the Chief Pharmacist, Dr. K.C. Koskei welcomed all participants to the meeting and saying that his organization as hosting institution was humbled that Kenya was chosen as the venue for the meeting. He acknowledged that AVAREF had crafted a unique position for itself to play the important roles of linking ethics committees with the regulators from different countries to ensure safe, efficacious and quality vaccines are made available to all in Africa. He expressed pleasure at the fact that AVAREF has the goal of ensuring that all African countries have the basic infrastructure and set up required to conduct clinical trials in their countries. He also acknowledged the support to Kenya of the WHO in the development of guidelines for review of applications for conduct of clinical trials in Kenya. He also commended WHO for the opportunities for joint reviews and joint inspections. He noted that the conjugate Men A vaccine, which was under clinical trials in West Africa and for which the first joint inspection was organized by WHO, is now pre-qualified by WHO and is about to be implemented. He took the opportunity to thank WHO and the partners for all the support to
Kenya and to AVAREF. He encouraged participants to visit the countryside and wished all a productive meeting.

In his keynote speech, the Hon Minister for Medical Services, Professor P. A. Nyong’o, EGH, MP, also welcomed participants and hoped that the environment of the meeting place would be conducive for productive work and valuable exchange of ideas and experiences. He noted with pleasure that all 19 African countries, which make up the network could be present. He also noted with pleasure that the meeting brought together Medicine Regulatory Authorities and Ethics Review Committees to initiate, harmonize vaccine research and development activities in Africa. He spoke about the lack of access to essential medicines for some populations, inappropriate prescriptions and counterfeit in drugs Africa. He said 50-90% of drugs purchased in Africa are paid for out-of-pocket, with the burden falling mainly on the poor who are inadequately protected by health policies. He welcomed the support of WHO and partners such as US FDA, EMA, Health Canada towards the common goal of helping to save lives. He wished all participants a successful meeting and declared the meeting officially opened.
WHO Representative for Kenya Remarks

- Hon. Professor Anyang Nyong’o, Minister for Medical Services,
- Representatives of NRAs/Ethics Committees from the 19 African countries,
- Regulators from US, Canada and European Medicine Agency,
- Partners working with WHO to support AVAREF activities,
- The European Union,
- WHO colleagues,
- Members from the media,
- Ladies and gentlemen,

WHO is delighted to host this important meeting and I also wish to take this opportunity to welcome you all to Kenya.

Vaccines and immunization are important public health tools towards the control, elimination, eradication and prevention of diseases globally and also in our region. The strategy of WHO in vaccine research and development and vaccine regulation involves setting the research agenda and building capacity for clinical development and evaluation of vaccines, defining standards, norms and guidelines for clinical trials and supporting the translation of data from clinical trials into policy and implementation. A critical area for capacity building in vaccine regulation in the African Region is that of ethical and regulatory oversight of vaccine clinical trials. This is the specific area of WHO support to countries in the African region through the African Vaccine Regulatory Forum (AVAREF). AVAREF has the following specific objectives:

- Provide information to countries targeted for clinical trials of vaccines.
- Promote and strengthen communication and collaboration between NRAs and Ethics Committees in countries where vaccines are being developed and those targeted for clinical trials in the African Region.
- Provide expertise to African NRAs in support of regulation and evaluation of vaccines.

Through this, AVAREF is thus addressing one of the strategy and vision as well as fulfilling one of the goals of immunization and vaccine development.

The network comprises of one representative each of the National Regulatory Authority and the National Ethics Committee of 19 countries in the African region. WHO has recognized the need
to support NRAs with oversight of vaccines and ethics in vaccine research in the region in 2005 and the network has been holding meetings since its inception.

The 4th annual meeting of the network was held in 2009 in Nigeria and produced recommendations whose status will be reviewed during this meeting. I am informed that through the working group and the last annual meeting, AVAREF developed the Pan African Clinical Trials Alliance (PACTA) which is a functional collaborative network for approval and oversight of medicines/ vaccines clinical trials, integration of Ethics Committee, NRA and PACTA activities. Many countries represented here have already started implementing some of the components and this will form part of the agenda of this meeting to get update on status of implementation as well as completion of the proposal for elements yet to be funded.

In 2008, one of the recommendations created the Pan African Clinical Trial Registry (PACTR) and AVAREF members have since endorsed registration of all vaccine clinical trials in the region as a precondition for submission of review by the NRAs. I am also aware that an update will be provided on the status of registration of clinical trials planned for the region on the PACTR.

The forum will also share information on new candidate DNA vaccines against TB, meningococcal A conjugate vaccine and update Malaria vaccines and a report on phase three trials of the malaria RTS,S. An opportunity will also be availed to share information on the European Medicines Agency new review procedure and criteria for pediatric vaccines and medicines.

Although the network has no secretariat, WHO has facilitated the annual and task meetings and workshops with inputs from the network representatives and collaboration from regulatory authorities such as USFDA, EMA and Health Canada. WHO has continued to provide technical support by organizing joint reviews of clinical trial applications as well as joint inspections and monitoring of ongoing clinical trials in the region. I would like to assure the network that WHO will continue to offer technical support to member states and will continue to work with partners for resource mobilization.

With these few remarks, I wish to take this opportunity to wish you happy deliberations and successful workshop and a safe journey after the workshop.
Address by Dr K. C. Koskei, Chief Pharmacist and Registrar, Pharmacy and Poisons Board, Kenya

Dear Ladies and Gentlemen, friends and colleagues,

It gives me great pleasure today to say “KARIBU KENYA”, that is WELCOME TO KENYA, to all delegates and participants at this 5th African Vaccines Regulatory Forum (AVAREF) in Nairobi, Kenya. We are humbled that you have chosen this to be your meeting venue.

AVAREF- the network for Regulatory authorities and Ethics Committees has crafted a unique position for itself to play the important roles of linking the ethics committees with the regulators, from different countries to ensure safe, efficacious and quality vaccines are available to all in Africa.

Indeed, I learn with pleasure that one of AVAREF’s key goal is to ensure that all African countries have the basic infrastructure and set up required to conduct clinical trials in their countries. There have been countries with very good set ups whilst others have lagged behind, potentially posing as a threat to the research participants in those countries.

In Kenya we are grateful for this support provided by the World Health Organization (WHO), which has helped us develop our “Guidelines for Applications to Conduct Clinical Trials in Kenya” which also has a component for clinical research on herbal medicines. This is currently in print and expected to be available for all next month. Moreover the opportunity provided to countries to conduct joint technical reviews and joint inspections of research protocols serves as an ideal opportunity for countries to share their technical input, learn from each other and provide an informed response to the applicant. This helps ensure safety of participants in line with international Good Clinical Practice (GCP) standards.

We also take this opportunity of acknowledging the support of various other medicine regulators and partners, namely the U.S. Food and Drugs Administration (U.S. FDA), Health Canada, the European Medicines Agency (EMA) and the European and Developing Countries Clinical Trials Partnership (EDCTP) towards this common goal. Having 19 African countries under one roof, both English and French-speaking, with over 50 participants is indeed commendable.

I am also very happy to note that the first joint review of the conjugate meningitis vaccine has been completed, it is WHO-prequalified and that it is scheduled to be launched for the first time on the 1st of October 2010 in Burkina Faso- indeed a proud moment for Africa.
I am convinced that these small interventions will in their own way; help achieve the relevant Millennium Development Goals (MDGs) in African countries.

I take this opportunity to once again thank WHO, the partners, the Ministries responsible for Health in Kenya and our Pharmacovigilance Department for coordinating such an important activity and bringing it to Kenya. I would encourage all to take some time out to visit our beautiful countryside, enjoy Kenyan delicacies and if possible, pop in to the nearby National Parks for getting the real feeling of being in Africa.

Thank you all once again and wish you all very dedicated and fruitful deliberations over these next five days.

God bless you and God bless AVAREF.
Keynote speech for the opening of the 5th meeting of AVAREF, delivered by Hon. Prof. Peter Anyang’ Nyong’o, EGH, MP Minister for Medical services

Dr Abdouli Jack, WHO, Country Representative

Ladies and Gentlemen,

It gives me pleasure to welcome you to participate in the 5th African vaccine regulatory forum meeting which we note with great pride is taking place here in Nairobi, Kenya. It is particularly encouraging to see so many of you here from nineteen countries in Africa.

I would like to welcome you all to this meeting and to our country, Kenya. I believe you will find the environment conducive for productive work and valuable exchange of ideas and experiences. I note with great pleasure that the meeting brings together, Medicine Regulatory Authorities and Ethics Review Committees to initiate, harmonize vaccine research and development activities in Africa.

The advancement and growing importance of the many medical sciences, which have developed during recent decades has emphasized both their integral nature and inter-dependence. Among these, the pharmaceutical sciences have particularly prospered and we have seen a new surge in the availability of drugs and pharmaceutical technology that has touched every aspect of the health status of mankind.

In this regard, the main responsibility of drug regulation is to safeguard the availability of good quality, safe and effective pharmaceuticals to all citizens. This is critical to any healthcare system. Access to drugs and vaccines is routine in many countries. But parallel to this we also see the negative consequences on populations who are denied access even to the most essential drugs. A vital part of healthcare is availability and rational use of essential drugs and vaccines.

Ladies and Gentlemen, much progress has been achieved over the years, but much remains to be done. Lack of essential drugs, irrational use and poor drug quality remain a serious African health problem. Let me mention just a few examples:

Over one-third of the Africa’s population still lacks access to essential drugs and even the most basic diagnostic technology. In the poorest parts of Africa, this number climbs to over 50 percent.
Fifty to ninety percent of drugs purchased in Africa are paid for out of-pocket. The burden falls mainly on the poor who are not adequately protected by health policies. Up to 75 percent of antibiotics are prescribed inappropriately.

Ten to twenty percent of sampled drugs fail quality control tests in many Africa countries and counterfeit medicines have been detected in many countries.

The wide use of injections and the high prevalence of unsafe practices put communities at risk of blood-borne diseases such as hepatitis B and C, and HIV.

Ladies and Gentlemen;

I note with appreciation that support given by World Health Organization and partners such as the U.S. Food and Drugs Administration, Health Canada, the European Medicines Agency and the European and Developing Countries Clinical Trials Partnership towards this common goal of saving lives.

It is our wish that this conference is successful, and we are committed, with you, to achieving its objectives. I hope that your discussions will be relevant and productive and that you will gain important experience and insight into the prevailing situation across the continent. Above all, we hope that your stay in Kenya in the next five days will be a pleasant and memorable experience.

It is now my pleasure to officially declare this important 5th Africa Vaccine Regulatory Forum Meeting open.
1. Introduction and Objectives

1.1. Objectives and expected outcomes (Professor B.D. Akanmori, WHO/AFRO)

Objectives of African Vaccine Regulatory Forum (AVAREF)

In this presentation, Professor Akanmori reminded the participants of the main objectives of AVAREF which are as follows:

1. To provide information to countries, which are targeted for clinical trials of vaccines against diseases, including meningitis, malaria and other new vaccines on different vaccine candidates and timelines for clinical trials.
2. To promote and strengthen communication and collaboration between National Regulatory Authorities (NRAs) and ethics committees, in countries where vaccines are developed and in those that are a target for clinical trials in the African region.
3. To provide expertise to regulators in support of regulation and evaluation of vaccines in the Africa region.

In addition, the specific objectives of this 5th AVAREF meeting were also stated as follows:

1. To review progress made since the 4th AVAREF Meeting in Abuja in 2009

   Under this the status of implementation of a number of planned activities would be reviewed as follows:

   - Review progress made by countries in implementing previous AVAREF recommendations and address constraints.
   - Review and endorse reports of the task teams set up upon previous recommendations and discuss the draft African Common Clinical Trial Documents (ACCTD).
   - Discuss and agree on the draft Terms of reference for and agree on the means and steps towards formalization of AVAREF.
2. **New Vaccines & Vaccine Development**

- Update participants on current status of TB vaccine research and development and the ethical and regulatory issues related to clinical evaluation of candidate TB vaccines.

- Appraise participants on the status of malaria vaccine R&D and the associated ethical and regulatory challenges.

- Inform participants about the status of phase III clinical trials of the lead candidate malaria vaccine, RTS,S and the associated regulatory as well as ethical issues.

- Update participants on the experience of countries in the region on the registration process as well as implementation of the new Conjugate meningitis A vaccine (MenAfrivac A).

3. **Vaccine safety**

- Review the role of regulators in safety of participants during vaccine clinical trials.

4. **Pan-African Clinical Trials Alliance (PACTA) Project**

- To review status of implementation of the three key components of the Pan-African Clinical Trial Alliance (PACTA) project.
  
  o Ethics Component – How to strengthen ethics and to harmonize ECs.
  
  o Registry Component – How to support countries to develop registries of clinical trials linked to the Pan-African Clinical trials Registry (PACTR).
  
  o Regulatory component – How to support regulatory authorities and promote adoption of common guidelines and to promote harmonization.

5. **External links**

- Receive and review reports from CIDA Canada, Health Canada, US-FDA, EMEA, CGD and to further facilitate the support to AVAREF by all these organizations.
- Facilitate open expert consultations between AVAREF Members and other regulators (EMA, US-FDA, health Canada) and promote the exchange of information between African regulators and regulators from Europe and North America.

6. Legislation of clinical trials

- Review capacity building plans/efforts on legislation of clinical trials and how to assist countries to develop and improve on legislation required to support ethics and regulatory oversight of vaccines research in countries of the region.

These objectives were clearly explained and any issues requiring clarification were provided to all participants.

Expected outcomes of the meeting

The expected outcomes for the meeting were also outlined as follows:

1. Progress of implementation of previous recommendations by member countries duly reviewed.
2. Reports of the task teams for previous meeting reviewed and endorsed.
3. Participants updated on progress on Tb and malaria vaccine development.
4. Plans developed for a joint review of GMZ2 Consortium malaria vaccine clinical trials application by target countries (Uganda, Gambia, Gabon and Burkina Faso).
5. Status of implementation of the three components of the Pan-African Clinical trial Alliance (PACTA) strategy reviewed.
6. Progress on the strengthening of legislation for clinical trials reviewed.
7. Consultations between AVAREF members and experts conducted.

Methods of Work

1. Pre-reading and review of draft documents.
2. Plenary presentations in open meetings and discussions.
3. Discussions and adoption by consensus of draft documents.
4. Group discussions/consultations with experts.

1.2. Status of implementation of AVAREF 4 recommendations

(Professor Bartholomew D. Akanmori, WHO/AFRO)

In this presentation the details of the status of implementation of previous AVAREF recommendations including those of the 4th AVAREF meeting were comprehensively reviewed.

AVAREF comprises 19 French-speaking, English and Portuguese-speaking African countries. It is the culminating point of a series of events organized by WHO since January 2005, as part of the WHO Initiative to strengthen the regulatory oversight of vaccine clinical trials in the African region. The activities involved the development of regulatory model procedures in 2005-2006, joint reviews and inspections of clinical trials starting in 2006 and culminated in the formal establishment of AVAREF in Accra, Ghana in 2006. All these activities were largely recognized like factors for the reinforcement of an informal network of regulatory authorities.

Subsequent plenary meetings have since been held in Ouagadougou in 2007 (2\textsuperscript{nd}), in Zanzibar in 2008 (3\textsuperscript{rd}) and in Abuja in 2009 (4\textsuperscript{th}).

