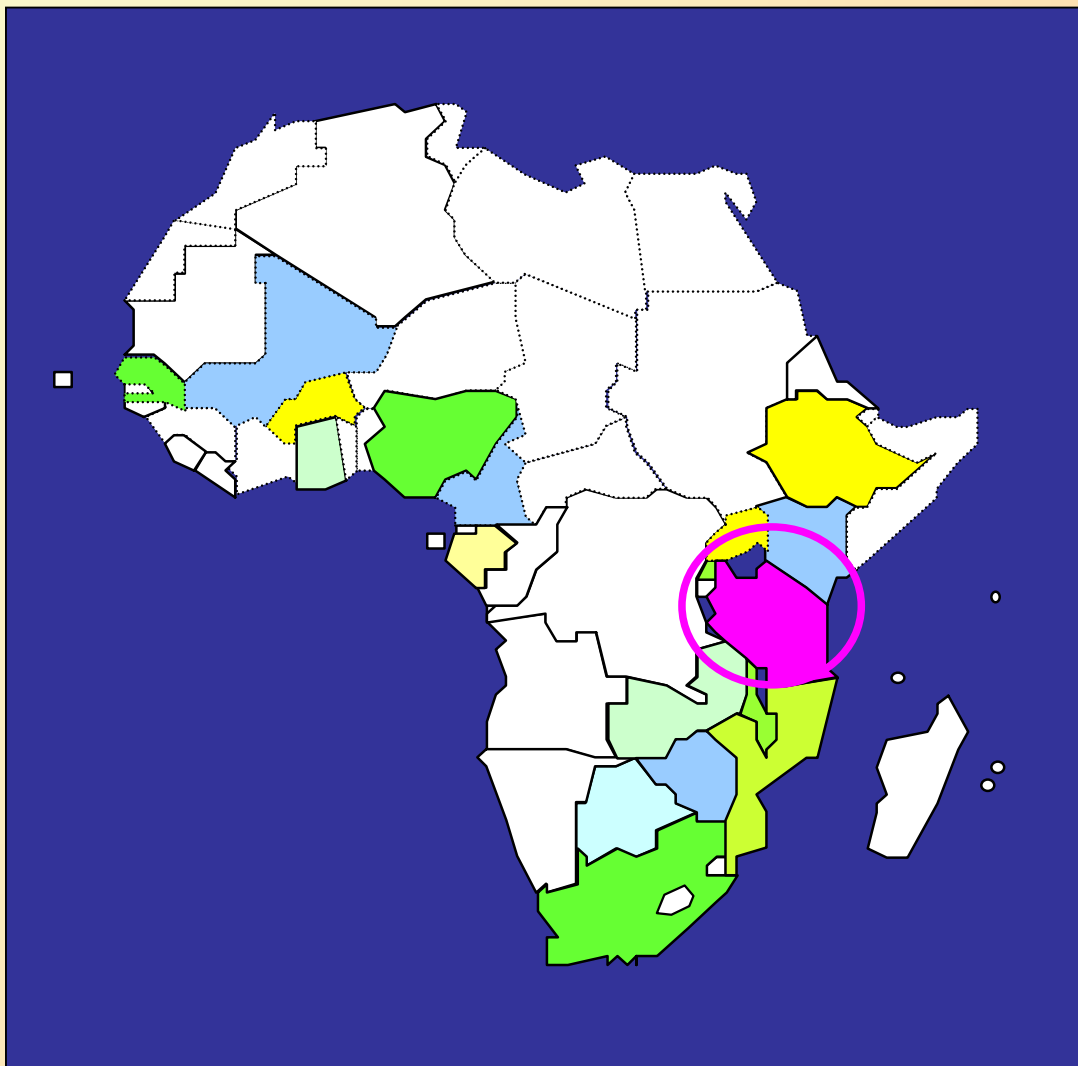




World Health
Organization

**THIRD MEETING
AFRICAN VACCINE REGULATORY FORUM
(AVAREF)**



*Zanzibar Beach Resort
Zanzibar, United Republic of Tanzania
28-31 October 2008*

Acknowledgments

The third annual meeting of AVAREF has been organized with the support from EDCTP, Bill & Melinda Gates Foundation, PATH/Malaria Vaccine Initiative and AERAS. In addition the regulatory authorities of United States of America, Canada, Belgium and Germany have contributed with the participation of their experts.

Table of contents

	Page
1. Opening ceremony.....	5
2. Introduction and objectives.....	8
3. Joint review of the clinical trial application for phase III trial of Malaria Vaccine RTS S.....	13
4. Integration of ethical review, regulation and registration of clinical trials in Africa.....	14
5. Harmonization of drug and vaccine clinical trial regulation in Africa...	29
6. County Progress reports.....	41
7. New TB vaccines.....	46
8. Recommendations and action points.....	55
9. Closing ceremony.....	58
Annex 1: Agenda	
General agenda.....	60
Satellites 2 and 3.....	61
New TB vaccines.....	64
Annex 2: list of Participants.....	65

1. Opening ceremony

Speech for the Opening of the third meeting of the African Vaccine Regulatory Forum, by Dr Mohammed Belhocine, WHO Representative to Tanzania

The Chairman of the meeting
The Coordinator of the meeting Dr Liliana Chocarro
Dr Noormahomed Inusse, The WHO Public Health Advisor, Zanzibar
Members of AVAREF
Representatives from National Regulatory Agencies
Colleagues from WHO HQ and AFRO
Colleagues from Manufacturers companies present
Representatives of Development Partners,
Distinguished Guests,
Ladies and Gentlemen,

I am delighted to be present here on behalf of the World Health Organisation for the opening ceremony of this important occasion of the opening of the third meeting of the African Vaccine Regulatory Forum.

I wish to take this opportunity to thank and congratulate the organizers of this workshop which has enabled the gathering of such distinguished people in the different areas of vaccines management and regulation. I also wish to thank the Revolutionary Government of Zanzibar and in particular the Ministry of Health and Social welfare for hosting this important meeting.

May I take opportunity to welcome you to the United Republic of Tanzania in particular Zanzibar – island of spices.

Ladies and Gentlemen, strengthening vaccine regulatory capacity in countries is critical toward the attainment of the goal of the WHO to “ensure that 100% of vaccines used in all national immunization programs are of assured quality”. It is also critical in the attainment of the Millennium Development Goal number four which aims at reducing by two thirds child mortality between 1990 to 2015.

The need for new vaccines to prevent as well as to combat the diseases affecting our communities cannot be overemphasized. The disease burden inflicted by tropical diseases continues to exact a huge price both in human suffering and in contributing to poverty and underdevelopment. Applications for clinical trials on the new vaccines and other therapies will definitely need to be conducted to determine their safety and effectiveness.

The regulatory oversight of clinical trials was initially considered to be important only for countries where medicines are manufactured. However, it is now recognized that regulatory agencies of developing countries, which have within their mandate to control the use of medicinal products, should also control the use of investigational products, that is, during clinical trials. Therefore, they should have the expertise and capacity to review clinical trial authorizations, to authorize the importation of clinical batches and to inspect the clinical trials.

Although countries that are target for clinical trials may not need to develop permanent resources at the same level as the National Medicines Regulatory Authorities of developed countries where vaccines are manufactured, when a clinical trial is to take place, the National Medicines Regulatory Authority of the target country would need the resources and expertise available within a short period of time.

Ladies and Gentlemen, the low level of expertise in the African countries with regards to regulation of clinical trials is a challenge which WHO and its Members States have recognized for some time now. In trying to mitigate this, WHO AFRO, in developing a strategy to support regulators, the "regional approach" was seen as the best way to address the needs for strengthening of regulatory systems. The establishment of the African Vaccine Regulatory Forum (AVAREF) should therefore be commended as it provides an avenue to build on the expertise available in the Region, strengthen the capacity of weaker countries and identify the need for support and training.

Since its inception, AVAREF has proven to be an efficient forum for regulators from the region and from other countries (USFDA, Health Canada, and European Agencies) to discuss challenging issues, identifying gaps, finding solutions to regulatory questions, ultimately working together to strengthen the regulatory authorities in Africa.

Ladies and Gentlemen, since the inception of AVAREF significant progress has been achieved particularly in the area of capacity building of various regulatory agencies in the Region as well as in sensitization of stakeholders, particularly Ministries of Health and Inter-Country Committee (ICC) members, on the necessity to improve the field of vaccine regulation. The process of developing IDP further fostered the communication and collaboration between National Medicines Regulatory Agencies, National Ethical Committees and National Immunization Programmes and Adverse Events following Immunization (AEFI) committees in the countries that developed Institutional Development Plans (IDPs). The developed template guidelines are already being used by some countries in their regulatory reviews of clinical trial applications. The information received during the NRA strengthening workshops on analysis of efficacy and safety data of vaccines is being used by countries to assess registration dossiers submitted by manufacturers. It is now clear that the "Regional Approach" is becoming a reality day by day.

Despite these achievements, there are still many gaps to fill in the area of vaccine regulation in the countries. We hope that the efforts initiated will continue in order to maintain the momentum launched in the countries. Efforts should also be extended to

make sure that all countries in the Region join the AVAREF and hence benefit from the positive outcomes already seen for the betterment of the African population.

On this note, Mr Chairman, ladies and Gentlemen, on behalf of the World Health Organisation, let me once again thank you and wish you success in your deliberations. I declare the meeting officially opened.

2. Introduction and Objectives

2.1 Objectives of AVAREF (Prof. Bartholomew Akanmori, WHO/AFRO)

Setting the tone for the meeting the speaker 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 targets 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 3rd AVAREF meeting were stated as follows:

1. To conduct a joint review of the GSK-Bio RTS,S malaria vaccine phase III clinical trial application dossier, by the countries targeted for the trial and with assistance of a regulator from Belgium and the European Medicines Authority (EMA).
2. To strengthen the mechanisms for the integration of ethical review and registration of clinical trials within the African region.
3. To develop a harmonized regulation protocol for drugs and vaccine clinical trials in Africa.
4. To update regulators on different on-going vaccine clinical trials in Africa.
5. To review the progress made so far by countries involved in AVAREF in the implementing recommendations from previous meetings.
6. To make appropriate recommendations on the way forward.

These objectives were clearly explained.

2.2 Implementation of recommendations from the second AVAREF meeting, content and expected outcomes (Dr. Liliana Chocarro, WHO/HQ)

The following is a report of the action (A) taken for each of the recommendations (R) from AVAREF-2

R1- AVAREF should be formalized to allow confidentiality agreements to share information between NRAs. WHO to establish a task force for information sharing.

A1- . An existing MOU between WHO and USFDA provides for inclusion of a third party. In addition there is ongoing dialogue for a Memorandum of Understanding (MOU) between WHO and EMEA, which may include AVAREF projects. There are recent examples of information sharing between Health Canada and developing countries facilitated by WHO, indicating that there are opportunities to initiate similar projects with this agency.

At the ICDRA meeting in September 2008, one of the recommendations was "WHO should produce a guidance and draft regulation for managing confidentiality issues among in regulatory authorities" reflecting the interest worldwide to take action in this field.

R2- Compilation of existing systems for regulation of clinical trials and distribution to all AVAREF members

A2- A basic questionnaire was prepared after the AVAREF-2 and the following countries have returned it completed: Ghana, Malawi, Nigeria, Rwanda, Senegal, Tanzania, Zimbabwe, Burkina Faso, Botswana, Gabon, The Gambia, Kenya, Cameroon.

R3- and **R4-** WHO to organize a satellite meeting to discuss coordination between Ethics Committees and NRAs. WHO to proceed with project to link regulation and registration of clinical trials. (Note: These two are presented together as they were merged in the implementation)

A3- **A4-** WHO advocated these initiatives and received support (funding) from EDCTP for an initial consultation meeting which will take place during AVAREF-3 as a satellite meeting to develop a strategy to link ethical review, regulation and registration of clinical trials in Africa

R5- NRAs of manufacturing countries (USFDA, Health Canada, EMEA) to explore ways to provide regulatory input to support African country NRAs hosting trials.

A5- The third AVAREF meeting will include a progress report from the 3 regulatory bodies.

R6- AVAREF countries to maintain communications through country offices and or Inter Country support teams (Dr. D. Kandolo, Dr. R. Mihigo and Dr. A. Onyeze) to report progress made in the implementation of a framework to regulate clinical trials. A communication plan should be developed

A6- No communication plan was developed but progress reports were received from Burkina Faso, Malawi and Ethiopia. This communication strategy must be improved so the colleagues from AFRO are always informed of the exchange of information.

R7- Expand training on pharmacovigilance to monitoring of Adverse Events Following Immunizations (AEFIs) during clinical trials, and SAEs.