The AVAREF countries were selected because they hosted or were targeted for clinical trials of vaccines against the HIV, malaria, tuberculosis and meningitis. Recognizing the roles of Ethics committees and national regulatory authorities in the regulation of clinical trials, the informal network includes representatives from ethics committees (ECs) and national regulatory authorities (NRAs) of the countries, supported by regulators from some developed countries, the United States Food and Drugs Administration (USFDA), Health Canada, and experts from European regulatory authorities that are experts at the European Medicines Agency. The other stakeholders concerned with the forum include the manufacturers, sponsors of clinical trials of vaccines, and the donors who support the process.
AVAREF proved to be an initiative, which stimulated considerable progress towards the harmonization of the regulation of clinical trials. Indeed, since its establishment in 2006, some of the achievements are:

- Development of communication chains, between the regulators of African countries and their counterparts of industrialized countries, making it possible to create an atmosphere of confidence, reinforcement and eagerness to harmonize procedures.
- Coordination between NRAs and ECs.
- Development and adoption of regulatory procedures models by many countries.
- Conduct of joint reviews of clinical trials applications and joint inspections of clinical trial sites for candidate vaccines (conjugate meningitis A and malaria RTS,S).
- Enthusiasm of the countries for more development and implementation of common projects, in particular for the integration of ethical review, regulation and registration of clinical trials as well as common technical guidelines has grown, resulting in the Pan-African Clinical trial Alliance (PACTA) project.

Moreover, AVAREF made it possible to learn major lessons, which will help to reinforce the regulatory system for clinical trials within the member States. Some examples are:

- The high level of expertise, wisdom and engagement shown in the countries although gaps were recognized.
- The mutual acceptance of these factors and the recognition of common challenges provided the incentive to create a space to work together.
- Activities of capacity building were used as a foundation for the harmonization and a model for “authentic learning” initiatives.
- Increasing ownership by the countries reflected in the search of future joint initiatives and the organization of meetings for the implementation of these activities.
The following is a report of the action (A) taken for each of the recommendations (R) from AVAREF-4:

**R1: Coordination between NITAGs and AVAREF**

1) The Forum supports the proposal to convene a consultation between NRAs and National Immunization Technical Advisory Groups (NITAGs) or Immunization program managers to discuss the terms of coordination between them. To be organised by WHO.

   *A1: Implemented: Proposal on how this will be done to be presented during the session on PACTA project-registry component.*

**R2: Guidelines for submission of clinical trial applications and GCP inspections.**

2) Draft guidelines for submission of clinical trial applications and for GCP inspections will be circulated among all AVAREF members by Jayesh (Kenya) and Eric (Ghana) respectively and will compile comments received until Monday Oct. 26 2009 to finalize the document. After that, the final version will be distributed to all AVAREF countries. AVAREF representatives will advocate for adoption by their agencies.

   *A2: Implemented. The document was circulated and comments received and incorporated. Jayesh M. Pandit will provide an update.*

**R3: Joint review of GMZ2 application by Burkina Faso, Gabon, the Gambia and Uganda.**

3) Uganda, Burkina Faso, Gabon and Gambia agree to jointly review the clinical trial application for the GMZ2 malaria vaccine. They have agreed to use the newly developed guidelines for the submission of the Clinical Trial Authorization. Submission will be received in November, countries will do the review independently and the joint review will be scheduled by mid February 2010 to be facilitated by WHO.

   *A3: Abandoned. European Malaria Vaccine Initiative (EMVI) withdrew from GMZ consortium. Other avenues being sought to implement this. To be discussed further.*
R4: Endorsement of the PACTA concept by Ministers of Health

4) It was agreed that the commitments from the Ministers of Health expressed in the 59th Regional Committee for Africa meeting in Kigali, 31 August – 4 Sept. 2009, would cover the initiatives proposed by AVAREF to integrate ethical review, regulation and registration of clinical trials. Therefore the proposed next step is to prepare a short document summarizing the concept of PACTA to be circulated from AFRO to Heads of NRAs and Ethics Committees as a means to implement the recommendations formulated by the Ministers. Bocar Kouyate will prepare a first draft to be circulated to AVAREF members; deadline for comments is 2 October. The English version will be sent to Samba Corr Sarr who will translate into French by 16 October.


This has not been fully implemented due to some difficulties to submit a document to the regional committee; in particular taking into consideration the length of the process. Moreover, the document (concept of the PACTA) was not finalized. Therefore, it is possible to prepare for 2011 regional committee meeting.

R5: Registration on PACTR or WHO primary registry as requirement for submission of CTA.

5) All AVAREF member countries agreed to include registration in PACTR or when justified another WHO primary registry or data provider as a requirement for the submission of CTAs.

A5: Members to provide updates during PACTR session.

- Senegal has started its own database thanks to support of US$50,000 from EDTCP which made it possible to recruit a Webmaster, an archivist. Consequently, it was possible to index all the clinical trials housed by Senegal. In Senegal, the resources which must accompany reforms often come from abroad.
To initiate the database, Uganda contacted South Africa which answered but that took a long time. Uganda could visit various sites. The country has begun the process of data acquisition which will lead to the development of a clinical trials register.

Zimbabwe hopes to make it an obligation next year for all clinical trials to be registered on PACTR before submission to the NRA. It revises its regulation consequently. The country requested the support of South Africa.

Gambia proposes to work with other countries to know how to proceed.

Nigeria started the process and requested the support of experts who had come in April 2010.

For the moment Burkina Faso adopted a decree after the last AVAREF. Moreover, two enforcement decrees are in the course of signature with the Ministry for Health.

Rwanda is still in phase of development of new directives, which are being elaborated by the Ministry for Health.

R6: National databases.

6) The Pilot countries; Tanzania (A. Fimbo), Uganda (N. Helen), Senegal (Samba), Nigeria (Beno), Mozambique (Albino Maheche), Burkina Faso (Semde) and Gabon (Sophie) agree on a set of data that will constitute the basis for national databases for CTs. Samba Corr Sarr (Senegal) will link with Health Research Web (HRWeb) for implementation. Modalities for access and exchange of information between NRAs and between NRAs and PACTR will be established in collaboration with HRWeb within six months. The progress report will be presented at AVAREF-5.

A6: Updates to be provided by countries.

R7: Links with the WRWeb.

7) AVAREF countries will introduce necessary data, on the Health Research Web concerning their regulatory system, governance and policies, guidelines, involved in the regulatory oversight of clinical trials within six months.
A7: Members will provide updates.

R8: Formalization of AVAREF.

8) TORs will be developed for the AVAREF formalization process. Kwasi and Dominique will provide support. Establishing a group of four persons (two from NRAs and two from ECs): A. Fimbo (Tanzania), Ahmed (Ethiopia), Bocar (Burkina Faso), and Aminu (Nigeria).

A8: Implemented – The draft TOR will be presented during the session on formalization.

R9: Fifth AVAREF meeting.

9) The next AVAREF meeting will take place in Addis Ababa during the week of 20 September. The host country commits to provide support to WHO for the formalities required for the organization of the meeting.

A9: Implemented, as the meeting is taking place on the dates recommended but the venue has been changed.
2. Tuberculosis Vaccines

2.1. Tuberculosis vaccines: Update on BCG and on the development of new TB vaccines (Dr Uli Fruth, WHO/IVR/HVI)

This presentation has permitted a review of the history of BCG vaccine and gave an update on the development of new TB vaccines.

BCG was administered at birth in more than 131 countries. Coverage is greater than 50% in all these countries.

Several clinical trials have shown consistently high efficacy of BCG vaccination against severe forms of childhood tuberculosis, principally meningitis and miliary disease, but variable efficacy against pulmonary tuberculosis in adults.

The other information on BCG, provided by the presenter is about:

- **Booster doses of BCG**: In this respect, a second vaccination can add appreciably to the protection against leprosy, without providing any protection against tuberculosis.

- **Factors influencing occurrence of adverse effects following BCG vaccination**, which are: the vaccine strain (Pasteur, Danish, Tokyo), the dose, the route of administration (errors), the population variability (age), the policy changes, and the reporting systems.

- **BCG complications in HIV+ infants**: definition of disseminated BCGosis, estimated incidence of disseminated BCG disease in HIV-infected infants vaccinated at birth with BCG, and the implications for WHO Policy. This policy has now four different scenarios, based on risk-benefit analysis: (1) If Infants are born to women of unknown HIV status: they should be vaccinated (2) Infants are born to HIV+ mothers, HIV status unknown, no signs & symptoms: they should be vaccinated "after consideration of local factors", (3) HIV+ infants, no signs & symptoms: should not be vaccinated, (4) Infants born to HIV+ mothers, unknown HIV status, signs & symptoms: should not be vaccinated.
The second part of the presentation focused on the development of new TB vaccine. It revolves around the following four questions: Why do we need (a) new TB Vaccine(s)? Which type(s) of new TB vaccine do we need? How far has the vaccine discovery process advanced? A strategy for acceleration.

There are some barriers to new TB vaccine development, as follows:

- Defined correlates of immunity (the level of protection provided by vaccines) are critical for measuring vaccine efficacy and getting regulatory approval. In this respect there are no validated correlates of immunity for TB vaccines.


- Limited facilities to produce live vaccines and for large-scale manufacturing.

- Need for new vaccine delivery strategies.

- Limited number of clinical trial sites for TB disease.

- Lack of Regulatory capacity for approving vaccines in developing countries.

The pipeline of tuberculosis vaccine candidates includes (B) attenuated *M. tuberculosis*, and (A) improved 'BCG, both to be used as pre-exposure (priming) vaccine. It is highlighted in the following table of TB vaccine candidates currently under development:

Table 1: Vaccine candidates in clinical trials.

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Source</th>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>VPM-1002</td>
<td>Max Plank/VPM TBVI</td>
<td>Phase I Europe</td>
<td>rBCG with chromosomal expression of Listeriolysin to enhance safety and potency</td>
</tr>
<tr>
<td>AERAS-rBCG</td>
<td>Aeras</td>
<td>Phase I US &amp; Africa</td>
<td>RecBCG with endosome perturbation and over-expression of Mtb antigens [AERAS-rBCG]</td>
</tr>
<tr>
<td>Mtb [ΔlysAΔpanCDA secA2]</td>
<td>Albert Einstein College of Med.</td>
<td>GMP product preclinical</td>
<td>Non-replicating, Mtb auxotrophic for lysine and pantothenate; attenuated for secA2</td>
</tr>
<tr>
<td>MTBVAC01 [ΔphoP, Δfad D26]</td>
<td>University of Zaragoza, Institute Pasteur, TBVI</td>
<td>GMP product preclinical</td>
<td>Live vaccine based on attenuation of Mtb by inactivation of phoP and fad D26 genes</td>
</tr>
</tbody>
</table>
**Booster TB vaccine candidates**

<table>
<thead>
<tr>
<th>Booster TB vaccine candidates</th>
<th>Oxford MVA85</th>
<th>Oxford/Isis/Emergent and Aeras</th>
<th>Phase I &amp; II Adult/Infants US &amp; Africa</th>
<th>Modified Vaccinia virus expressing Mtb Ag85A</th>
</tr>
</thead>
<tbody>
<tr>
<td>AERAS402/Crucell Ad35</td>
<td>Cruell/Aeras</td>
<td>Phase I &amp; II Adult/Infants US &amp; Africa</td>
<td>Adeno 35 with transgene for Mtb antigens 85A, 85B &amp; TB10.4</td>
<td></td>
</tr>
<tr>
<td>M72</td>
<td>GSK/Aeras</td>
<td>Phase I &amp; II Adults US &amp; Africa</td>
<td>Fusion Protein M72 [Mtb antigens Rv1196 &amp; Rv0125] in AS02 adjuvant</td>
<td></td>
</tr>
<tr>
<td>HyVac4</td>
<td>Sanofi Pasteur/SSI/Intercell and Aeras</td>
<td>Phase I Adults EU &amp; Africa</td>
<td>Fusion protein of Mtb antigens 85B &amp; TB10.4 in IC31 adjuvant</td>
<td></td>
</tr>
</tbody>
</table>

**Therapeutic TB vaccine candidates**

<table>
<thead>
<tr>
<th>Therapeutic TB vaccine candidates</th>
<th>RUTI Unitat de tuberculosi</th>
<th>Phase I Europe (HIV+)</th>
<th>Fragmented inactivated TB cells</th>
</tr>
</thead>
<tbody>
<tr>
<td>M. vaccae</td>
<td>NIH, Immodulon, Aeras</td>
<td>Phase III 2004</td>
<td>Inactivated whole cell M vaccae; phase III in BCG-primed. HIV+ population completed; reformulation pending</td>
</tr>
</tbody>
</table>

The most advanced to date is the MVA85. Since 2002, a series of Phase I and IIa clinical trials with MVA85A have been completed. In these clinical trials they found that MVA85A is safe and highly immunogenic in all populations tested to date, including:

- BCG-naïve and BCG-vaccinated subjects,
- Subjects latently infected with *Mycobacterium tuberculosis*,
- Subjects infected with HIV in the UK,
- Adults and infants in the Gambia,
- Adults and adolescents in South Africa.

In 2009, a Phase IIb proof-of-concept efficacy trial commenced in South African infants. This clinical trial will allow evaluating the protective efficacy of this strategy in humans, and is the first of the new generation of TB vaccines to enter into efficacy testing.

Some endpoints have been defined to be used in TB vaccine trials, including:

- In adult trials: culture confirmed, smear positive, X-ray positive, clinical symptoms,
- In infant trials: Defined/confirmed, probable and possible TB versus TB/not TB.

A new recombinant BCG vaccine has the following potential public health benefits:

- Well defined manufacturing methods and preclinical data: CMC review & GMP inspections.

- Better safety profile than current BCG: licensing a safer TB vaccine for HIV+ population.

- Modern effectiveness data: preventing TB disease and inducing relevant immunity: GCP review in developing countries.

- A “live” prime for a new booster TB vaccine for adults & adolescents.

However, there are some TB vaccine pre-introduction challenges, which are:

- Lack of impact and cost-effectiveness data to act as guidance for TB vaccine development

- Lack of definition of desirable vaccine characteristics (Target Product Profile¹)

- Absence of global vaccination strategies to target adult and adolescent populations.

Finally, the presenter gave a timeline for the vaccine development, illustrated bellow:

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¹ The product specifications bellow are called the target product profile (TPP):

- Vaccine performance indicators: efficacy endpoints, safety, level of efficacy/effectiveness, duration of protection.

- Public health impact indicators – mortality, disability, hospital use.

- Prospective issues: potential safety issues/constraints, impact of partially efficacious/effective vaccines, country community (behavioural, etc) issues.

- Programmatic issues: relation to in-country health intervention programs, route of delivery, etc.
In addition, he gave information on the Global partnership to stop TB, established in 2000 and whose secretariat is housed in WHO. This partnership is a global movement to accelerate social and political action to stop the spread of TB.

In conclusion, this is a critical moment in time for TB vaccine development, since:

- Many promising vaccine candidates are coming along.
- In the absence of both reliable animal models as well as an immune surrogate of protection, only clinical efficacy trials will bring us closer to a licensed vaccine.
- Regulatory capacity is a crucial prerequisite for the timely availability of a new TB vaccine.
2.2. Tuberculosis vaccines: FDA perspective on clinical development (Rosemary Tiernan, MD, MPH, Center for Biologics Evaluation and Research, Food and Drug Administration, USA)

To understand FDA’s perspective on clinical development, this presentation addresses clinical development issues and their challenges.

In this perspective there are at least some factors driving the current clinical development and approval process:

- Before going into a phase 1 clinical trial pre-clinical data should support the first in human trial. For the phase 1 clinical trial safety must be studied in adults before children. This phase 1 trial is initiated to gain basic safety and immunogenicity information.

- Phase 2 trials must provide additional safety data and qualitative, quantitative information on the immune response elicited by the vaccine. Results of phase 2 study will establish the foundation for dose-finding and key aspects of adjuvants, including potential safety concerns (potential typical local and systemic reactions).

- Adjuvants are defined as constituent materials under 21 CFR 610.15. Under 21 CFR 610.15 an “adjuvant shall not be introduced into a product unless there is satisfactory evidence that it does not adversely affect the safety of the product”. They are not active ingredients under 21 CFR 210.3 (b) (7). “ Active ingredient means any component of a drug product intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease, or to affect the structure or any function of the body of man or other animals. Active ingredients include those components of the product that may undergo chemical change during the manufacture of the drug product and be present in the drug product in a modified form intended to furnish the specified activity or effect”.