A7- The course on Clinical Trial Authorization includes a module on safety monitoring plan. Safety monitoring during clinical trials is recognized as an important issue that requires action to provide guidance to regulators of countries hosting clinical trials. The Developing Country Vaccine Regulator's Network (DCVRN) will discuss harmonization of safety monitoring reports in trial host countries and communication framework between countries in multicenter trials.

Other highlights since the last AVAREF meetings are:

- All clinical trials of Conjugate Meningitis A Vaccine were authorized by African host countries and all the clinical trial sites (The Gambia, Senegal, Mali) were inspected
- AVAREF countries (Ghana, RSA) attended the EMEA GCP Inspectors workshop in October 2008. The EMEA GCP Inspectors working group in collaboration with WHO will designate GCP inspectors to establish a communication strategy so all local NRAs are informed and can participate in GCP inspections by European inspectors in Africa
- Networking for success: AVAREF model, presented by Markieu Janneh-Kaira at ICDRA and greatly commended
- Agreement with PATH/MVI resulted in a joint review of CTA for Malaria vaccine with 7 AVAREF countries (Burkina Faso, Gabon, Ghana, Kenya, Malawi, Tanzania, Mozambique)
- Dialogue initiated with EMVI/AMANET to conduct similar activities with another vaccine (The Gambia, Gabon, Burkina Faso, Uganda)

AVAREF-3: Format and Content

The format of this meeting is complex as there will be 3 satellite meetings for the first three days. These are as follows:

- Satellite meetings (Monday to Wednesday)
 - 1) Joint review of Malaria vaccine clinical trial applications: Ghana, Gabon, Burkina Faso, Malawi, Kenya, Tanzania, Mozambique with expert support from head clinical and head product reviewers from the NRA of Belgium (manufacturing country)
- Satellite meetings (Monday to Wednesday)
 - 2) Consultation on Strategy to link ethical review, regulation and registration of clinical trials in Africa
 - 3) Integration/Harmonization of drug and vaccine clinical trial regulation in Africa

Satellites 2 and 3 will have a joint session on Monday afternoon and Tuesday morning, they will work separately until Wednesday and they will report the outcome of their deliberations on Thursday morning in the plenary session.

The expected outcomes of the satellite meetings are as follows:

1) Joint review of Malaria Vaccine CTA

- African regulators will validate their findings from their preliminary reviews through discussion with peer regulators and experts from the Belgian NRA
- The advantages of using a harmonized format for the CTA will be assessed and reported to all AVAREF members
- Review group will prepare a common report of observations and will discuss with the manufacturer/sponsor
- Additional information or amendments requested by the review group will be submitted by the manufacturer to each NRA for the completion of the formalities according to national requirements for the authorization of the clinical trial
- Enhanced quality of the review of a CTA
- Strengthening of regulatory capacity in host countries
- Strengthening of collaboration between regulatory bodies

2) Integration of Ethical Review, Registration and Regulation of Clinical Trials in Africa

- Identify the key elements that justify the need to have a regional strategy to link ethical review, regulatory approval and registries of clinical trials
- Prepare a proposed strategy to maximize efficiency and transparency with regards to oversight of clinical trials
- Propose the composition of a task force that will work with WHO to implement the proposed strategy
- Prepare a report to be presented in the plenary on Thursday morning that will include:
 - highlights of the discussions
 - proposed strategy
 - recommendations for countries and for WHO and action points

3) Harmonization of regulation of clinical trials of medicines and vaccines

- Identify key elements to optimize the use of resources at the national level for the oversight of clinical trials of drugs and vaccines
- Identify the advantages/disadvantages of harmonized regulatory guidance documents for all processes relevant to oversight of clinical trials
- Prepare a list of documents that can be proposed for common use in the region
- Propose a plan for optimization of resources in the region with regards to evaluation of clinical trial applications and inspections

-
- Identify types of capacity building activities sponsored by WHO that should be done in common for drug and vaccine trials and those that should be done separately
 - Propose a list of required training and tentative timeline
 - Prepare a report to be presented at the plenary on Thursday morning that will include:
 - Highlights of the discussions
 - Key elements identified
 - Proposed plan of action and recommendations for countries and for WHO

AVAREF-3: Plenary sessions

- Thursday morning
 - Brief report from Satellite 1
 - Report and discussions for Satellites 2 and 3
- Thursday afternoon
 - Progress reports from African countries
 - Reports from USFDA, Health Canada and EMEA on regulatory changes relevant to clinical trials in developing countries
- Friday morning
 - Session on New TB vaccines
- Friday afternoon
 - Closed session for regulators: planning regulatory support activities for TB vaccine trials
 - Recommendations/action points

3. Joint review of the clinical trial application for phase III trial of Malaria Vaccine RTS S

During the AVAREF-2 the seven countries (Ghana, Burkina Faso, Gabon, Malawi, Kenya, Mozambique, Tanzania) where the phase III clinical trials of the RTS S candidate manufactured by GSK would be conducted, agreed to receive a harmonized dossier, upon agreement on the content.

In April 2008, the four Anglophone countries from this group were invited to attend the MALVAC meeting in Geneva and they also participated in a pre-submission meeting facilitated by WHO, where the regulators had an opportunity to discuss with GSK the requirements for submission to Ethics Committee, timelines, and other details.

During this meeting, regulators requested that the dossiers be sent two months prior to the joint review in order to give them an opportunity to their reviewers to assess the dossier and come to the joint review with specific questions for the experts from the NRA Belgium, and to maximize the quality of the discussions with their peer regulators.

Accordingly, the dossiers were submitted to the countries in August, and the joint review was scheduled for the week of AVAREF-3.

Dr. Pieter Neels and Dr. Genevieve Waterloos, from the Regulatory Authority of Belgium- country of manufacture- received a copy of the same dossier sent by GSK to all seven African countries, and participated in the joint review to provide expert support.

Mozambique was not represented. The six countries that were present discussed their findings, and the experts from Belgium assisted in the analysis of the observations. The overall review was the result of the observations from African regulators, plus the added insights from the regulators from Belgium. A consolidated report was prepared, and this was presented on the third day to GSK with the presence of representatives from PATH/MVI.

This exchange was productive as some of the questions were clarified, others were resolved by establishing a formal request to GSK to provide additional information. It was agreed that each country would reply individually to the company and that the company would submit the requested information individually.

The experience was very positive for all participating countries. One observation was that the model procedure for the submission of clinical trial applications needs to be revised as the content of the dossier should be expanded. This is a reflection of the progress made by the participating countries, since when the model procedure was developed most of them did not have any in place.