- Early on in clinical development of a novel adjuvanted preventive vaccine, a comparative study of adjuvanted vs non-adjuvanted vaccines should be conducted to demonstrate that the immune response elicited by the adjuvanted antigen is significantly better than that
elicited by the same antigen alone. For sample size determination, the sponsor should pre-define what would constitute a meaningful difference. One statistical approach to addressing the added value of a vaccine adjuvant is described in two FDA guidance documents (i.e., the 2007 Draft Guidance for Industry on Clinical Data Needed to Support the Licensure of Influenza (Trivalent and Pandemic) Vaccines.


- In addition, although a placebo group is not required in a Phase 1 clinical study of an adjuvanted vaccine, inclusion of a placebo group may enhance interpretation of the initial safety data. The use of a saline placebo is preferred over an adjuvant alone arm, if there will be only one control group.

- The following trial design issues will be considered: Logistics, population, BCG and live vaccine issues and strategies, endpoints, and safety. (i) **Logistics:** It will be important to define the epidemiology and determine the incidence of TB in the setting where phase 2 trials will be conducted. The study population is usually expanded to more closely represent those for whom the vaccine will be indicated, for example, in terms of age, and other characteristics. Temporal aspects of the immune response are also important, such as the time to peak response, and the duration/durability of response. Challenges include differentiating the endpoints of TB infection and disease. Diagnostics for infection: diagnostic tests must be validated (e.g. QuantiFERON®-TB Gold Test and TSPOT.® TB and PPD) and need to explain whether these tests could interfere with immunogenicity measurements that will be used in the clinical study). Precise case definitions are needed for active TB disease and latent TB infection. If feasible, Phase 2 studies may provide pilot information about the efficacy endpoints in advance of phase 3 studies. Safety follow-up should be at least for six months after the last vaccine dose. Co-infections make evaluation of fever challenging especially in the setting of malaria and dengue.

(ii) **Study population:** Potential study populations include immunocompetent adults with no evidence of latent or active TB infection and who have not received BCG, sensitized immunocompetent adult who may be a BCG recipient or be PPD positive (but not e.g. a recent converter for whom INH therapy would be indicated), and immunocompetent
child. The safety concerns reside mainly with the sensitized population. FDA recommends that preclinical studies are performed in sensitized animals prior to initiating phase 1 or 2 studies in this population because of concerns regarding the Koch phenomenon, i.e. giving a TB vaccine to a sensitized patient with latent TB may exacerbate TB disease. Realistically, the sensitized patients may represent the population in which most TB vaccines will be tested i.e. BCG recipients residing in the developing world. (iii) Special consideration in vulnerable populations: It will be important to outline any risks associated with administering live vaccines, including BCG to the study population. When discussing clinical studies in children, it may not be possible to withhold BCG from any study arm, even in a country that has “BCG failures”. It is important to exclude pregnant patients. (iv) Live TB vaccine risks: Live mycobacterial vaccines may cause disseminated disease in immunosuppressed patients such as patients with HIV. Potential problems regarding recombinant BCG vaccines and the development of antibiotic resistance include live vaccine strains which may have higher minimum inhibitory concentrations (MICs) for INH and/or vaccines which carry plasmid markers with resistance to antibiotics that may be needed to treat disseminated mycobacterial infections. Live vaccines that elicit a positive PPD response is more of a risk/benefit issue for the U.S. population. (v) Prime-boost strategy: If study subjects receive BCG as infants (“BCG prime”), there is need to provide a rationale for when to administer the study vaccine “boost” considering issues such as: When is the most immunologically feasible time to boost with study vaccine? When is the most practical time to boost with study vaccine e.g. at time of entry to elementary school? (vi) Immunogenicity endpoints: Immunogenicity assays should be validated for phase 3. The tests used include cell-mediated immunity, humoral immunity using IgG serum ELISA or IgG ELISPOT using peripheral blood mononuclear cells (PBMC). (vii) Efficacy endpoints in phase 2: Although it will be of interest to evaluate PPD conversion, immunogenicity data and the results of animal challenge data, these will not be considered sufficient to demonstrate vaccine effectiveness. Field trials will be necessary to evaluate the impact of vaccination on the development of TB infection and disease in the study population. It is important to agree on case definitions and methods for diagnosis of TB infection vs TB disease. It will be important to have discussion regarding any tests that will be used to
diagnose active or latent TB infection. (viii) vaccine efficacy trials, (ix) safety monitoring to protect subjects by monitoring local, systemic, and potential end-organ toxicity. Ultimately FDA may need to study this vaccine in an HIV, malaria and TB endemic area. This presents challenges regarding maintaining the safety of a study population that has many reasons to be immunosuppressed (nutritional deficiencies and HIV) and challenges regarding the evaluation/differential diagnosis of fever, weight loss in this population.

In conclusion, regarding phase 2 studies for TB vaccines the presenter:

- considered some of the challenges,
- stated that early phase studies should support the efficacy of the product,
- pointed out that the path to licensure may be different depending on a country’s unique TB epidemiology,
- stated that it is required that field trials for efficacy should be performed,
- stated that the advice of the Vaccines and Related Biological Products Applications (VRBPAC) Advisory Committee may be sought at any stage of clinical development.

2.3. Update on tuberculosis vaccine clinical trials in Africa, The Gambia (Markieu Janneh-Khaira, Chief Pharmacist/Registrar)

The session on the tuberculosis vaccines was closed with this presentation of Gambia on a candidate tuberculosis vaccine trial.

This trial is a Phase II open labelled, randomized controlled trial. The purpose of the study is to evaluate the safety and immunogenicity of GSK Biologicals’ candidate tuberculosis vaccine (M72/AS01E) when administered IM according to different (within and outside) Expanded Programme of Immunisation (EPI) schedules to healthy infants living in a tuberculosis endemic area.

The trial included 300 infants divided into 2 equal cohorts of 150 each.

Subjects of one experimental group received 2 doses of GSK’s investigational vaccine, one month apart, concomitantly with the last two doses of their primary EPI vaccines regimen. In another
experimental group subjects receive 1 dose of GSK's investigational vaccine concomitantly with the last dose of their primary EPI vaccines regimen.

One group gets GSK's investigational vaccine when the child is six to seven months old after having finished the initial series of EPI vaccines. The other group gets GSK's investigational vaccine together with their early normal primary EPI vaccines.

For the cohort outside the EPI, 42 infants have been vaccinated to date.

In conclusion, only the above application has been received this year. This application received ethics approval and regulatory approval from NRA in April 2010. Recruitment of subjects, as well as vaccination and follow-up are ongoing. Data are continually reviewed by a local monitor and a GSK safety monitoring team. To date, no safety issues were detected.
3. Malaria vaccines

3.1. Overview of clinical trials of relevance to Africa: malaria vaccines (Vasee Moorthy MD PhD, WHO/HQ/IVR)

Dr Moorthy presented some relevant results of clinical trials conducted in Africa, which can be summarized as follows:

- Phase 2 field efficacy data with RTS,S/AS01 in 850 Kenyan and Tanzanian infants aged 5-17 months. Overall, there was an adjusted rate of efficacy against all malarial episodes of 56%. This protection occurred in a setting with reducing transmission intensity and 70% bednet use. Efficacy against severe disease promising in phase 2 studies to date.

- Phase 3 trial study design: Since, in Phase 2 testing, the vaccine candidate was shown to confer significant protection against \textit{P. falciparum} infection and clinical disease, including severe malaria, the RTS,S/AS01(E) malaria vaccine candidate has recently entered Phase 3 testing (\textit{Hum Vaccin.} 2010 Jan;6(1):90-6). Up to 16000 children in 2 age categories (six to 12 weeks in co-administration with EPI vaccines, five to 17 months,) were included for total trial duration per child of 30 months. According to this study, the RTS,S/AS01E vaccine, when broadly implemented and judiciously integrated with other malaria-prevention measures, would have a major public-health impact in Sub-Saharan Africa.

- University of Oxford/Okairos AdCh63/MVA ME-TRAP: A pre-erythrocytic vaccine delivered by Adenovirus serotype 63 prime followed by modified vaccinia Ankara boost. Led to 20-25% protection in challenge trials in Oxford. Adult Phase 1b started June 2010 in Kilifi, Kenya. EDCTP funded project to continue potentially to Phase 1-2b in Kenya, Gambia and/or Burkina in next few years.

- Blood stage combination vaccine known as GMZ2. Developed by Statens Serum Institut, Denmark. A phase 1a occurred in Germany (Tübingen). A phase 1b has been completed in Gabonese children aged 1-5 years in 2010. EDCTP funded project to continue to Phase 2 trial with >2000 children in Ghana (Navrongo), Gabon (Lambarene), Uganda (Makerere University), and Burkina-Faso (CNRFP).
- Allele-specific efficacy in Mali. AMA1/AS02 blood stage vaccine tested in paediatric randomized clinical trial in Mali (n=400). 17% efficacy for primary endpoint (non-significant). ~70% strain-specific efficacy in pre-specified secondary analysis.

- SE36, blood stage candidate vaccine. Developed and Phase 1a trial by Osaka University, Japan, Group of Prof. Horii. Based on the N-terminal domain of serine repeat antigen (SERA5) of Plasmodium falciparum. Adult Phase 1b underway in Kampala. Paediatric Phase 1b to start in 2011.

- Irradiated or genetically attenuated sporozoite vaccines. First phase 1 trial of vialled irradiated sporozoites started in May 2009 under FDA IND. WHO Malvac 2009 meeting in Senegal identified key issues that would need to be addressed if these were to progress to field evaluation (MALVAC 2009: Progress and challenges in development of whole organism malaria vaccines for endemic countries, 3–4 June 2009, Dakar, Senegal Vaccine 28 (2010) 4695–4702).

- Overall 11 research centres spanning seven African countries are hosting a Phase 3 clinical trial.

3.2. Transmission-blocking and whole organism malaria vaccines: Regulatory challenges (Ralph E. Leblanc, PhD, US-FDA, Center for Biologics Evaluation & Research Office of vaccines research and review)

This presentation focuses on FDA’s regulatory concerns with regard to malaria transmission-blocking vaccines (TBVs).

Although much progress has been made in malaria prevention efforts, the development and licensure of a safe, effective malaria vaccine remains a challenge. Malaria vaccines could be one of the most cost-effective interventions to reduce the enormous burden of disease in the developing countries. A transmission blocking vaccine will target the sexual stage of the parasite, by inducing antibodies against antigens, and prevent the spread of malaria through the community; such a vaccine would have the potential to reduce the burden of disease and death from malaria.
To obtain a license for a biological product, section 351(a) of the Public Health Service (PHS) Act requires a manufacturer to demonstrate that the biological product is “safe, pure, and potent”, and that the manufacturing facility meets standards designed to assure that the product “continues to be safe, pure, and potent.”

Section 351 of the Public Health Service Act and section 505 (b) of the FD&C Act do not limit approvals to those products that treat, mitigate, diagnose or prevent conditions or diseases found in the U.S.

FDA, in accordance with 21 CFR 10.115(g), published a guidance focusing on development and licensure of vaccines targeted against infectious diseases or conditions endemic in areas outside the United States. This guidance entitled, “Guidance for Industry: General principles for the development of vaccines to protect against global infectious diseases” is available from Internet:


This guidance gives clarifications, which are intended to ensure that potential sponsors and vaccine manufacturers understand that a) FDA can license vaccines to protect against infectious diseases or conditions not endemic in the U.S.; b) the regulatory pathways to U.S. licensure for the development of vaccines to protect against infectious diseases not endemic in the U.S. are the same as for vaccines to protect against diseases that are endemic in the U.S.; and c) sponsors may submit data from clinical trials conducted outside the U.S. to support product licensure.

The legislation (FDA Amendment Act of 2007, by adding section 524) recognizes the importance of having products to treat and prevent tropical diseases that disproportionately affect poor and marginalized populations and for which there is no significant market in developed nations.

FDA encourages sponsors to develop and license vaccines to protect against global infectious diseases by submitting an Investigational New Drug (IND) Application (21 CFR Part 312), even if the U.S. market for that vaccine may be limited and the primary target populations for the vaccine are in developing countries.

FDA regulations permit the acceptance of foreign clinical studies in support of a Biological Licence Application (BLA) approval, provided certain conditions are met. Foreign studies performed under an IND must meet the requirements of 21 CFR Part 312. Under 21
CFR 312.120, FDA will accept as support for an IND or to support an application for marketing approval, a well-designed and well-conducted foreign clinical study not conducted under an IND, if certain conditions are met, including that the study was conducted in accordance with GCP and including review and approval by an independent ethics committee.

Some considerations for clinical development have been exposed. They can be summarized as follows:

- Phase 1 clinical trial for safety testing in a small number of subjects (in adults, then children). The focus at this stage is the evaluation of immune response:
  - Development of an ELISA for evaluation of TBV-induced antibodies,
  - Assess whether vaccine induced antibodies have the ability to inhibit oocyst development in a membrane feeding assay (MFA).

- Phase 2 safety and immunogenicity studies:
  - To further evaluate the safety and immunogenicity of the vaccine candidate.
  - Duration of antibody response (evaluation over several seasons, use of MFA to identify whether the vaccine is biologically active, is the product promising to justify a phase 3 clinical field trial with a clinically meaningful outcome.

- Relevant questions surrounding challenge in MFA standardization include: How does strain variation in the natural environment impact evaluation of TBV assessed by MFA that uses lab-adapted strains? How to account for feed-to-feed variation? How to maintain average number of oocysts per mosquito in a control feed? What are appropriate negative controls? How to account for a level of natural TB immunity in an exposed population?

- The establishment of a correlate of protection is not a requirement for vaccine licensure.

- Phase 3 “field” clinical endpoint studies to demonstrate vaccine effectiveness and safety likely required for licensure.

- Considerations for subject population (paediatric population vs total community).
- How to define “effectiveness” of a TB vaccine? Clinical endpoints to be considered: Morbidity/mortality (composite endpoints), Careful selection of case definition, Time to 1st episodes/multiple episodes? Total number of episodes/defined time interval? Parasitemia rates/defined time interval?

- Vaccine Effectiveness (VE): the acceptable lower bound for VE is determined case by case.

The second part of the presentation focused on whole organism vaccines against malaria, including:

- Historical context: irradiated sporozoite vaccine delivered by mosquitoes.

- Challenges of isolating sporozoites from irradiated mosquitoes and delivering a purified product.

- Determining initial human doses: the role of pre-clinical animal models.

- The role of malaria challenge studies in evaluating efficacy.

- Moving from malaria naive to malaria exposed subjects: trial design.

- The IND process.

- The common deficiencies related to IND submissions: manufacturing, preclinical, clinical.


- Preclinical safety assessment of malaria vaccines.

3.3. Special challenges of approving phase I clinical trial of a malaria vaccine (Delese Mimi Darko, Food and Drugs Board, Ghana)

The presentation had the aim of presenting the challenges and recommendations resulting from the approval of a phase 1 clinical trial of malaria vaccine.
It is a blood stage malaria vaccine, which is proposed with three ascending doses given at 0, one and six months of age in comparison with placebo. The trial was submitted in March 2009, started in May 2010, and will include 3 cohorts consisting of 20 healthy subjects each.

A GCP inspection has been conducted. To date, no serious adverse events have been reported. The team is waiting for a safety monitoring committee report before proceeding to cohort 2.

Ms Darko presented some challenges, which may be summarized as follows: (1) Chemistry, manufacturing and control data: lack of data on stability of the genetic construct (recombinant product), characterisation and purification of IP (drug substance), stability of the drug substance and drug product, lack of data on the drug substance used toxicological studies, GMP status of the manufacturer of drug substance/product, release specifications for drug product; (2) Non-clinical and clinical data: safety pharmacology (central nervous system, cardiovascular system, gastro-intestinal tract), lack of pharmacokinetic data, lack of reproductive toxicological data, lack of juvenile toxicological data, difficulty in obtaining first-in-man study reports from sponsor, lack of toxicokinetic data (animal to human exposure ratio); (3) Provision of Insurance Certificates; (4) Administrative Documents.

Finally, she showed pictures of the clinical research facilities for this phase I clinical trial in Ghana. The facilities are modern and include facilities for admission and resuscitation of participants.

3.4. Country experiences in inspections of the phase 3 clinical trials of GSK RTS,S/AS01E malaria vaccine (MosquirixR) Mal-055,

Ghana, Delese Darko, head of Department of Pharmacovigilance and Clinical Trials, Food and Drugs Board Ghana, Box CT 2783 Cantonments Accra.

The GCP inspection process used by Ghana was based on the guidelines developed by AVAREF and focused on: 1) Trial Site: recruitment/screening areas, vaccine preparation room, vaccination room/Life Support Systems (LSS) room; 2) Research Centre: laboratories, investigational products storage facilities, data management; 3) Documentation review: investigators file/training records, delegation/responsibility logs, screening, randomisation &
vaccination logs, SOPs, drug accountability, mock shipment records (if applicable); 4) Data management & storage: electronic Case Record Forms (eCRFs) (source doc) randomly selected: entry, retrieval, corrections; 5) Quality assurance: GCP training records, local safety monitors report, sponsor’s monitors report (Quintiles).

Deficiencies identified during this inspection have contributed to some achievements, including:
i) sensitization of investigators and study teams to the principles of GCP, ii) notification now required at start of a trial or cohort, iii) quarterly reports to be submitted, timely and direct submission of all SAEs, iv) NRA now has database for compilation of SAEs, v) one trial report rejected as outcome of above, vi) guidelines for conducting clinical trials have been reviewed.

**Malawi.** Aaron Glyn Sosola, Pharmacy, Medicines & Poisons Boards.

The on-site inspection focused on the following: informed consent process, consulting area, procedure rooms, investigational product storage area, clinical laboratory, waste disposal, documentation.

The results of this inspection were presented.

About 100 SAEs have been found. They included fever, pneumonia, and diarrhoea. Also, five deaths have been found.

**Burkina Faso.** Rasmane Semde, Directeur de la réglementation pharmaceutique, 03 BP 7009 Ouagadougou, Burkina Faso.

Burkina Faso did not carry out an inspection of the clinical trial, nor even delivered official approval for the clinical trial because the country had no relevant regulatory framework. The country has just adopted a decree regulating the clinical trials and two complementary legislative texts fixing the conditions for granting authorizations and the operation of the regulation structures are in phase of adoption.

**Tanzania.** Adam Fimbo, Pharmacist, Tanzania Food and Drugs Administration, P.O. Box 77150, Dar Es Salaam, Tanzania.
The feedback of Tanzania concerning the Inspection of RTS’S trial can be summarized as follows:

- The trial has been approved by TFDA on 15 April 2009.
- Approved by the National Ethics Committee on 29 May 2006.
- Inspection conducted from 25 to 26 August 2010. One site was inspected (Korogwe site) + nine vaccination sites. Inspection used the clinical trials inspection manual and checklist.
- Standards used for inspection: Good Clinical Practice (GCP), ICH guidelines, approved study protocol including amendments, site and study specific Standard Operating Procedures (SOPs) and TFDA requirements.
- Facilities - Areas inspected – paediatric ward at Magunga hospital, Pharmacy for storage of medicines, data management unit, archive, clinical laboratory and administration unit.
- Organization and management - staff employed for the study (total 102).
- Review of patient’s data and informed consent issues.
- Assessment of efficacy and safety data:
  - Recording of efficacy and safety data in the CRF and checking whether they are in agreement with the source data obtained during the trial. Data related to endpoints was compared with source documents.
  - Adverse events date recording in the CRF.
- Monitoring and auditing.
- Scope.
- Monitoring plan and whether this is followed.
- Monitoring visits log to include dates of the visits.
- Clinical laboratory.
- Accreditation of the laboratory.
- Space to avoid mix-ups.
- Environmental conditions.
- Security and safety measures e.g. fire extinguishers.
- Equipment status and apparatus used equipment operation, maintenance and calibration.
- Approved test methods and procedures.
- Quality assurance systems and proficiency.
- Materials and reagents storage and management.
- Data generated by automatic systems, i.e. graphs and computer printouts.
- Samples collection and management records.
- Transcription of raw data into the source documents and other records.
- The integrity of data reported was quality assured.
- Multisite so they are planning to inspect another site (Bagamoyo).
- The report has been compiled, some major and minor non-conformances were observed and the report will be tabled before the Clinical Trials Technical Committee for decision.
- Sponsor and Investigators will be required to submit a corrective action report one month after receiving the report.

**Gabon.** Dr. Bipolo Sophie, Direction du Médicament et de la Pharmacie (DMP), Ministère de la santé, des affaires sociales, de la solidarité et de la famille BP 7138 Libreville Gabon.

The trial site in Gabon is located within the Unité Médicale de Recherche de Lambaréné (URML), located at the Schweitzer Hospital. The ethics committee approval was given in 2008. Thereafter, the protocol was submitted to the Ministry for Health.

A site inspection has not been carried out. However, at the beginning of the trial a preliminary visit was made to the URML by the ethics committee, accompanied by the NRA (Direction du Médicament et de la Pharmacie). It related to the laboratory, the sampling room, the unit for vaccine conservation, the personnel and the documentation.
The ethics committee considers, in collaboration with the DMP, to make a visit of follow-up during the first quarter 2011.

3.5. Recommendations of the joint technical group of experts on malaria vaccines (Vasee Moorthy, WHO/HQ/IVR)

This presentation provides information to participants on WHO technical guidances, the establishment of the Joint Technical Expert Group (JTEG), some of its recommendations, and finally some challenges for developing a malaria vaccine policy.

These technical guidances include publication of a literature review on methods of preventive interventions against malaria, and a report of a WHO consultation on the measurement of malaria vaccine efficacy in phase 3 trials.

The JTEG on malaria vaccines was established in April 2009 jointly by WHO Global Malaria Programme, Initiative for Vaccine Research (IVR), and with WHO AFRO involvement.

A first JTEG meeting allowed to make recommendations based on phase 3 interim data, concerning malaria transmission intensity, malaria control measures, strain selection effects.

Data from the complete phase 3 trial will most likely be required for WHO to consider policy recommendation, likely around 2015. In addition, JTEG recommends that participants in the phase 3 trial should be followed up for at least five years per child at the same frequency and intensity, as during the initial trial period.

Finally, the development of malaria vaccination policy raises some questions and many challenges, including:

- What is the incremental benefit of adding malaria vaccine to ACTs, bednet, spraying programmes?
- How to integrate with combination vaccines including Hep B vaccines and impact on neonatal Hep B immunization?
- Recent reduction in disease burden,
- Vaccine introduction in developing countries often supported by Phase 3 and post-marketing effectiveness trials in high income countries,
- WHO guidance recommended by JTEG for Phase 4 trial designs.

The table below gives an indicative timetable for data availability and policy timings.
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4. Safety during vaccine clinical trials

4.1. Independent Data Monitoring Committee (IDMC): mission and functioning (Dr Zulfiqarali Premji, MD, MSc, DTM & H, PhD, School of Public Health and Social Sciences, Dar-Es-Salaam, Tanzania)

This presentation focused on the establishment, mission and functioning of an IDMC for the Malaria RTS,S paediatric vaccine program.

The IDMC has identified six individuals, including the chair, respectively from Malawi, Tanzania, Ghana, United Kingdom, Canada and the United States, with expertise in malariology, paediatrics, clinical trials, and statistics & epidemiology. These members were selected by a joint decision of the sponsor, MVI, and the IDMC chair.

IDMC aims to protect the ethical and safety interests of participants recruited into the RTS,S candidate malaria vaccine programme studies, while protecting as far as possible the scientific validity and public health relevance of the data.

By networking with local safety monitors at each study site, IDMC reviews and provides advice on the following: IDMC Charter, IDMC operating procedures, protocols/ICFs and amendments, clinical development plan, study data during the trial.

Review of serious adverse events (SAEs) is done on an individual basis or tabulated. Review of SAEs is done within 24 h in the following situations: if they are related to vaccination, occurring within 7 days post vaccination, or in case of death. Additionally, IDMC provides interim reviews of unblinded data (reactogenicity, safety, immunogenicity, efficacy).

Based on the data analyzed, IDMC may advise whether the trial should be continued, changed or discontinued.
4.2. Regulatory requirements on safety during clinical trials in the European Union (Dr Pieter Neels, Federal Agency for Medicines and Health Products, CHMP member, Vice-Chair Vaccine working party, Belgium)

The relevant legislation governing clinical trials, including their safety, were presented. This legal framework in European Union includes the following:


- Directive 2005/28/EC of 8 April 2005 laying down principles and detailed guidelines for good clinical practice as regards investigational medicinal products for human use, as well as the requirements for authorization of the manufacturing or importation of such products.

Eudralex - Volume 10 of the publications “The rules governing medicinal products in the European Union” contains guidance documents applying to clinical trials. It includes the following chapters: Applications for a clinical trial, Monitoring and pharmacovigilance, Quality of the Investigational Medicinal Product, Inspections, Additional information, and Legislation.

Further guidance on safety reporting can be found in a EU harmonised document entitled: “Detailed guidance on the collection, verification and presentation of adverse reaction reports arising from clinical trials on medicinal products for human use”.

The other important issues that affect safety include pharmacovigilance, and benefit-risk evaluation during clinical development.
With regard to pharmacovigilance, Suspected Unexpected Serious Adverse Reactions (SUSARs) need to be reported electronically. For example, in a clinical trial in Belgium, Sponsors should report SUSARs within seven days in case of lethal or life threatening SUSARS, and within 15 days in the other cases. An annual safety report must be submitted by the sponsor, taking into account all newly available safety information received during the reporting period.

Examples of benefit-risk considerations can include:

- Is the disease burden fully documented?
- Is extrapolation from other parts of the world feasible and acceptable?
- Is the disease comparable (Attack rate, infectivity, seriousness)?

4.3. **Regulatory requirements on safety monitoring during clinical trials (Rosemary Tiernan, MD, MPH, Center for Biologics Evaluation and Research, Food and Drug Administration, USA)**

This presentation primarily addressed the regulatory framework that supports safety monitoring and adverse event reporting for clinical trials conducted under US IND.

According to 21 CFR 312.22, FDA's primary objectives in reviewing an IND are, in all phases of the investigation, to assure the safety and rights of subjects, and, in phase 2 and 3, to help assure that the quality of the scientific evaluation of drugs is adequate to permit an evaluation of the drug's effectiveness and safety.

The responsibilities for the Independent Ethics Committees/Institutional Review Board, the Sponsor and the Investigators were described.

Concerning the sponsor, some of these responsibilities include monitoring and ensuring that the study is conducted in accordance with the protocol, and informing the FDA and the participating investigators of any adverse events or risks with respect to the drug. FDA has produced guidance documents for monitoring which outline acceptable standards but are not legal requirements. Guidance advises sponsors to develop their own standard operating procedures (SOPs) for monitoring. These should be written in sufficient detail to cover general aspects of clinical investigations.
According to 21 CFR 312.32, the sponsor shall notify FDA and all participating investigators in a written IND safety report of any adverse experience associated with the use of the drug that is both serious and unexpected. Each notification shall be made as soon as possible and in no event later than 15 calendar days after the sponsor's initial receipt of the information. The sponsor shall also notify FDA by telephone or by facsimile transmission of any unexpected fatal or life-threatening experience associated with the use of the drug as soon as possible but in no event later than seven calendar days. According to 21 CFR 312.33, a sponsor shall submit an annual report of the progress of the investigation that includes a list of subjects who died during participation in the investigation, with the cause of death for each subject, and a list of subjects who dropped out during the course of the investigation in association with any adverse experience, whether or not thought to be drug related.

The Institutional Review Board (IRB) means any board, committee, or other group formally designated by an institution to review, to approve the initiation of, and to conduct periodic review of, biomedical research involving human subjects. The primary purpose of such review is to assure the protection of the rights and welfare of the human subjects. This role of protecting human subjects is detailed in the regulations (21 CFR 56 & 50).

Investigator’s responsibilities will include ensuring that an investigation is conducted according to the investigational plan, protecting the rights, safety, and welfare of subjects; and control of drugs under investigation. In addition, specific responsibilities of clinical investigators include the following items: control of investigational drug [21 CFR 312.61], recordkeeping and retention [312.62], investigator reports [312.64], assurance of IRB review [312.66], handling of controlled substances [312.69].

The regulations at 21 CFR 312.70 provide procedures for the disqualification of clinical investigators, if the FDA has information that the investigator (including a sponsor-investigator) has repeatedly or deliberately failed to comply with the requirements of part 312, part 50 or part 56, or has submitted false information.

In conclusion, public expectations for vaccine safety are high, particularly for paediatric vaccines. In addition, large pre-licensure controlled safety databases for vaccines are desired. However, there is much progress in developing international standards for case definitions, safety data collection and reporting that applies to vaccine development.
5. Conjugate meningitis A vaccine

5.1. The control of epidemic meningitis in the African region
(presented by Prof. Bartholomew D. Akanmori, WHO/AFRO)

This presentation reviewed the status of and the strategies for the control of the epidemics of meningitis in the African region, including the current challenges with the implementation of these strategies.

Meningitis epidemics in the African meningitis belt constitute an enormous public health burden, and efforts are being made to control epidemics. Bacterial meningitis is most commonly caused by one of three types of bacteria: Haemophilus influenzae type b (Hib), Neisseria meningitidis, and Streptococcus pneumoniae. N. meningitidis is the one with the potential to cause large epidemics. Twelve serogroups of N. meningitidis have been identified, based on differences in the capsular polysaccharides and immunological reactivity. African epidemics of cerebrospinal meningitis are caused predominantly by sero-groups A, C and W135.

Meningococcal meningitis is characterized by a short incubation period (two to 10 days), followed by sudden onset of symptoms: high fever, stiff neck, intense headache, altered consciousness, vomiting, and photophobia. Infants may have illness without sudden onset and stiff neck.

The traditional endemic areas of the world (the meningitis belt) include the savannah areas of sub-Saharan Africa, from Gambia and Senegal in the west to Ethiopia and western Eritrea in the east, with an estimated total population of 500 million.

The estimated number of cases in the meningitis belt in the last 10 years is approximately 700 000, with roughly 10 to 50% fatality rate.

Generally, 10-20% of patients who survive meningitis may develop neurologic disabilities or other sequels such as deafness, visual sequelae.

WHO promotes a two-pronged strategy comprising epidemic preparedness and epidemic response. Preparedness focuses on surveillance, from case detection and investigation and
laboratory confirmation. This implies strengthening surveillance and laboratory capacity for early detection of epidemics. Some examples of specific activities include: adaptation and use of SOPs by peripheral health workers, acquire and preposition drugs, vaccines, lab reagents & equipments at district and sub-district levels, strengthening supervision by national level to support epidemic districts, training health and lab personnel at district level, training in data management and mapping (Excel, Epi Info, and Health Mapper).

Epidemic response consists of prompt and appropriate case management with oily chloramphenicol or ceftriaxone and reactive mass vaccination of epidemic districts. It is estimated that a mass immunization campaign, covering 85-90% of the 2-29 years, can avoid 70% of cases.

In addition, the availability and affordability of conjugate vaccines are essential to eliminating meningococcal disease as a public health problem and ensuring routine health services are able to control sporadic cases in the shortest possible time.

Year 2009 was characterized by great epidemics in Nigeria and in Niger whose main responsible germ was N. meningitidis A. These two countries notified 85% of the suspect cases and 66% of the deaths reported in the African area. During this year, there was an insufficiency in national stocks of vaccines and a delay with the funds raise and the acquisition of the vaccines through the International Coordinating Group (ICG) on vaccine provision, with for consequence a late response and a propagation of epidemics. Vigilance from countries is recommended for the year 2010 in spite of a calm epidemiologic situation in some countries at risk of meningitis epidemic such as Burkina Faso, Ethiopia, Mali and Sudan.