4. Integration of ethical review, regulation and registration of clinical trials in Africa

Introduction

4.1 Why register clinical trials and why integrate ethical review, registration and regulation of clinical trials (Dr. Davina Gherzi, Clinical Trial Registry Platform, WHO)

About clinical trial registration

The registration of all interventional trials is considered to be a scientific, ethical and moral responsibility. In August 2004 the International Committee of Medical Journal Editors (ICMJE) announced that, as of 13th September 2005, they would no longer publish manuscripts reporting the results of clinical trials unless a minimum amount of information about those trials had been registered in a publicly accessible clinical trials registry. This policy was informed by a large body of evidence demonstrating the existence of publication bias and selective reporting, and their impact on the ability of health care providers and consumers to make informed health care decisions. In a number of high profile cases, trial sponsors were found to have withheld negative trial outcomes from the public, regulatory agencies and others. These cases gained significant, negative media attention and the demand for transparency increased. More recently, the 2008 revision of the Declaration of Helsinki now states that "Every clinical trial must be registered in a publicly accessible database before recruitment of the first subject".

About the ICTRP

In November 2004, at the Ministerial Summit on Health Research, those present called for action by "*All major stakeholders*, facilitated by *WHO secretariat*, to establish a platform linking a network of international clinical trials registers to ensure a single point of access and the unambiguous identification of trials." (The Mexico Statement on Health Research). This was further expanded on during the 58th World Health Assembly (WHA 58.34) held on 25th May 2005. The global scientific community, international partners, the private sector, civil society, and other relevant stakeholders were called upon to "establish 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".

As a result of the WHA resolution WHO established the International Clinical Trials Registry Platform (ICTRP) which currently has 2 key elements: the Network of Collaborating Trial Registries (the Registry Network) and the Clinical Trials Search Portal. The Registry Network provides a forum for the exchange of information across registries, and the Clinical Trials Search Portal provides a single point of access for the

identification of trials. Data searchable on the portal is provided by registries that meet WHO criteria for quality and content. The WHO Clinical Trials Search Portal was publicly launched on 4th May 2007.

Why register clinical trials

- To improve transparency and accountability
- It is an ethical responsibility
- To improve public trust
- To address publication bias and selective reporting
- To identify gaps
- To build research infrastructure and capacity
- increase participation in clinical trials
- contribute to systematic reviews
- speed access to results
- increase effectiveness of research funding
- impending increase in number of trials
- improve access to research information
- increase efficiency of the research process
 - e.g. ethical review
- enhance transparency and accountability
- improve equity and ownership
- facilitate policy development

Assessing the situation

4.2 Research ethics policies and practices in the African Region (Dr Bocar A. Kouyaté, Comité National d’Ethique Recherche en Santé Burkina Faso)

In the African Region, growing number of studies in the region indicate that there are a number of factors that limit implementation of research ethics in research for health. These particularly relate to absence of legislation, policies, functional ethics committees (ERCs) and lack of capacity to undertake ethics review (human resources, training, funding). That’s was already established with regional study by (Kirigia and all (2003), Kirigia and Wambebe’s (2006), Milford et al’s (2006). In 2007, WHO/AFRO conducted a regional survey to describe the national health research information and knowledge systems including research ethics in 46 countries across Africa to be presented in Algiers 2008 and Bamako 2008.

Methods In 2007, two surveys were administered by WHO/AFRO in countries across the region (Health Research Systems Analysis modules and a questionnaire sent directly to the Ministry of Health in 46 WHO/AFRO member countries)

Results

- Lack of legislation mandating attention to research ethics (concern that ethics procedures can therefore be ‘bypassed’)
- Encouraging that most countries in the Region report having a functional ethics committee
- However, some countries report not having either an ERC or SRC
- ‘Decentralized’ system of ethics review may lead to ‘fragmentation’, inconsistent operating procedures, ‘ethics review ‘shopping’
- Lack of policies and legislation requiring informed consent is a concern
- Relatively few institutions have mechanisms for conflict of interest (could undermine objectivity and independence)
- Training in ethics is limited and there is a lack of institutional support
- However, there are increasing capacity building initiatives in the region e.g. PABIN, SARETI, AMANET, IRENSA etc, as well as national workshops on research ethics.

Limitations

- Despite high response rate (43 (93%) of member countries responded (total= 634 institutions) and information received from respondents in 44 Ministries of Health (96%)), there were a number of gaps in responses to questions
- Criticism that the institutional instrument was too long (*borrowed from S. Johnson from LSTHM/UK*).

Points for discussion

- Links between ERCs and NRA ?
- Better knowledge and enforcement of domestic laws and regulations by all relevant stakeholders of research for health?
- Need for harmonization of norms without uniformity?
- Need for sub regional networking or making a good use of existing networks?
- Clinical trial registry national, regional, international?
- Quality assurance of ERCs: what are the criteria and modalities of evaluation?

4.3 The AIDS, Tuberculosis and Malaria Clinical Trials (ATM) Registry (Dr. Charles Shey Wiysonge, Project Manager, The ATM Registry)

The presentation provided answers to these questions: why was the AIDS, Tuberculosis and Malaria (ATM) Registry established? what does it offer? what is its future? The ATM registry is led by the South African Cochrane Centre and the Cochrane Infectious Disease Group, and funded by the European and Developing Countries Clinical Trials Partnership (EDCTP). The registry is the result of a concerted global effort to promote clinical trial registration and to harmonize all clinical trial registration activities. This

global movement was born at the Ministerial Summit on Health Research in Mexico City (November 2004), endorsed by The 58th World Health Assembly (May 2005) and promoted by the International Committee of Medical Journal Editors (since 2005). Despite the benefits of prospective clinical trial registration, few clinical trials in Africa were registered. The ATM Registry <http://www.atmregistry.org/> was therefore established to promote the prospective registration of clinical trials in Africa.

HIV/AIDS, tuberculosis and malaria together kill millions of people living in Africa each year, and the number of deaths and infections continue to increase by the second. There are already a large number of completed clinical trials evaluating interventions for these three diseases. However, with the current momentum to discover new ways to control these diseases it is anticipated that there will be a significant growth in the number of clinical trials investigating these diseases over the next few decades. The challenge will be to ensure that all of these trials are identified and that the trial information is made widely available in an open-access repository. This explains why during this initial phase of the ATM Registry (2006-2008), it is only registering trials in HIV/AIDS, tuberculosis and malaria to demonstrate proof of concept. Once fully established, the goal is that the ATM Registry will become the register of choice for all clinical trials, on any disease, in any country in Africa.