Two categories of meningococcal vaccine are currently available – polysaccharide vaccines and protein-polysaccharide conjugate vaccines (referred to as conjugate vaccines).

Today, the stock of polysaccharidic vaccines with manufacturers is insufficient. It is estimated that the request could reach 40 million doses while production is limited to a maximum of 21 million doses of AC and 1-2 million doses of ACWY.

WHO is working with vaccine manufacturers to avoid disruption of supply in the transition to conjugate vaccine.
With regard to the combined vaccines, MVP project made it possible to develop a vaccine, which was prequalified by WHO in June 2010. Some of the benefits of this vaccine are: immunogenicity (X20 more increase in antibodies compared to existing PS-ACWY vaccine), longer immunity (> 3 years), herd immunity, use in under 2 years olds, inclusion in routine EPI, impact on carriage status, cost negotiated at $ 0.40.

Many investments are carried out for the introduction of this vaccine, including funds raise from GAVI ($370.2 million, and $84.5 million approved), DELL and IDA for a total of $18.5 million. Moreover, a support is granted to Burkina-Faso, Mali and Niger for the planning, the implementation, and the following-up/evaluation of mass vaccination.

Current challenges in the control of seasonal epidemics of meningococcal disease include the following:

- Several districts/countries in the meningitis belt affected at around the same time.
- Health systems over-stretched by large case-loads.
- Relative shortage of vaccines for large scale response in case of epidemic.
- Health system and infrastructure needs (funds, diagnostic facilities and expertise etc.).
- Cost of providing care.
- Long term care of post-meningitis sequelae.
- Conducting very large scale mass campaigns and ensuring high quality.
- Mobilising resources for the introduction process in all countries of the meningitis belt.
- New vaccine (monitoring of AEFI, impact assessment).

5.2. Rollout of meningitis A conjugate vaccine in West Africa
(Richard Mihigo, WHO/AFRO. Presented by Prof. Bartholomew D. Akanmori, WHO/AFRO)

After a short historical background about the MVP project, including the clinical development program, the plan of introduction of Men A conjugate vaccine (MenAfrivac) was presented. This one is summarized as follows:

- Progressive introduction in the 3 hyperendemic countries (Burkina Faso, Mali, Niger) in West Africa in 2010-11:
  - Accelerated procedures for licensure of the new vaccine by National
Regulatory Authorities done in all three countries. WHO recommends that countries receiving vaccines through the UN system comply with two regulatory functions: licensing of the product and post-marketing surveillance (particularly for AEFI). The licensing function can be met in different ways: countries give an automatic approval of prequalified vaccines, countries apply the expedited procedure for review of imported prequalified vaccines recommended by WHO, registration facilitated by collaboration with WHO through review of prequalification reports, lot summary protocols and samples upon agreement by the manufacturer.

- Meeting resources requirements ($US 11 million funding gap).
- Rollout in the remaining countries of the belt (2011-15).
  - No funding commitment yet from GAVI to secure $US 285 million.
  - Co-funding from countries and partners also to be secured ($US 190 million).
- Meningitis epidemics elimination requires implementation of a comprehensive strategy:
  - Preventive vaccination with MenAfriVac™.
  - Epidemic response with existing polysaccharide vaccines.
  - Strengthening of surveillance system and impact assessment.

The initial mass vaccination was carried out as envisaged in Mali, in Burkina and in Niger, respectively as follows:

- In Mali, it was launched on 13 September 2010 in two medical districts (Dioïla and Fana) and made it possible to reach at the day 8 a cover rate of 98% in Dioïla and 97% in Fana. This vaccination campaign recorded one severe case of Adverse Events Following Immunization (AEFI) and six minor cases of AEFI. A good system of post-marketing monitoring was set up to supervise the campaign up to 48 H post-vaccination.

- In Burkina Faso, the vaccination campaign was launched on 13 September 2010 in the district of Kaya. A system of post-marketing monitoring was set up. No AEFI was reported.

- In Niger, the vaccination campaign was launched on 21 September 2010 in the district of Filingué. No AEFI was reported.
5.3. Country experiences on registration of conjugate meningitis A vaccine (Rasmané Semdé, Director of drug regulatory, Burkina Faso, and Godefroy Coulibaly, National ethics committee, Mali)

For the evaluation of the conjugate meningitis A vaccine for licensure submitted in August 2010, Burkina Faso did not make a thorough study of the full dossier because the product had been the subject of a prequalification by WHO in June 2010. A simplified procedure was implemented. This included the review of the prequalification during a meeting held in Geneva with the participation of two people from the DGPML (NRA of Burkina Faso), as well as a review about the implementation of the observations formulated by the three countries participating in the above-quoted meeting (Burkina-Faso, Mali and Niger). These observations related, among others, to labeling, the instructions for use, and the insertion of thermal indicator on each bottle.

Considering this procedure, Burkina-Faso gave an approval at the 7 September 2010 meeting of the technical commission in charge of licensing drugs. Consequently, a project of licensing Decree was submitted for the signature of the Minister of Health. While waiting for the signature of this decision, a special license for introduction was given to allow the introduction of 400 000 doses necessary for carrying out the first vaccination in September 2010.

The NRA of Mali was absent at this meeting. However, the information provided by the representative of the national ethics committee reported a procedure similar to that Burkina Faso. The country took part in the meeting in Geneva based on its decision about the introduction of the vaccine after the prequalification by WHO.
6. Formalization of AVAREF

6.1. Formalization of AVAREF (presented by Modou Fall, The Gambia)

It was a summary presentation of an exhaustive document about the terms of reference (TOR) on the formalization of AVAREF, which was distributed to the participants. These TOR were elaborated by a task team made up of the following members:


The structure of the document was presented as follows:

- Introduction
  - Preamble and Rationale
  - Objectives of Formalization
  - Expected Outcomes
  - Vision and Mission

- Principles
- Confidentiality

- Principal activities (Areas of collaboration)

- Membership and structure

- Roles and responsibilities of key participants

During the discussion some questions were raised including the following:

- Clarification of the roles of partners and experts and their relationship to the structures.
- Accountability of the whole members.

- Need for specification of who the focal point is.

- Questions on the capacity for the obligatory financial contribution of the countries.

- Collaboration with the existing organizations.

- Maintaining VS change of the name “AVAREF”.

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An important clarification has been provided. It indicated that the document should not be confused with a mere description of task, which would give more detail on the tasks of the various members and the relationships which exist between them.

The participants transmitted in writing their observations on the document to Dr Kwasi Nyarko. This latter will take into account these comments in the revised version. Moreover, a French version will be produced (see the recommendations for the people in charge of the translation) and circulated for review by the NRAs and ECs.

6.2. Resource mobilization initiative: database of experts
(Professor Bartholomew D. Akanmori, WHO/AFRO)

Capacity building in both regulatory and ethical oversight for vaccine (and complex drug development) is a primary driver for the establishment of AVAREF. In addition, AVAREF members have in the past, and continue to express interest in ability to have access particularly to scientific and/or clinical expertise required for evaluation of submissions such as clinical trial applications.

There are growing number of resources and/or expertise within the AVAREF member countries and elsewhere interested in contributing to capacity building within the AVAREF community. Resources include reviewers within each NRA and EC, Experts from universities, hospitals, and consultants within each member country, Experts within competent and functional NRAs elsewhere such as Health Canada, FDA, EMA, etc.

Moreover, the use of information technology coupled with the benefits of the platform provided by the formalization of AVAREF will facilitate the creation of a Resource Mobilization Initiative (referred to in the past as Database of Experts): Increased access to information technology including web-based databases, creation of virtual communities or blogs; Formalization of AVAREF enables member countries to pool resources to facilitate achievement of work targets. Databases (or pools) of qualified experts exist elsewhere that could be utilized to achieve the objectives.

To accomplish this resource mobilization initiative the following implementation plan was suggested:

- Seek approval of AVAREF Members.
- Convene task team meetings in Q1 2011.
- Complete inventories and identify gaps.
- Seek support of WHO/QSS and other regulators (Health Canada, US-FDA, EMA, TGA).
- Establish functional database before AVAREF 6.

More specifically the following activities should be conducted:
- Compilation (and pooling) of expertise within each NRA and EC within Africa:
  - Survey of NRAs and ECs to incorporate existing resources into the database.
  - Develop a strategy to recruit other experts from functional and competent NRAs.
- Reporting of Pool of Experts available to AVAREF members.
  - Development of Reporting Templates and systems to continuously update the database.
  - Developing tools such as qualification tools, confidentiality forms, etc.

A task team has been established: Tanzania, Ethiopia, Ghana, Nigeria, Uganda, Cameroon, Gabon, and Senegal. The terms of reference of this task team, among others, will include: identification of the key expertise which countries lack, summary of the profiles of experts required by countries, development of a database of experts. Finally, this initiative will contribute to the achievement of AVAREF mandate. It is also consistent with the formalisation initiative.
7. Legislation of clinical trials

7.1. Development of a course on legal framework for regulation of clinical trials in Africa (Aaron Glyn Sosola - Pharmacy, Medicines, and Poisons Board, Malawi)

The presentation had the aim of presenting the approach resulting from the meeting on the development of a course on legal framework for regulation of clinical trials in Africa. This meeting was held in Geneva from 19 to 20 July 2010.

During the assessment by WHO in 2005, the forum recommended for the development of a course on legal framework for the regulation of Clinical Trials in Africa.

Task Force members (Umit Hamdi Kartoglu - WHO, Liliana Chocarro - WHO, Aaron Sosola - NRA Malawi, Bobby Chauhan - Health Canada, Catherine Parker - Health Canada) agreed with the following proposals:

- Pre-implementation stage:
  - Explain the differences of critical elements of a legal framework for regulatory oversight (law, regulation, decrees, resolutions, guidelines, etc.).
  - Identifying roles and responsibilities of key governmental stakeholders required to enable and implement legal framework.
  - Analysis of legal frameworks (formulation of key questions, gap analysis, which methods to be used, how to look into framework from multiple perspectives - define if the scope and depths and level of detail is appropriate for the given element in the legal framework).
  - Formulate key responses, instructions and questions to legal advisers to address the identified gaps.
  - Develop a compelling argument for change.
  - Identify key stakeholders that should be informed/consulted of the formulated/revised legal framework.
  - Develop communication strategy aligned with existing resources.

- Post-implementation stage:
  - Design and implement a plan to evaluate whether initial objectives have been met.
- Develop a compliance and enforcement strategy to be included in the regulatory framework.

The target audiences concerned with this course will include the people working within the NRAs, people in charge of policy development, reviewers, and GCP inspectors, and all the people in charge of regulatory oversight of clinical trials.

During the phase of discussion it was agreed that countries would receive a notification and a questionnaire of evaluation from WHO.

The initiative was welcomed by the participants. It was also underlined that there is the need for the people who will be trained to invest themselves fully so that the training contributes to improvement of the system. Moreover, this concern should be taken into account in the elaboration of the course and possibly in the selection criteria of the candidates.

7.2. Country updates on legal framework changes

Malawi: Aaron Glyn Sosola - Pharmacy, Medicines, and Poisons Board (PM&PB), Malawi.

According to Dr Sosola, in 2006, he was informed that a clinical trial denied in South Africa was accepted thereafter in Malawi. That saddened him and consequently he committed himself to changing the legal framework in Malawi.

With the enforcement of WHO in 2006 that all NRAs should evaluate, authorize, register and monitor clinical trials, in accordance with ICH E6 (R1) on ‘Registration of clinical trials’, PM&PB of Malawi started preparing documents and guidelines on clinical trials in accordance with Good Clinical Practices (GCP).

From 2006, WHO has been sending PM&PB staff to various GCP, monitoring and authorization courses in order to equip them with the necessary technical skills. Other stakeholders such as EDCTP and Kendle SA have also assisted with courses in this area. However, up to September 2008, clinical trials involving medicinal products have always been approved by ethical committees only.

Meanwhile, a draft of regulatory directives was developed by adaptation of WHO and ICH clinical trials directives. The project was submitted for review by WHO, US-FDA, and the EMA. In 2008, an amended Act to accommodate clinical trials was approved by PM&PB. Final
Regulatory guidelines were also approved, in September 2008, by the PM&PB Board of Directors, which is a legal entity of the drug regulatory authority. The legislation for clinical trials was passed by Parliament in 2008 on Section 42-44 of Pharmacy Act.

Furthermore, Malawi has developed forms, guidelines and other documents to improve oversight of clinical trials, including:

- Application form for authorization to conduct a clinical trial.
- Guidelines for review/evaluation of clinical trial applications for medicines, vaccines and biologicals.
- Procedures for review/evaluation of clinical trial applications for medicines, vaccines and biologicals in Malawi.
- GCP inspection checklist.
- Pharmacy guidelines for investigational drugs.
- Indemnity form for conducting clinical trials.
- Serious adverse events (SAEs) reporting manual.
- Serious adverse event form.
- Directive for importation and release of investigational medicinal products.
- Regulatory requirements on storage and export of samples/specimens collected from participants/clinical trial subjects during clinical trials for testing.
- Material Transfer Agreement (MTA) Form.

Moreover, in June 2010, PM&PB organized in-country training course on clinical trial authorization with assistance of WHO-Geneva to train the committee on how to evaluate a protocol. WHO sent 4 experts to facilitate this training.

**Burkina Faso**

The country adopted in May 2010 a decree regulating clinical trials. Also, two complementary legislative texts respectively fixing the conditions for granting authorizations and the operation of the structures of regulation are in the phase of adoption.
At the institutional level, one considers the creation of a service within the NRA in charge of clinical trials.

**Senegal**

The adoption of the Law of 9 March 2009 provided a significant improvement. This law made it possible to adopt the decree N°2009-729 of 3 August 2009 dealing with the creation, the organization and the operation of the Comité National d’Éthique pour la Recherche en Santé (CNERS) [National Ethics Committee for Research in Health]. Currently, the roles are sufficiently clarified. The NRA - Direction de la Pharmacie et des Laboratoires (DPL) initiates inspections. The CNERS has a program for following-up trials, and a specific commission is in charge of this. However, the DPL does not have yet revised a good part of its texts to take into account the evaluations related to clinical trials. It is also envisaged to revise application fees. Currently, these are estimated at approximately US$350 by protocol coming from an institution, at US$200 for independent ones. The protocols initiated by the researchers are reviewed for free.

**Ethiopia**

- The following standard operating procedure (SOP) in relation to vaccine and clinical trial has been prepared and adapted: SOP for how to prepare for and conduct GCP inspection; SOP for how to write GCP inspection report. As a result of these SOPs one trial (on July 2010) GCP inspection was performed and report of the inspection was sent to the principal investigator.
- Draft requirements for the registration of vaccines were prepared.
- Ethics committee (composed of 13 members and one of them is representative of the national regulatory authority) was re-established in a new form. Ethics committee is organized under the ministry of Science and Technology and it is one of the mandates of the ministry of Science and Technology.
- As a result of November 2009 meeting in Mombasa, institutional development plan was prepared and sent to WHO (Mr Lahouari Belgharbi) according to the instruction of the organizer but not responded yet.
- Bioequivalence data assessment training was provided for 13 staffs of the product registration and licensing directorate, where clinical trial and vaccine assessment and authorization is organized, and invited experts by the national regulatory authority in collaboration with USP QM and WHO.

- Legal changes: on the previous proclamation it was not possible to conduct clinical trials on children and pregnant woman. However based on the new regulation approved last year (2009) it is possible to perform clinical trials on these subjects provided that if the trial is not possible to be performed on adults (more than 18 years) individuals.
8. PACTA project

Registry component

8.1. An introduction to the International Clinical Trials Registry Platform (ICTRP) and what it can tell us about clinical trials recruiting in Africa (Christopher Jones, ICTRP, WHO)

The purpose of this presentation was to outline the importance of clinical trial registration, what the ICTRP can tell us about clinical trials recruiting in Africa, and how clinical trial registration is an integral part of ethical and regulatory oversight.