There are currently no other African registers, apart from the South African National Clinical Trials Registry, to meet the prospective registration needs of clinical trials conducted in Africa. The trial information contained in the ATM Registry will provide a rich source of information to describe the scope, quality, location, ethics and funding patterns of trials conducted in Africa. Such a resource and its analysis thereof are potentially valuable to those involved in research priority setting in Africa, especially pertaining to clinical trials. At the close of the pilot phase of the ATM Registry in July 2009, a comprehensive review of the scope, characteristics, ethics and funding sources of HIV/AIDS, tuberculosis and malaria trials conducted in Africa will be compiled and made available. If by then the ATM Registry gets WHO International Clinical Trials Registry Platform (ICTRP) primary register status, its scope will be extended to include clinical trials on all diseases. If by then, the ATM Registry does not get the primary register status, the project will terminate.

4.4 The South African Clinical Trial Register (Dr. Rajen Misra, Medicines Regulatory Authority , South Africa)

The South African (SA) Clinical Trials Register forms part of the international call to make trial info publicly available:

- ICMJE from 1 July 2005 will not publish trials unless included on research register
- WHO calls for public registration

-
- Global pharmaceutical industry released plans to make trial data publicly available

The benefits of SA Clinical Trials Register are:

- Promotes collaboration among researchers, the private sector & community through sharing research information
- Assists people to identify trials they can participate in
- Decreases pub bias & reduces duplication of research efforts
- Promotes best use of limited research resources
- Contributes to global efforts to reduce/eliminate disease
- Provides a forum to educate public on clinical trials
- Tool to monitor and manage clinical research in South Africa

The register will enable patients, family members, health professionals, industry and the public to access information on SA based clinical research studies

Who Registers?

- Sponsors are responsible for ensuring a trial is fully registered on SA Clinical Trials Register
- Unfunded trials – PI takes on the responsibility for registering
- Multi site / multi sponsor trials – lead sponsor
- Registration is done at www.doh.gov.za find shortcut link to Clinical Trials Register

What is to be registered?

- Full spectrum of clinical trials conducted in SA
 - ICMJE definition – “any research project that prospectively assigns human subjects to intervention and comparison groups to study the cause and effect relationship between a medical intervention and a health outcome”
 - ‘Medical intervention’ refers to any intervention used to modify a health outcome including drugs, surgical procedures, devices, behavioural treatments, process of care changes.
 - Registration requires trial has at least one prospectively assigned concurrent control or comparison group
- All trials must be registered but to ensure innovation / competitiveness is not compromised Phase I trial data will not be publicly recorded

Scope of the register

- The register requires all clinical trials to be registered
- This means all trials that do not require Medicines Control Council approval must register

-
- The prerequisite is that all trials must undergo ethical and scientific review
 - Only trials that have ethical clearance are considered for registration

What trial information is publicly available?

- Brief Title
- Recruitment Status
- Anticipated Start Date
- Anticipated End Date
- Gender
- Ethnicity
- Age
- Inclusion / exclusion criteria
- Contact Details

Update since the system commenced

- Registration started on the 1st December 2005
- There are close to 663 applications to date 27 10 2008
- Was 70 at last presentation 1 year ago

Updating the Register

- To ensure that the information available through the data bank is timely and accurate, it is asked that the sponsor/PI reviews, verifies, and updates all active protocol records on a **six-monthly basis**, at a minimum.
- The research team must confirm the starting date of the study.
- Information on trials unexpectedly closed (e.g. clinical hold) should be **updated within 10 days** after the closing or sooner (if possible).
- The sponsor/PI must also inform SA Clinical Trials Register of the trial completion date (i.e. date that analysis is concluded for the protocol), **within 10 days**, and provide a summary of findings within a year of study completion.

4.5 The link between National Regulatory Authorities and National Ethics Committees: case of Uganda (Helen B Ndagije, Head, Drug Information Department, National Drug Authority, Uganda)

- **What is NDA**

National Drug Authority (NDA) is the competent national regulatory authority in Uganda that was established to ensure quality, safe and efficacious human and veterinary medicines and other health care products through the regulation and

control of their production, importation, distribution and use. NDA was established by a statute of parliament in 1993 as a corporate body reporting to the Minister of Health and employs about 100 staff members.

- **Vaccine regulation in Uganda**

The scope of regulation also includes vaccines as well as drugs. The regulation of clinical trials in Uganda has evolved over time starting out from the model of the HIV vaccine and spreading out also to include drugs. Licensing of medicine outlets, issuing marketing authorisation and post-market surveillance are some of the measures taken to assure the quality of vaccines and medicines.

NDA works in close collaboration with Uganda National Council for Science and Technology (UNCST) in authorisation of clinical trials. The role of UNCST is to provide for oversight of policies that can foster scientific and technological development of the country. UNCST approves clinical trials among many other studies in collaboration with the Office of the President. The representation of UNCST on the NDA clinical trial committee has contributed greatly to the improvement in the regulation of clinical trials.

- **Progress**

Much progress has been made since AVAREF last year. NDA has developed guidelines for the conduct of clinical trials in Uganda through a consultative process which are in the process of being gazetted. Joint inspections between NDA and UNCST have also been conducted. EDCTP has supported UNCST to working out a system of accreditation of the 18 Institutional Review Committees (IRC) and to support networking of the IRC chairpersons.

There is still need for advocacy and proving awareness of NDAs role in regulation of clinical trials. The collaboration between NDA, UNCST and IRCs needs to be strengthened. A training gap for members of clinical trial committee still exists.

Expectations and recommendations

- We hope to have more Good Clinical Practice Inspections conducted especially prior to the starting of trials. strengthening the link between AEFI surveillance and the national pharmacovigilance system will also go a long way in promoting integration of the regulation of vaccines and medicines.