Since 2005, as a pre-condition of consideration for publication, the International Committee of Medical Journal Editors (ICMJE) has required interventional patient-controlled clinical trials to be registered in a public trial registry before the onset of patient enrolment.

The problem with this though is that it only covers research that is specifically intended for publication. So in 2008, the World Medical Association revised the Declaration of Helsinki making prospective registration a requirement “Every clinical trial must be registered in a publicly accessible database before recruitment of the first subject”.

The ICTRP was established in 2006 in response to demand from countries through the World Health Assembly for “a voluntary platform to link clinical trials registers in order to ensure a single point of access and the unambiguous identification of trials with a view to enhancing access to information by patients, families, patient groups and others” WHA 2005. It is “a global initiative that aims to make information about all clinical trials involving human beings publicly available”. WHO's policy is that the registration of all interventional trials is a scientific, ethical and moral responsibility.

The ICTRP is not an international authority, but a country-led initiative.

The ICTRP works with a growing number of registries around the world. Each registry transmits to the WHO central repository the minimum data set of all records they have registered. This information is then made available to everyone on the ICTRP clinical trials search portal website.
The ICTRP is currently engaged with 12 registries, and in discussions with a number of others. One of these registries is the Pan African Clinical Trials Registry.

ICTRP may be accessed at: www.who.int/ictrp in English, French, and the other four official WHO languages.

The ICTRP allows us to make the following observations:

- In the Americas, with just 8% of the world's population, we find that 41% of publically registered trials are recruiting there.

- In Africa, with 11% of the population, we find only 1% of the registered trials. This finding can be interpreted as follows: either trials are not being conducted in Africa, or trials are being conducted but are not being registered or trials are being registered but incompletely or inaccurately.

- Starting from mid-2005 with the implementation of ICMJE's requirement for prospective registration and WHO resolution, we see a sharp rise in the number of registered trials in the region outside South Africa. However, this then decreases in the following years.

- It is also found elsewhere in the world increased registration rates following the introduction of a legal requirement.

8.2. PACTA project - Registry component: pilot implementation experience in Tanzania (Adam Fimbo, Tanzania Food and Drugs Authority)

At the 4th AVAREF meeting in Abuja in September 2009, Tanzania as well as Uganda, Senegal, Nigeria, Burkina Faso and Gabon offered themselves as pilot countries in order to experiment with the introduction of a set of data, which will be used as a basis for the national registers of clinical trials. In the same way, all AVAREF country members agreed to include registration in PACTR or when justified another register or data provider as a requirement for the submission of CTAs for review by the NRA or EC.

Consultation through emails amongst AVAREF pilot countries began immediately after AVAREF 4. The 20 minimum data elements of the WHO ICTRP were discussed and agreed
upon with the addition of 4 more elements. The added elements were (i) sites of recruitment, (ii) ethical and regulatory approvals, (iii) regulatory inspection status (for positive outcomes), and (iv) any safety alerts/concerns issued.

Tanzania's experience can be summarized as follows:

1) Gaining experience from other Registry Platforms:
   - Contacted the WHO ICTRP for advice and possible support. Specifically asked for models that can be adopted/adapted.
   - WHO connected TFDA with the National Patient Safety Agency (NPSA) of the UK. This allowed TFDA to access their system, the Integrated Research Application System (IRAS). IRAS is a single online system for applying for permissions and approvals for health and social care/community research in the UK. IRAS can be accessed at www.myresearchproject.org.uk. Now, TFDA is in regular contact with NPSA on how to customize and install the system.
   - The WHO also connected TFDA with BIREME (Latin American & Caribbean Center on Health Sciences Information). Consultations are still ongoing to learn the functions of their register (LATINREC register).
   - TFDA also reviewed the requirements of the ICMJE as the WHO requires potential registrants to register their trials in either a Primary Registry in the WHO Registry Network or an ICMJE approved registry (http://www.icmje.org/)


3) Drafting Regulations: The Tanzania Food, Drugs and Cosmetics (Clinical Trials Control) Regulations, 2009 have defined the National Registry as a database created by the
Authority that houses and manages information about a clinical trial submitted by an applicant. The Regulations require applicants to register their trials in the National Registry (Regulation 6). The clinical trial information required to be provided in the National Registry include descriptive information (Regulation 7(2) (a)) recruitment information (Regulation 7(2) (b)), Location and contact information (Regulation 7(2) (c)), Administrative data (Regulation 7(2) (d)). An applicant is required to upload data in the National Registry not later than 21 days after the first patient is enrolled in a clinical trial (Regulation 7(6)). The Authority will ensure that clinical trial data is posted in the National Registry not later than 30 days after submission (Regulation 7(7)).

4) Creating a National Registry: The TFDA has approved a budget for creation of the National Registry. This has considered all the databases and/or other Registries accessed. A link will be established within the TFDA website (www.tfda.or.tz). It has been partially completed and is currently being tested internally to see how it works.

5) Agreeing on future steps: pre-testing the Registry; sensitizing stakeholders – MoHSW, National Ethics Committee (NEC), sponsors, investigators, and the general public; piloting with other AVAREF countries; conducting training on its use; getting more experience from other countries on how to operate and manage the Registry including regular updating and monitoring; deciding on who should be the custodian of the Registry; official launching of the Registry.

8.3. Pan African Clinical Trials Registry (Amber Abrams, South African Cochrane Centre, presented by Professor Bartholomew D. Akanmori, WHO/AFRO).

The presentation introduced the Pan African Clinical Trial Registry and the importance of clinical trial registration in general. The presenter discussed how www.pact.org is contributing to capacity building amongst the health research community, providers of healthcare, and healthcare consumers and he gave some updated data on the registry.

The PACT registry is led by the South African Cochrane Centre (SACC) based at the South African Medical Research Council (MRC) and the Cochrane Infectious Disease Group, based at the Liverpool School of Tropical Medicine, and was developed by a three-year funding grant.
from the European and Developing Countries Clinical Trials Partnership (EDCTP). It works in partnership with the Cochrane HIV/AIDS review group.

Registering clinical trials is necessary for ethical, scientific and economic reasons, including the following: reduction in publication bias, fulfilling researchers’ ethical obligation to research participants, ensuring transparency and enhancing public trust in the conduct of clinical research, increasing participant enrolment in research trials, reducing duplication of research and better utilization of limited resources.

The WHO ICTRP is not a clinical trials registry but a platform that collects data from partner registries. This platform’s goals have guided the development of www.pactr.org into the first primary registry on the African continent. The PACTR provides the ICTRP with data monthly.

As a member of the WHO Network of Primary Registries, www.pactr.org gives researchers in Africa the opportunity to register their clinical trials with the registry of choice for the African region. PACTR seeks to provide feasible ways of overcoming obstacles specific to African trialists. Since African trialists face additional challenges in trial registration, such as limited, unreliable and costly access to the internet, often African collaborators in multi-country clinical trials need to request their partners on other continents to register the trial for them. Thus, as a registry designed by Africans for Africans, trials may be registered online, by email, postal mail or facsimile. Registration is free, and information on registered trials is easy to search and free to access.

PACTR, as the only WHO-endorsed primary registry in Africa, is the only centralized information resource for clinical trials on the continent. A variety of stakeholders can use www.pactr.org to increase knowledge, awareness and information sharing.

For policy makers, regulators and ethics review boards www.pactr.org can:

1) Provide transparency of process: collects information on ethics approvals and trial progress, can assist with streamlining policy and ethics decisions, assists policy makers in protecting their constituents.

2) Reduce duplication of efforts and assist in reducing money and effort spent on reviewing proposed research.

3) Facilitate information translation between review boards and regional policy makers.
For healthcare professionals (like clinicians, nurses, etc.) and their patients www.pactr.org can:

1) Track information on interventions for use on patients.

2) Provide information on ongoing research, or completed, unpublished trials to fill gaps in information.

3) Assist in locating trials to suggest to patients to participate in.

4) Assist in locating alternative treatments, or additional information on suggested treatments.

Thus, the registry assists in information dissemination and knowledge translation on clinical trial work for access by consumers and their doctors.

PACTR can assist healthcare research funders and sponsors in:

1) Understanding/locating present trial activities to inform grant decisions.

2) Determining where research funding is needed to inform development of grant calls or setting research agendas.

3) Determining if proposals for research funding duplicates work already in progress.

4) Networking or research on other funding agencies.

PACTR can assist healthcare researchers in understanding and locating present trial activity, determining where research is needed, determining if planned research duplicates work already in progress, determining appropriate collaborators, and networking.

To date 67 applications have been made (36 with registry numbers, five incomplete and 26 not eligible). Sample sizes range from 10 participants to 15 000 with the median sample size of 360.

Perhaps the greatest achievement of www.pactr.org in the last year has been the growth of the registry. It has nearly tripled since the formal launch at the last AVAREF meeting. At the end of September 2009 it had 25 submitted applications and 11 registered trials, today there are 67 applications and 36 registered trials.
Ethics component

8.4. Collaboration between the ethics committees and the national regulatory authority – PACTA Project (Bocar Kouyaté, presented by Samba Corr Sarr)

This presentation related mainly to the communication of the results of a survey aiming at describing the ethical review, the registration and the regulation of clinical trials in 6 AVAREF countries, Burkina Faso, Ghana, Tanzania, Uganda, Nigeria and South Africa.

The goal of the initiative is to support the creation of a standard framework of the procedures, which associate the ethical review, the regulation, and the registration of clinical trials for AVAREF countries within the framework of the PACTA.

The methods used comprised the review of existing laws on research for health, clinical trials and the regulation on the registration of drugs, collaboration with other departments of WHO, consultation of national Web sites, the examination of existing documents (documents of AVAREF, report of NEBRA). A questionnaire was addressed to the countries concerned.

The principal results are summarized as follows:

- South Africa, Tanzania and Uganda have the most complete regulatory framework and procedures for ethical evaluations.
- South Africa is the only country having a Registry for registration of clinical trials (the SANCTR). Tanzania works to establish a Registry for clinical trials/database.
- No country has a specific information system making it possible to know what occurs when a protocol is rejected.
- Burkina Faso and Ghana have a system, which lies especially on the ethical review by institutional committees, with a follow-up at the national level.

The following suggestions could contribute to the reinforcement of the procedures:

- Recording and accreditation of the institutional ethics committee by a national committee or a body in charge of the follow-up of ethics in research.
Many countries installed a mechanism of approval. This could be useful for the Registry of clinical trials.

Registration to the PACTR could be added as a requirement to the approval of clinical trial protocols.

For the next stages, it is advisable to carry out this survey in the other AVAREF countries. Also, a task team should meet on the PACTA in Geneva on 9 November 2010.

**Registry component**

**8.5. Update on the African Common Clinical Trials Document**

*(Dr Jayesh M. Pandit, Pharmacy and Poisons Board, Kenya)*

Two key documents have been proposed for common use in the AVAREF countries: Common Clinical Trials Application, and Evaluator’s Clinical Trial Review Report.

These documents were distributed to all the members in order to collect their comments. After sending of an email on 29 September 2009 as well as other reminding messages, only three answers were obtained. It was finally suggested to adopt the documents in the form suggested.

Documents remain a generic tool for all countries, and every agency can put their own names and logos on the document. It is still possible to update the subsequent versions.

The other common technical documents developed are:

- Importation and release of clinical batches.
- Storage and export of specimens collected during clinical trials for testing.
- GCP inspection guidelines.

The two documents previously enumerated will be sent by Jayesh at a translation team made up of Gabon, Rwanda, Cameroun and Senegal. Two weeks will be granted to those to make the translation.
8.6. PACTA project - Strengthening of regulatory component
(Dr Nora Dellepiane and Dr Liliana Chocarro
WHO/IVB/QSS/VQR, presented by Dr Nora Dellepiane)

WHO has taken many initiatives to support regulatory authorities providing tools, expertise and funding so they develop the necessary structures to enable them to exercise their mandate with regards to regulatory oversight of clinical trials. These include the establishment of platforms (AVAREF); mentoring, advocacy, funding, promoting cooperation arrangements; promoting expression of needs, and facilitating access to required resources. Here, the presenter emphasized that countries are the main actors, and WHO is a catalyst and mentor.

More specifically, WHO has organized some activities that contribute to strengthening the regulation of clinical trials, including:

1) Participation in training courses:
   - Clinical Trial Authorization in Pretoria: two participants from Zimbabwe, three from Tanzania, two from Malawi, the Gambia, Uganda, Zambia, Cameroun, Botswana, Senegal, and South Africa.
   - GCP inspections:
     - 2009 Cape Town: Gambia x2, Malawi x2, Nigeria x2, Tanzania x3, Zimbabwe, Ghana, and Uganda.
     - 2009 Jakarta: Botswana, Malawi, Tanzania, Zambia, and Zimbabwe.
   - Evaluation of clinical data for registration of vaccines:
     - 2009 Bali: Tanzania, Nigeria x3, Zimbabwe, and Malawi.

2) WHO sponsored participation in relevant meetings
   - EMA GCP inspectors working group
     - 2008: Ghana, RSA
     - 2009: Ghana
     - 2010: Tanzania, Malawi, Kenya, and Nigeria.
- EMA reflection paper on clinical trials in third countries: Ghana, Tanzania, Malawi, South Africa.

- Participation in regulatory workshop organized by Health Canada: the Gambia, Tanzania, Nigeria, Malawi, and Ghana.

- WHO guidelines: consultations
  - Pneumo vaccine: Nigeria (2009)

3) In-country training

- Malawi July 2009: 13 members of the newly established Clinical Review Committee trained in CTA. Local cost, accommodation, transfers and materials covered by NRA Malawi.

- Current request from Botswana.

Other ways of supporting NRAs include:

- Advocacy and fundraising for AVAREF countries - CIDA, Health Canada, GAVI, others.

- Contributions in kind (expertise available for meetings and specific consultations) - EMA/European NRAs, Health Canada, USFDA/CBER.

In conclusion, WHO can provide funding for meetings, drafting groups, expert support, facilitate collaboration and discussion fora, provide training, but WHO cannot do for countries the internal advocacy for endorsement by the NRA, and the decision to adopt guidelines developed upon request from countries.

In some cases following suggestions of AVAREF countries courses were planned by WHO but no applications were received and the course had to be cancelled. It is important that countries, which request courses, also ensure that they nominate participants for the courses.
8.7. WHO approaches for regulatory support in medicines and vaccines area (Dr Samvel Azatyan, Manager, Medicines Regulatory Support Programme, WHO/QSS/ Essential Medicines and Pharmaceutical Policies)

Building regulatory capacity is a critical function of ensuring access to essential drugs. Weak regulatory frameworks and lack of enforcement can lead to various bottlenecks limiting access to essential medicines and vaccines.

WHO describes some approaches for regulatory support, including the following:

- Developing evidence - assessments of regulatory systems worldwide (53 National Medicines Regulatory Authorities (NMRAs) assessed in all six regions, 26 NMRAs in Africa);
- Providing direct technical support (capacity building, tools and guidance) to regions and countries (with IVB);
- Stimulating/initiating collaboration between regulators from various countries on various regulatory activities;
- Facilitating the establishment of “centres of excellence” for regulatory affairs;
- Promoting harmonization.

The communication was limited mainly to a presentation about the importance of the assessment task of the regulatory systems and the methods used.