4.6 The link between National Regulatory Authorities and National Ethics Committees: Zimbabwe (R. Kuwana, Medicines Control Authority of Zimbabwe)

- **Legislation**

Two principal legislation is used:

1. Medicines and Allied Substances Control Act (since 1969) + Regulations – provides for
 - Establishment of a medicines regulatory authority, the *Medicines Control Authority of Zimbabwe*
 - Registration of medicines
 - Licensing and Control of premises and persons handling medicines.
 - Control of clinical trials* (in collaboration with the Medical Research Council and Department of Veterinary Services).
 - Procedure for handling prohibited drugs and
 - General provisions.
2. Medical Research General Notice (Regulations) of 1974
 - establishes the Medical Research Council of Zimbabwe

- **Responsibilities of the two statutory bodies**

MRCZ – National Ethics Review Board, controls all clinical trials

MCAZ – Science and Ethics. Has oversight only over trials that involve use of a medicine(s)

- **Shared responsibilities:**

- Share representatives at each other's Board and Technical Advisory Committees
- Joint meetings with stakeholders or investigators when concerns are shared e.g. Pre – submission meetings, or investigation of non compliance by an investigator
- Joint Trial site inspections – each focuses on mandated matters
- Review of SAE reports – causality assessment using a joint review committee
- Joint training – as trainees for common understanding of GCP requirements and as facilitators to train investigators

4.7 The link between National Regulatory Authorities and National Ethics Committees: case of The Gambia (Markieu Janneh-Kaira)

Progress made in the regulation of clinical trials

-
- Legal framework for regulation of Medicinal Products of 1984 did not include regulation of CT but this has been revised and updated to include regulation of Clinical Trials since 2006.
 - Development of Guidelines/ regulatory procedures:
 - -Submissions of CT
 - -Regulatory review of submissions
 - -Importation & release of clinical batches of vaccines
 - CT applications submitted to Scientific Committee (SC) or Ethics Committee (EC)
 - Review and approval given by the SC and Ethics Committee
 - Authorization of CT without knowledge of NRA - usually not involved in process but this is now improving
 - Better collaboration between the EC and the NRA
 - Capacity building in CT regulation including joint review of protocols and joint GCP inspection. These joint reviews are facilitated and coordinated by WHO
 - This has led to the first independent GCP inspection conducted by NRA inspectors

Models for achieving a regional platform for trial registration

4.8 Developing a common platform for clinical trials registration in Latin America and the Caribbean (Renato Murasaki, BIREME)

BIREME is a PAHO Specialized Center, established in Brazil since 1967, in collaboration with Ministry of Health, Ministry of Education, Secretary of Health of the State of São Paulo and the Federal University of São Paulo. The mission of BIREME is to contribute to the development of the health in Latin America and the Caribbean countries by the promotion of the use of the scientific and technical health information. This mission is supported by the Virtual Health Library development in the Region, including other networks such as SciELO, ScienTI, ePORTUGUESe and the Global Health Library.

BIREME/PAHO/WHO proposal is to develop a common platform for clinical trials registration in Latin America and the Caribbean with the following scope:

1. the development of a common clinical trial registry platform applicable at country and regional levels following WHO ICTRP criteria
2. operation of a LA&C Regional Clinical Trials Registry intended to be a WHO primary registry, interoperating with national registries
3. development of the project under the open source modus operandi

4. a service model to host the operation of national and regional registries, according local needs and technology infrastructure

5. a sustainable model for technical cooperation to support the adoption and usage of the platform according the national and regional conditions.

This proposal may also be applied for other regions and countries, considering South-South cooperation as well.

In 2009, BIREME/PAHO/WHO will participate in the development of a brazilian clinical trials registration platform, in cooperation with Brazilian Ministry of Health and other national institutions.

4.9 Models For Partnership In Health Research (Dr. Andrew Y. Kitua NIMR- Tanzania and European and Chairperson, Developing Countries Coordinating Committee (DCCC) of EDCTP).

Partnership can be defined as individuals or groups who share something or own something in common. Partners of a Business company or organization share the RISKS and PROFITS of the business and trust each other.

Bad partnership is when there is imbalance in the shares such that one or more of the partners takes greater share of the risks or the benefits. It is when there is exploitation and mistrust between the partners or a situation whereby the relationship becomes that of a labourer and owner.

The best model of partnership has 11 principles namely:

1. Decide on the objectives together
2. Build on mutual trust
3. Share information, develop networks
4. Share responsibility

5. Create transparency
6. Monitor and evaluate the collaboration
7. Disseminate the results
8. 8. Apply the results
9. 9. Share profit equitably
10. 10. Increase research capacity
11. 11. Build on the achievements

Reference: Swiss Commission for Research Partnership With Developing Countries. KFPE -1998

<http://www.kfpe.unibe.ch>

4.10 Recommendations from Discussion Group 2 (Satellite 2)

The Integration of ethical review, regulation and registration of CTS should take the following into consideration:

- Developing a centralized clinical trial registry
- Put checks in place to control access to CT registry to ensure confidentiality
- Development of Quality Assurance systems for ECs and regulatory authorities
- Training for EC and NRA members and investigators
- Establish stronger collaboration between NRAs and ECs in the review and approval processes.
- More joint reviews needed to enhance capacity within the ECs .
- Harmonization of activities of ECs at country levels and hoping to extend it to regional level
- Sub regional networking, networking of ECs in countries
- Need to disseminate knowledge of domestic laws and regulations to guide ethical conduct of CTs
- Enhance information sharing among different countries
- Develop guidance documents for regulators
- Should enforce mechanisms towards establishing common principles towards harmonization of relationship between ECs and NRAs
- Documentation of final outcomes/ decision making at all levels within the review process.
- Defining criteria on how to link independent review to the national ethical committee
- Defining relationship/ working arrangements of DSMBs and regulatory authorities.

Vision

- Creation of functional collaborative network for approval and oversight of medicines/vaccines interventional clinical trials in Africa.
- Network will work towards compliance with international ethical and regulatory standards, bearing in mind specific conditions and needs in Africa, to assure the safety and well being of trial subjects and validity of generated data. This network will also facilitate the conduct of good quality clinical trials in Africa by sharing information, benchmarking on positive examples and capacity building. Network will promote good research and regulatory practices and contribute to elimination of unnecessary regulatory barriers. Although National regulatory authorities and Ethics Committees/Institutional Review boards are key players in the network, it is recognized that close co-operation with other stakeholders like sponsors,

investigators, patient and international organizations is important to complete the vision.

- Harmonized regulatory standards, a common clinical trial registry, co-operation on oversight of clinical trials and pharmacovigilance, transparency and continual effort to build mutual trust are most important instruments to achieve the vision.

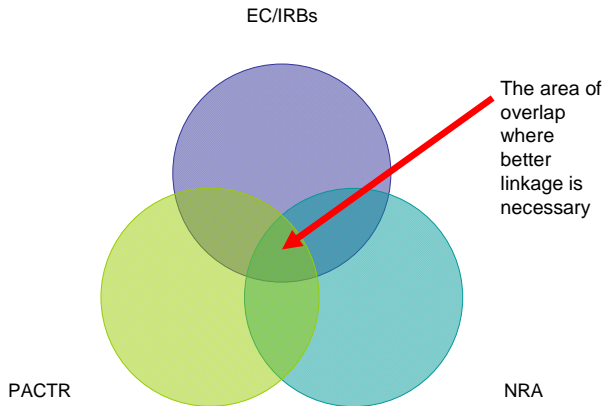
Key elements

1. Responsibility to research participants
2. Address the challenges posed by the continuously evolving research environment
3. Capacity building
4. Compliance with international standards
 - ICH, Declaration of Helsinki, WHO, CIOMS, ICMJE
5. Improve link between EC/IRBs and NRAs
 - A regional registry is the link
6. Information exchange

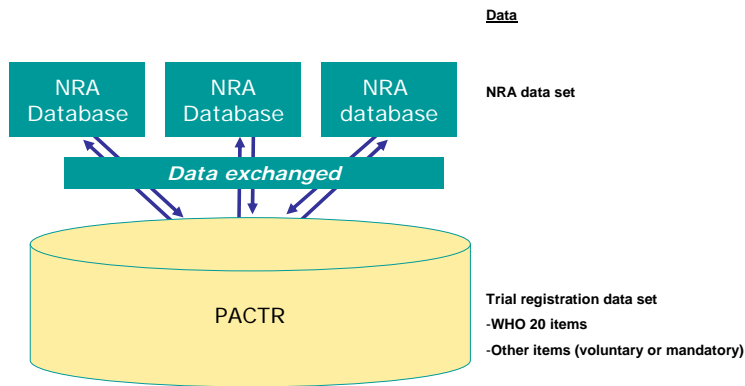
Justification (why key elements are needed)

- Common platform
 - For joint review
 - Registration
 - Other sharing
- Better coordination of mandatory clinical trial authorization decisions
 - One stop shop for all stakeholders
- All protocols submitted should be registered in a WHO Primary Registry before submission to the NRA or EC/IRB.
 - However needs a tracking system (publicly accessible audit trail)
- Need to identify gaps and set research priorities
 - Understand areas that have either been over or under researched
- Ethical responsibility to study participants
- Need to comply with internationally accepted standards
- To address the issue of EC/IRB and NRA “shopping”
- To address concerns regarding conflict of interest and its potential impact on decision making
- To strengthen communication between NRAs and EC/IRBs
- Environment that will attract sponsors.
 - Need to conduct trials in right conditions and produce valid outcomes
- Need for agreed definitions
 - Of stakeholders
 - Of roles and terms
 - Of responsibilities
 - Responsibility for registering trial

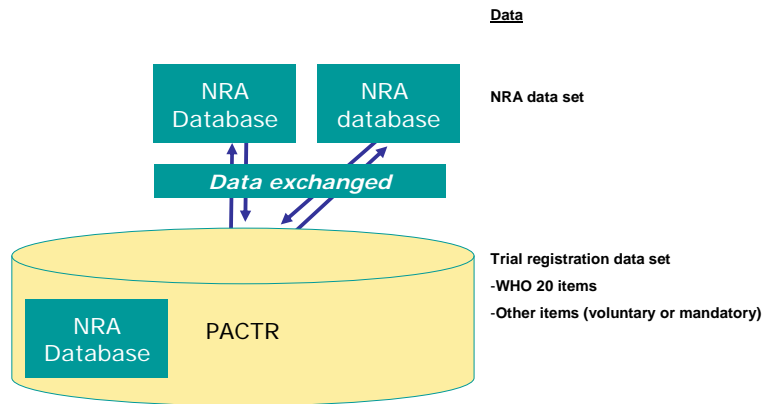
- Responsibility for notifying registry of NRA decision / EC decision / etc
- For data quality



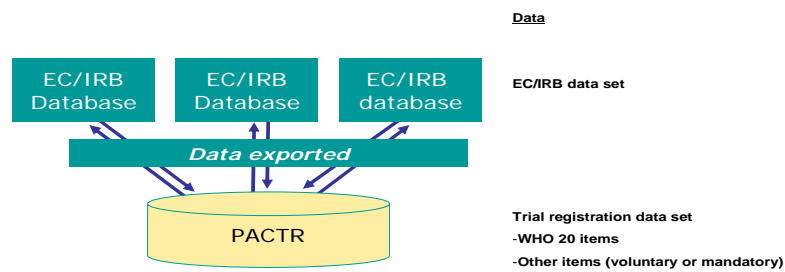
PACTR-AFRO NRA data sharing model Intermediate solution



PACTR-AFRO NRA data sharing model Longer term solution?



PACTR-AFRO EC/IRB data sharing model



This proposed strategy

- Provides flexibility in models but not compromising standards
 - Allow for different data flow models (eg)
- NRA needs to ensure the integrity of the data submitted to it, and that decisions it makes are entered onto to the Registry

-
- Eg protocols that are rejected
 - National legislation necessary to enforce
 - Need reliable mechanisms for data exchanged (eg between registry and NRA)
 - Registry provides minimum data (WHO 20 items) to NRA/ECs (eg paper or electronic)

The proposed milestones are as follows:

Establish working group	Oct 2008
Expand the scope and rename the ATM Registry (eg PACTR)	Nov 2008
First draft strategic plan	12 Nov 2008
Prepare concept paper	12 Nov 2008
Circulate strategic plan and concept paper to working group	13 Nov 2008
Present concept paper at Bamako Ministerial Forum	17 Nov 2008
Working Group to agree on processes it will follow (meeting frequency, circulation of minutes, etc)	Dec 2008
Working Group to agree on minimum modifications that need to be made to ATM Registry database in order to address short term need	Jan 2009
ATM make changes to database	Feb 2009
Agree on pilot projects <ul style="list-style-type: none"> • South Africa; Uganda; Other 	Mar-Jul 2009
Prepare and submit manuscript for publication (recognizing need)	Jan 2009
Finalize strategic plan	Jan 2009
Approach potential funders	Feb 2009

5. Harmonization of drug and vaccine clinical trial regulation in Africa

5.1 Use Of Structures, Resources And Procedures For Regulation Of Drug And Vaccine Trial Oversight (Dr R N Misra, Clinical Evaluations & Trials Directorate , Medicines Regulatory Authority of South Africa)

Medicine Regulation in South Africa is conducted via a cluster in the National Department of Health which has four Directorates. It consists of the Inspectorate which deals with the Good Manufacturing Practice (GMP), Pharmaceutical and Analytical which looks at the Quality aspect of the medicine. Then there is Clinical Evaluation and Trials which is in charge of approving the clinical trials, accessing the data results in the clinical unit and establishing the balance between safety and efficacy for market authorisation, and the Pharmacovigilance unit which looks at post marketing surveillance. Finally there is an Operations and Administration directorate which coordinates all the activities. This cluster acts as a secretariat to the independent Medicine Control Council (MCC) which consists of 24 part time experts in various fields as spelt out in the Medicines and Related substances control Act, Act 101 of 1965. They operate via 10 specialised committees who make recommendations to Council.