In line with one of the WHO strategic objectives “to strengthen National Regulatory Authority's capacities”, assessment is done in order:

- To identify strengths and weaknesses;
- To make recommendations on identified gaps for improvement;
- To develop institutional action plan/road map;
- To propose/suggest supporting activities to satisfy the identified needs.
The WHO Data Collection Tool for the review of Drug regulatory Systems has been designed to help regulatory authorities perform such an assessment. The module 12 allows the assessor to review how the regulatory authority is performing the control of clinical trials that are conducted on its territory. The guidance provides technical advice on how to conduct this review. The assessment methodology is based on several concepts, which should be taken into account and followed. An assessment should not be based on impressions, feelings or any subjective considerations. Furthermore it is important for the assessor to collect objective evidence of his observation. Evidence may be collect by different means. However, the evidence collected through interviews should, whenever possible, be confirmed by more objective means. Investigational clues that point to possible deficiencies or gaps should be thoroughly investigated. Consensus should be reached at the end with the assessed party.
9. External links

9.1. WHO vaccine prequalification and EMA “Article 58” scientific opinion procedures alignment (Dr Marie-Hélène Pinheiro, European Medicines Agency)

To ensure that there was no disruption in the supply of vaccines and medicinal products that are important for developing countries and that there is no disincentive for the timely discovery and development of these products, a consultation and collaboration between EMA and WHO led to the Article 58 in the new Regulation.

Article 58 of the European Commission regulation No. 726/2004 established a mechanism whereby the European Medicines Agency (EMA) may give a scientific opinion within the context of its cooperation with the World Health Organization, with respect to the evaluation of certain medicinal products for human use that are intended exclusively for markets outside the European Community. For this purpose, an application shall be submitted to the Agency in accordance with the provisions of Article 6. The Committee for Medicinal Products for Human Use, may, after consulting the WHO, draws up a scientific opinion in accordance with Articles 6 to 9. The provision of Article 10 shall not apply”.

The procedure for implementation of Article 58 Scientific Opinion procedure, effective since May 2005 begins with the request from the company to EMA to assess the eligibility of the product for Scientific Opinion.

For further information about EMA/CHMP scientific assessment reports, please read the “Guideline on procedural aspects regarding a CHMP scientific opinion in the context of cooperation with the World Health Organization (WHO) for the evaluation of medicinal products intended exclusively for markets outside the community”, at the following web site: http://www.emea.europa.eu/pdfs/human/regaffair/557904en.pdf and also the following Q&A: http://www.emea.europa.eu/htms/human/article58_QaA/list.htm.
In 2010, as results of discussions between EMA and WHO, concrete proposals for improvement are suggested to further accelerate availability of vaccines in developing countries, including:

- Enhance synergies between EMA/WHO and the NRAs,
- Avoid duplication/overlapping of assessment activities,
- Work more efficiently (resource/workload/evolution of scientific Technologies/availability of specific new expertises),
- Shorten the time elapsed between positive EMA scientific opinion and WHO prequalification i.e. avoid step wise approaches,
- Review EMA “Article 58” and WHO vaccine prequalification evaluation procedures, and explore options to increase opportunities for further collaborative/streamlining assessments between the EMA and WHO secretariat and Experts networks, based on existing legal framework and procedures.

The current time for the adoption of a scientific recommendation of the CHMP is estimated at approximately 22 months, including the time of standard WHO prequalification process (12 months). The preliminary proposals for an improvement would make it possible to shorten the total deadline in seven months as from the date of validation of the submission.

A revision of the “procedure for assessing the acceptability, in principle, of vaccines for purchase by United Nations agencies” is currently underway. The first draft published in July 2010 is available for download and public comment until 8 October 2010.

A revision of EMA “Article 58” guideline “Guideline on procedural aspects regarding a CHMP Scientific Opinion in the context of cooperation with the World Health Organisation (WHO) for the evaluation of medicinal products intended exclusively for markets outside the EU” is under preparation. It is expected to be release for external consultation in October or November 2010 on EMA website: www.ema.europa.eu together with an updated page to access all related information on this topic.

9.2. Canadian HIV Vaccines Initiative (CHVI), Health Canada’s role in regulatory capacity building for HIV (Bobby M.
In August 2006, a Memorandum of Understanding (MoU) was signed between the Government of Canada and the Bill and Melinda Gates Foundation to further strengthen global efforts to accelerate the development of HIV vaccines. The MoU led to the creation of the Canadian HIV Vaccine Initiative (CHVI) in February 2007, with dedicated funding of $139M over five years. This included $111M from the Government of Canada and $28M from the Gates Foundation. On 20 July 2010, during the XVIII International AIDS Conference in Vienna, the Government of Canada and the Bill & Melinda Gates Foundation announced the renewal of the CHVI. Funding previously allocated to the CHVI has now been re-focused due to change in priorities. Re-allocation of funding allows for Health Canada’s Regulatory Capacity Building Program.

The Biologics and Genetic Therapies Directorate (BGTD) of Health Canada is involved in several capacity building initiatives including collaboration with WHO to ensure vaccine safety for distribution; vaccine and clinical trial regulation training (e.g. India); and participation in Pan American Network for Drug Regulatory Harmonization (PANDRH) and the African Vaccine Regulatory Forum (AVAREF). These regulatory capacity building initiatives are critical tools in supporting NRAs to implement appropriate policies to address their needs regarding vaccines and clinical trials, including those related to HIV/AIDS. Additional funding provided through the CHVI would allow for BGTD to play a greater role in addressing regulatory capacity needs identified by NRAs.

Since 2009, Health Canada's Health Products and Food Branch (HPFB) offer an annual International Regulatory Forum (IRF). This forum provides NRAs with an understanding of the Canadian approach to regulation, which in turn can provide a foundation for them to develop a legislative/regulatory framework for vaccines and clinical trials. CHVI funding allows the scope of the HPFB-IRF to be expanded to include:

- sponsorship of NRAs, identified by the WHO, involved in HIV/AIDS vaccine clinical trial applications to participate in HPFB-IRF;
- training to address the needs of NRAs specifically involved in HIV/AIDS vaccine clinical trial applications (e.g. the regulation of clinical trials, good clinical practices, pre-market and review process, good review practices, lot release and international collaboration).

The next HPFB-IRF (October 2010) may involve sponsorship of more than eight participants (Ethiopia, Kenya, Ghana, Tanzania, The Gambia, Burkina Faso, Senegal and Thailand). This year program will include regulation of clinical trials, pre-market review of biologics, viral and bacterial vaccines, and international collaboration.

In addition, upon request from an NRA, or identified through the WHO, BGTD would establish a “one on one” mentoring/training program, especially useful for NRAs that have or are expecting clinical trial applications for HIV/AIDS vaccines, but do not have the necessary legislative/regulatory framework in place. Health Canada would provide scientific expertise in the parallel review of a clinical trial application, thereby acting as a resource by which specific concerns may be addressed and regulatory confidence in the NRA could be increased.

Finally, BGTD has committed to attend AVAREF and assist the WHO on a training program for African nations on the development of regulations for clinical trials.

9.3. How can the FDA support the goals of AVAREF? (Ralph E. Leblanc, PhD, US-FDA, Center for Biologics Evaluation & Research, Office of vaccines research and review)

The support that the FDA can give to AVAREF was exposed and it can be summarized as follows:

1) USFDA/Center for Biologics Evaluation & Research (CBER), Office of vaccines research and review is committed to working with the WHO to assist members of AVAREF in addressing regulatory issues; and strengthen the regulatory capacity within these countries. However, USFDA/CBER ability to provide assistance depends on its available resources.

2) Depending on available resources USFDA/CBER will continue to support the AVAREF network through WHO in the assessment of clinical data and product quality in
vaccine registration dossiers; and also in building expertise and capacity relevant for the evaluation of these products.

3) To optimize its assistance it will be critical for USFDA/CBER to learn about the specific needs of the various NRAs within the AVAREF network: regulatory systems in place in the various NRAs including regulatory requirements and guidelines; requirements for regulatory filing; legal timelines for assessment; availability and experience of review staff, other in-house expertise and external consultants. Based on this information, WHO and USFDA may be able to define an approach that can be tailored to the needs of the members of the AVAREF.

4) U.S. congress requested report from the FDA on activities that address neglected tropical disease. Formal report and recommendations are due in March 2011. Proposal from AVAREF could be part of those recommendations.

5) Identification of common training requests: joint reviews (malaria, HIV, TB clinical trial protocols), GCP training, adverse event monitoring, effective team building.

6) Individual NRA capacity building requests: broadening the scope of NRA authorities and responsibilities, review of legal framework and strengthening national authority.

9.4. EMA clinical trial third country Initiative (Dr Pieter Neels, Federal Agency for Medicines and Health Products, CHMP member, Vice-Chair Vaccine working party, Belgium)

Regarding the situation reflecting the globalization of clinical research, which raises other equally important challenges, namely:

- Reaching a common understanding and framework for ethical and scientific standards,
- Achieving a strong regulatory and ethical framework in all countries where clinical trials are conducted,
- Assistance through sharing of expertise and capacity building,
- Role of Regulatory Authorities through global regulatory networks,
EMA has established some proposal to ensure that the Marketing Authorization Applications (MAA) process deals with those challenges.

These directives include a publication, in 2010, of a draft “Reflection paper on ethical and GCP aspects of clinical trials conducted in third countries for evaluation in marketing authorisation applications for medicines for human use, submitted to the EMA”. The document is under public consultation until 30 September 2010, and highlights the need for cooperation between international regulatory authorities. The paper proposes a series of measures to ensure a robust framework for the oversight and conduct of clinical trials, no matter where in the world investigators’ sites are located and patients are recruited. The proposal in the draft reflection paper deals with the following subjects:

**Topic 1.** Clarify the practical application of ethical standards for clinical trials, in the context of the EMA activities.

**Topic 2.** Determine the practical steps to be undertaken during the provision of guidance and advice in the drug development phase.

**Topic 3.** Determine the practical steps to be undertaken during the Marketing Authorisation evaluation phase. It includes the consideration of the submission, the validation, the assessment, and inspection of information collected by the applicant.

**Topic 4.** International cooperation in the regulation of clinical trials, reviews and inspections performed in host countries, and capacity building in this area.

A regulatory action plan has been proposed in this document, including the following proposals:

1) The European Medicines Agency should establish a pool of experts to advise the CHMP in its assessment of the ethical aspects of clinical trials submitted with the MAA, and define their membership, required expertise, mandate and procedures, and the process by which the CHMP, EMA or other agency scientific committee, may consult them. Such consultation may be on general matters of principle involved in establishing requirements and guidance, or specific cases involving particular trials and products.

2) EU Competent Authorities should develop a system for review of MAA dossiers, and identify studies of potential ethical or GCP concern, involving review at the time of
validation by the EMA product team, and during the assessment by the assessment team and CHMP, supported by the EMA product team.

As a part of the consultation process on the reflection paper, the EMA held an international workshop on 6-7 September 2010 with many stakeholders from around the world to discuss a way forward for a global framework of clinical trials. The discussions highlighted three main points:

- The need for cooperation and networking between regulatory authorities and also ethics committees involved in the supervision of clinical trials, including capacity building activities.
- The need for greater transparency of clinical trials, including clinical trials registers and the provision of information about ethical and GCP aspects in the European Public Assessment Report (EPAR).
- The need to involve patients early on in the design of protocols to ensure the adequate protection of clinical trials subjects.

In conclusion, new guidelines are probably not required, but there is a need to work together for a common understanding of existing guidelines. Furthermore, there is a consensus that more GCP and ethical standards collaboration is needed.

9.5. Prequalification of vaccines for UN supply, facilitation of registration of prequalified vaccines (Dr Nora Dellepiane, WHO/IVB/QSS/VQR)

This topic was put on the agenda thanks to the questions about prequalification, which debated at day three of this meeting. The presenter exposed the prequalification procedure: its principles, pre-conditions for application and steps of the procedure as such.

WHO prequalification of vaccines is a service provided to UN purchasing agencies by WHO to assess the quality, safety and efficacy of vaccines. The WHO prequalification of vaccines ensures that candidate vaccines meet WHO recommendations and are suitable for the target population, at the recommended schedules with appropriate concomitant products and meet the needs of the programme.
The following are the conditions for acceptance of applications:

- The NRA of the producing country is found to meet all the critical indicators defined for prequalification purposes following a WHO independent assessment.

- The candidate vaccine is licensed by the responsible NRA (Scientific opinion by EMA accepted).

- WHO guidelines/recommendations available.

- The vaccine is listed in the vaccine priority list (low priority vaccines may be postponed).

Steps of prequalification procedure include:

- Scientific and technical review of a Summary dossier (Product Summary File).

- Testing of final product characteristics.

- Consultation with NRA of exporting country and agreement for mutual collaboration between NRA and WHO/QSS.

- Audit of manufacturing facilities (jointly with NRA).

As regards the supply of vaccines, the functions of regulation for the countries depend on the source of the products. When vaccines are sourced through a UN centralized procuring mechanism such as UNICEF or the PAHO revolving fund two regulatory functions need to be met by the user (receiving) countries; these are the registration/licensing function and the post-marketing surveillance. When vaccines are sourced directly by the country from a foreign manufacturer, two additional functions must be met; lot release and laboratory access. Lastly, in case of national manufacturing the six recommended functions are ensured by the countries themselves (regulatory inspections and clinical trial regulatory oversight). Countries where clinical trials are being performed need to exercise their regulatory oversight independently of their vaccine sourcing mechanism.

WHO offers to countries procuring vaccines through UN agencies a procedure to expedite the review process of imported prequalified vaccines with view to granting a MA. Therefore marketing authorization process can be simplified and expedited. This procedure is available on the Internet on the WHO’s website link below:

This procedure is intended for countries that source their vaccines through UN agencies, or who are using information from the WHO prequalification process as a basis for selection of vaccines for use in their national immunization programmes, importing them through direct procurement. It provides guidance on how NRAs of such countries can expedite the regulatory review for such products. This procedure is not intended to affect any post-approval activities in place in the countries using it.

9.6. Report on the consultation on interactions between National Regulatory Agencies and National Immunization Technical Advisory Groups (NITAGs/NCIPs) (Dr Nora Dellepiane and Dr Liliana Chocarro WHO/IVB/QSS/VQR, presented by Dr Nora Dellepiane)

In the context of the Global Immunization Vision and Strategy (GIVS) situation analysis in several countries shows isolation between NITAGs and NRAs, dichotomy between registration and recommendation for use of vaccine, lack of adequate coordination between NRAs and the immunization programs that may lead to problems.

Consensus of two specific consultation sessions related to the interactions between NRAs and NITAGs are of great interest: the New and Under-utilized Vaccines Implementation (NUVI) working group and the 11th NRA/NITAG consultation meeting of Developing Countries' Vaccine Regulators Network (DCVRN).

The participants at these two meetings concluded the following:

1) The NUVI working group:
   - Relation between NRAs and NITAGs are not satisfactory.
   - Where both organs do exist, exchange of information between NITAGs and NRAs is often insufficient.
   - Vaccines, in particular OPV, Pneumococcal, BCG and Rotavirus vaccines, are sometimes not used as indicated in the market authorization.
   - Some NRAs consider that once they have made a decision on vaccine introduction, they no longer have a role to play in the next steps.
- The respective roles of the NRAs and NITAGs are not clear to all actors.

2) NRA/NITAG consultation meeting of DCVRN:

- Reported NITAG-NRA interactions are reasonably good in some countries, but that there is an opportunity to improve and formalize expedited interactions; inclusion of NRA ex-officio members in the NITAG is one way of ensuring these interactions.

- There is a constraint to information sharing between NRA and NITAG due to the proprietary and confidential nature of the information in License applications. This may be addressed through discussion and agreement with the applicant and confidentiality agreements by NITAG members.

- A NITAG could advise the Public Health Program in advance to issuance of the marketing authorization by the NRA, of the need to implement or include a certain vaccine in the vaccination program once it is licensed. This can enable suitable preparations for implementation if license is seen to be imminent. In these situations, input and advice from the NRA regarding safety and efficacy of the vaccine can aid the NITAG recommendation.

- In the post-market situation, the NITAG may have important AEFI surveillance information that should be shared with the NRA, or the NITAG may request information from the NRA on quality/safety issues relating to a vaccine already in use (e.g. one rotavirus vaccine and PCV-1 DNA contaminant).

- There would be value for each country to organize a meeting every two or three years between the NITAG, the Public Health Immunization Program, private immunization professionals, vaccine suppliers and the NRA, to discuss the success of interactions between these groups.
Recommendations

1. The member countries of AVAREF recognize all the actions being taken by WHO towards the formalization of AVAREF and the establishment of an interim secretariat in WHO/AFRO. The AVAREF member countries will continue to work towards achievement of all the goals of formalization through the implementation of all the processes before the next annual meeting to be held in September 2011.

   Furthermore, the AVAREF countries reviewed the draft terms of reference for the formalization of AVAREF developed by the Task Team and provided comments for revision. The document will be revised by Kwasi Nyarko and Bartholomew Akanmori and sent to all NRAs and ECs for review before formal submission to NRAs by WHO AFRO. Deadline for dispatch to all NRAs and ECs will be 15 October and for receipt of final comments from all NRAs and ECs will be 15 November 2010. WHO AFRO will send out final version to all NRAs by 5 December 2010.

2. Having recognized the limitation of resources especially experts to assist with reviews of CTAs and registration dossiers, the AVAREF member countries fully endorse the initiative by WHO to assist in creating a database of experts and to facilitate the use of experts of competent authorities such as the EMA, Health Canada and USFDA.

   AVAREF members recommend that a task team be constituted by WHO from countries which volunteered (Gambia, Tanzania, Senegal, Ethiopia, Nigeria, Uganda, Ghana, Cameroon, Gabon) and should meet by first quarter of 2011 to start the implementation of this project. The terms of reference of the Task Team among others will include:

   a. Identification of the key expertise which countries lack.

   b. Summary of the Profiles of experts required by countries.

   c. Development of a database of experts
3. The AVAREF member countries welcomed the newsletter and expressed willingness to contribute towards the first edition to be produced by WHO. WHO AFRO to produce the first edition of the newsletter by Q2 2011.

4. WHO to facilitate a forum for the interaction between NRAs and EPI managers to bridge communication gaps. Various platforms including but not limited to the annual EPI Managers Meetings for the countries of the three IST (IST West, IST South Eastern and IST Central) and the Annual African Regional Conference on immunization/Task Force on Immunization meetings could be used for this interaction, which may involve an initial number of countries to be determined by WHO. The EPI Managers meetings will take place in Q1 2011, while the ARCI/TFI will take place in Q4 2011.

5. AVAREF member countries expressed satisfaction with the progress made on the development of the course on how to develop a legal framework for regulation of clinical trials. The members recommend that WHO completes the development of the course module on legal framework for regulation of CT and initiate the training in Q3 2011 and that assessment questionnaires for NRAs should be sent to countries by early November 2010.

6. The final version of the African Common Clinical Trial Documents (ACCTD) developed by AVAREF members and presented by Jayesh Pandit of Kenya will be translated within two weeks into French by Gabon, Rwanda, Cameroon and Senegal. The final versions in English and French will be sent out to all members for their adoption and implementation. Countries will report on the implementation at the next meeting. WHO will notify what documents have been adopted to ensure that countries consider the next steps, including implementation.

7. NRAs should revise their IDPs and develop feasible proposals there from, in order to secure funding from WHO to improve their institutional capacities. The revised IDPs should be available by the first quarter of 2011. Proposals should include both
medicines/vaccines/technologies and ethics components. The IDPs should provide details of the training needed, rationale and number of people requiring the training in each area with names of candidates and their responsibilities if possible. The updated IDP information will serve as the criteria to be used by WHO for the selection of AVAREF member countries to participate in capacity building initiatives organized by partners such as the Health Canada mentorship capacity building programme from 2011–2016 and also to support applications to training provided by WHO.

8. The IDPs will also serve as a basis for the development of capacity building proposals to seek support for AVAREF member countries by WHO from USFDA, EMA and Health Canada.

9. The AVAREF member countries recognize the importance of joint reviews of CTAs and joint inspections of clinical trial sites as major opportunities for capacity building for NRAs and ECs. The members therefore request that WHO should continue to support and facilitate joint reviews and joint GCP inspections in AVAREF member countries. In this regard, WHO should urgently convene a joint review of the pending GMZ-2 CTA for the four member countries (Uganda, Ghana, Burkina Faso, Gabon) targeted for the clinical trials).

10. The AVAREF members were very satisfied with the progress made by Tanzania (one of the pilot countries selected from the previous AVAREF meeting) developing their own databases of clinical trials and establishing mechanisms for the registration of vaccine clinical trials in the country. AVAREF member countries pledged to establish their own databases and put in place mechanisms for registration of all vaccine clinical trials to be linked to PACTR with the support of WHO, WHO International Clinical Trials Registry Platform (ICTRP) and partners.

11. The AVAREF members expressed an interest in knowing their role in the prequalification and registration of vaccines in their countries. In this regard the AVAREF member countries have recommended that WHO facilitate two training workshops (one in French and another in English) next year to train authorities in the new WHO expedited review procedure and thus
facilitate the registration of the conjugate meningitis A vaccine in the rest of countries of the meningitis belt. The countries for each workshop to be determined by WHO, with the first of these workshops to be conducted by June 2011.

12. The next AVAREF meeting will be held from 26 to 30 September 2011. The venue will be one of these countries: Mozambique, Malawi, Zimbabwe or Cameroon. The host country NRA and EC should commit to provide support to WHO for the formalities required for the organization of the meeting.
WR’ closing speech

Dr Abdoulie Jack
WHO Representative/Kenya

Representatives of NRAs/Ethics committees from the invited countries
Regulators from US, Canada and European Medicine Agency
Partners working with WHO to support AVAREF activities, the European Union
WHO colleagues, the aims of AVAREF are as follows:

1. To provide information to countries, which are targeted for clinical trials of vaccines against diseases, including meningitis, malaria and other new vaccines on different vaccine candidates and timelines for clinical trials.

2. To promote and strengthen communication and collaboration between National Regulatory Authorities and ethics committees, in countries where vaccines are developed and in those that are targets for clinical trials in the African region.

3. Provide expertise to regulators in support of regulation and evaluation of vaccines in the Africa region.

The need for new vaccines to prevent as well as to combat the diseases affecting our communities cannot be overemphasized. The burden of tropical diseases such as malaria, tuberculosis and HIV/AIDS continues to exact a huge price both in human suffering and in contributing to poverty and underdevelopment of the African continent. Vaccines remain the most effective public health tool for the prevention of communicable diseases. But vaccines are unique, since unlike other forms of therapies they are normally given to healthy individuals to protect them against disease. This requires that they are very safe and effective. To ensure this, very high standards of reviews are required by scientific committees, ethical committees and regulatory authorities during their development and production and before their introduction.

The aims of AVAREF are therefore very critical and will significantly improve the way vaccines are tested and introduced into Africa. Through its objectives, AVAREF will be ensuring that vaccines are safe, effective and available to all those who need them in order to reduce the unacceptably high disease burden in African countries. This is very critical in enabling us to
attain some of the Millennium Development Goals. AVAREF was involved in the joint review of the application and joint inspection of the clinical trial sites for the conjugate Meningitis A vaccine. It has now been prequalified by WHO, registered by the countries and is being rolled out in Burkina Faso, Mali and Niger. This will eventually lead to the control of epidemics of meningitis as a public health problem in our region.

I am informed that during the week you worked very hard and achieved a number of objectives. On behalf of WHO Representative for Kenya, I want to express that we are pleased to learn that within the last 4 days you were able to:

- Receive information on the clinical trials for vaccines in your countries.
- Improve and strengthen the communication and collaboration between NRAs and Ethics committees in the countries where vaccines are being developed and those targeted for clinical trials in the African Region.
- Provided expertise in support of regulation and evaluation of vaccines specifically for the African NRAs and ECs.
- Updated on information:
  - on the status of Tb vaccine research and development.
  - on the status of registration and deployment of the Meningococcal A conjugate vaccine.
  - on the status of development of Malaria vaccines and reviewed a report on phase 3 clinical trials of the candidate malaria vaccine RTS,S.

You were also updated on various new procedures and criteria for review of various vaccines by the European Medicines Agency and the US food and Drugs Administration.

I am also informed that you have also agreed to formalize AVAREF and will shortly complete and endorse the terms of reference for the formalization of AVAREF.

We are therefore glad that you have achieved the set objectives of the meeting and wish to assure you that WHO will continue to facilitate the forum, support the organization of joint review applications for clinical trials and joint inspections of clinical trial sites. Furthermore, WHO will work in collaboration with partners for resource mobilization to strengthen the forum.
I wish to take this opportunity to thank you all for the active participation and welcome the continued support of our partners and look forward for the forum to expand the membership to the rest of the 46 countries of the WHO African region.

I also wish you all safe travel back home.

It is now my pleasure to declare this 5th meeting of AVAREF officially closed.

Thank you.
Annex 1: Agenda

Fifth Meeting of the African Vaccine Regulatory Forum (AVAREF)
20-24 September 2010, Safari Park Hotel
Nairobi, Kenya
Session 1 – Opening of Meeting

Monday 20 September 2010

08:30 – 09:00   Registration

09:00 – 10:30   Opening Ceremony

  Introduction of AVAREF, B. Akanmori, WHO/AFRO

  Speech by Head of NRA, Kenya* Head, Med. & Poisons Board/Kenya

  Welcome Speech, WR/Kenya, Dr Abdoulie Jack

  Keynote Address and Opening, Hon. Minister for Medical Services – Professor Anyang Nyongo

  Objectives & Expected Outcomes, B Akanmori WHO/AFRO

  Announcements, WHO Secretariat

  Group Photograph and Coffee Break

11:00 – 11:30   Status of Implementation of recommendations from AVAREF 4
                B. Akanmori

11:30- 12:30   Discussion

14:00-14:30  Update on R&D for TB vaccines in (1), Uli Fruth, IVR/HQ

14:30-15:00  Update on R&D for TB vaccines in (2), Uli Fruth, IVR/HQ

15:00-15:30   Coffee Break
<table>
<thead>
<tr>
<th>Time</th>
<th>Event</th>
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<tr>
<td>15:30-16:00</td>
<td>Regulatory challenges in the evaluation of clinical trials of TB vaccines, Rose Tieman USFDA</td>
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<tr>
<td>16:00-16:30</td>
<td>Updates on Tb vaccine clinical trials in Africa, Countries</td>
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<tr>
<td>16:30-1700</td>
<td>Discussion</td>
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**Tuesday 21 September 2010**

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<tr>
<th>Time</th>
<th>Event</th>
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<tr>
<td>09:00-09:20</td>
<td>Overview of malaria vaccines in clinical trials in Africa, Vasee Moorthy, HQ/IVR</td>
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<td>09:20-09:35</td>
<td>Special challenges of approving phase I clinical trial of a malaria vaccine, M. Darko, Ghana</td>
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<tr>
<td>09:35-09:40</td>
<td>Experiences of other countries</td>
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<td>09:40-10:10</td>
<td>Regulatory challenges of evaluation of clinical trials of whole organism and transmission-blocking malaria vaccines in humans, Ralph Leblanc, USFDA</td>
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<tr>
<td>10:10-10:30</td>
<td>Discussion</td>
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<tr>
<td>10:30-11:00</td>
<td>Coffee Break</td>
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<tr>
<td>11:00-11:40</td>
<td>Country experiences in inspections of the phase 3 clinical trials of GSK RTS,S/AS01E (Mosquirix®) Ghana – Mimi Darko, Burkina Faso, Gabon, Tanzania, Malawi, Mozambique, Kenya, Nigeria</td>
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<td>11:40-12:00</td>
<td>Recommendations of a WHO expert committee on follow-up in the phase 3 clinical trials of GSK RTS,S/AS01E, Vasee Moorthy, HQ/IVR</td>
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<td>12:00-12:20</td>
<td>The WHO Policy recommendation pathway for malaria vaccines</td>
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<td>12:20-12:40</td>
<td>Discussion</td>
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<td>12:40-14:00</td>
<td>Lunch</td>
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<td>14:00-14:30</td>
<td>Role of DSMBs in monitoring safety during clinical trials, Z. Premji, NMRC</td>
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<td>14:30-15:00</td>
<td>Regulatory requirements on safety during clinical trials(I), P Neels, EMA</td>
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15:00-15:30 Coffee Break
15:30-16:00 Regulatory requirements on safety during clinical trials(I). R. Tienan, USFDA
16:00-16:30 Discussions

Wednesday 22 September 2010

09:00-09:20 Control of epidemics of meningococcal meningitis in the context of the African Health agenda. B Akanmori WHO AFRO.
09:20-09:40 Update on implementation of the Men A Vaccine. R Mihigo WHO AFRO
09:40 – 10:10 Country Experiences on registration of Conj Men A Vaccine. Mali & Burkina Faso.
10:10-10:30 Discussion
10:30-11:00 Coffee Break
11:00-11:15 Why the formalization of AVAREF. Akanmori B, WHO AFRO
11:30 – 12:00 -AVAREF Newsletter B. Akanmori, WHO AFRO
-Database of Experts, B Akanmori, WHO AFRO
12:00 – 12:30 Lunch
13:30 – 14:00 Development of the course on Legal framework for regulation of clinical trials - Aaron Sosola.
14:00-14:20 Feedback from AVAREF members on the proposed focus.
14:20-15:00 Country updates on legal framework changes.

Thursday 23 September 2010

9:00-10:30 Registry component
9:00-9:20 Assessment of different platforms. Christopher Jones, ICTRP, WHO
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<tr>
<th>Time</th>
<th>Session</th>
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<tbody>
<tr>
<td>9:20-9:40</td>
<td>Pilot implementation experience in Tanzania                      Adam Fimbo, TFDA</td>
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<td>9:40-10:00</td>
<td>Update form the Pan-African Clinical Trial Registry. Amber, MRC</td>
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<td>10:00-10:30</td>
<td>Discussion</td>
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<td>11:00-12:30</td>
<td>Ethics component</td>
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<td>12:30-13:00</td>
<td>Update on ongoing activities</td>
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<td>Proposed strategy and action plan</td>
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<td>Bocar Kouyate, NEC Burkina Faso</td>
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<td>13:00-13:30</td>
<td>Regulatory component</td>
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<td>13:30-14:00</td>
<td>Update on the ACCTG</td>
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<td>Jayesh Pandit, NRA Kenya</td>
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<td>14:00-15:00</td>
<td>Discussion. Consensus on action plan to strengthen the regulatory</td>
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<td>component of PACTA</td>
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<td>15:00-15:30</td>
<td>Coffee Break</td>
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<td>15:30-16:00</td>
<td>Summary of training, L. Chocarro</td>
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<td>16:30-17:00</td>
<td>General discussion</td>
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Friday 24 September 2010

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<th>Time</th>
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<tr>
<td>9:00-9:30</td>
<td>WHO Prequalification</td>
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<td></td>
<td>Introduction- Institutions that support AVAREF                        Nora Dellepiane, WHO-HQ</td>
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<td></td>
<td>EMA and WHO collaboration on Prequalification                         Marie Helena, EMA</td>
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<td>9:30-10:00</td>
<td>Health Canada                                                           Bobby Chahuan</td>
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<td>10:00-10:30</td>
<td>EMA, Reflection paper on clinical trial in third countries             Pieter Neels</td>
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<td>10:30-11:00</td>
<td>Coffee break</td>
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CIDA-Canada

11:00-11:20 USFDA/CBER, Rose Tiernan

11:20-11:40 Center for Global Development- Tom Bollyky

11:40-12:00 Collaboration with NITAGs, Nora Dellepiane, WHO-HQ

12:00-12:30 Discussion

12:30-13:30 Lunch

13:30-15:00 General discussion
   Recommendations and action points
   Closure
## Annex 2: List of participants

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<tr>
<th>NAMES</th>
<th>COUNTRY</th>
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