The regulatory framework is controlled by

- ACT 101 of 1965, the Medicines and Related Substances Control Act (Sect 21): control over use of unregistered medicines → review, approval and monitoring of clinical trials and the special access approval
- The act also is the basis of registration of a medicine and vaccine
- Evaluation of clinical data is approved by Clinical Committee (in consultation with Biological Committee in the case of vaccines)
- Post marketing monitoring is reviewed by Pharmacovigilance committee.

- Sect 21 Of ACT 101 specifically allows for:
 - Approval of usage of unregistered medicine or microbicide
 - Situation one: special access or named patient usage for emergency cases or if contraindication to use of registered medicine
 - Situation two: Usage in a clinical trial subject to MCC and Ethics committee approval.

The clinical trial committee (CTC) was established by Minister of Health and provides regulatory framework for the review of clinical trials. It reviews and recommends approval of the conduct of clinical trials, ensures safety and protection of rights of patients. It works closely with the Pharmacovigilance committee which reviews adverse

events (AE) reports for clinical trials (CT) and with GCP inspectors. The expertise of the CTC, include:

- General medicine, toxicology, oncology, psychiatry, pharmacology, biostatistics, pharmacokinetics, virology, microbiology,
- Public health, epidemiologist, paediatrics, haematology, palaeontology, cardiology, immunology

The role of the MCC in Clinical Trial regulation is to provide mandatory authorisation and therefore no clinical trial may commence before approval by both MCC as well as the local Ethics Committee. The MCC is the only body that can exercise regulatory control over the conduct of clinical trials and it ensures the universal principles of autonomy, beneficence and justice is respected. MCC has the authority to terminate a clinical trial where there is evidence of GCP violations.

In the approval of Clinical trials the MCC considers the following aspects:

- a. Scientific rationale
- b. Safety and
- c. Ethics
- d. Does the trial contribute to new scientific knowledge?
- e. Is it scientifically appropriate, plausible?
- f. Is it ethical, relevant and can patient safety be assured?
- g. When the trial is undertaken in South Africa the subjects should benefit from the results of the research and to ensure that they are appropriately informed of the risks.

For SCIENTIFIC RATIONALE one considers the following:

- Does the trial contribute to new scientific knowledge?
- Is it plausible and scientifically appropriate?
- Optimal study design
- Should the trial be conducted in the RSA
- Is there adequate PRECLINICAL evidence of safety and efficacy and stability of product and formulation?

In assessing safety the following considerations are made:

- Balance of risks versus benefits
- Is there adequate data from pre-clinical studies?
- Are the animal models used appropriate?
- Is there adequate monitoring in place? DSMB
- Pharmacovigilance and GCP inspection reports
- Is safety stipulated as an objective?
- Has adequate attention to GMP and formulation and stability of trial product manufacturing and scale up process. Certificate of analysis for investigational lot.

NEW STRUCTURE

-
- SAHPRA –South African Health Products Regulatory Authority.
 - Paperless system.
 - In-house capacity building and internal reviews to keep to time lines.
 - Parastatal Entity with retentions of fees.
 - Market related remuneration to attract and retain appropriate skills –private sector and developed world.

HARMONISATION OF CLINICAL TRIALS:

- Details of the informed consent process and quality assurance of the process with special reference to concept of placebo and randomisation
- Need SOP of process and focused groups discussions and details of community consultation and involvement especially in relation to HIV Vaccine trials
- All previous phases data –positive and negative
- Referral to the basic science and natural immunity process
- Process of managing patients who test positive at the screening or any time during the trial in HIV Vaccine trials
- Risk of over-researching a particular community and steps to ensure full spectrum of population
- Precautions taken when vaccine are ineffective and what follow will occur in patients who will not have immunity
- Ethics of doing trials in infants and appropriate informed consent

Clinical Trial Application Process

- SCREENING CHECKLIST_.doc
- CTF1 May03 v1.doc
- Completing CT applications May03 v1.doc

These are on website www.mccza.com.

MRA clinical trials process:

- Reception, Screening and Response
- Evaluation process and Preparation for CTC meeting
- CTC meeting, Response from Applicants on Recommendations and MCC meeting

The entire process must be completed within the 8-week cycle of CTC and MCC meetings.

Clinical Trial Database – an NRA administrative tool, in MS Access was demonstrated.
([MCC Clinical Research Database.mdb](#))

5.2 Existing and planned regional activities concerning regulation of clinical trials (Dr. Margaret Sigonda, National Regulatory Authority of Tanzania)

Activities related to regulation of CT in the region are done through regional harmonization initiatives

- These include:
 - Southern Africa Development Community (SADC)
 - East African Community (EAC)
 - East, Central & Southern African – Health Community (ECSA-HC)
 - African Vaccine Regulatory Forum (AVAREF)
- SADC
 - Developed draft guidelines for clinical trials of medicines
 - Developed specific guidelines for clinical trials of ARVs
- EAC
 - Agreed to develop CT guidelines
 - Planned joint training in evaluation & inspection of CT (long term)
- AVAREF
 - Developed CT guidelines for vaccines & biologicals
 - Developed template for evaluation/review of CT vaccines & biologicals

5.3 Complex Regulatory Systems and Regulatory Harmonization from Regulator Point of View (Dr. Immanuel Barth, Paul Erlich Institute, Germany)

After more than a decade of discussions about the need and content of an harmonized approach to clinical trials in Europe the "*Directive 2001/20/EC on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use*", the "GCP-Directive", had been enacted on April 4th, 2001. The Directive was adapted and published as regulations and administrative provisions by each EC member state and enacted in national law the latest by May 1st, 2004.

The GCP-Directive applies to all Phase I to IV trials intended to investigate clinical, pharmacokinetic or pharmacodynamic effects of investigational medicinal products and to identify any adverse reaction.

Before the May 1st 2004 the previous system in Europe consisted of 15 national independent approaches with National Regulatory Agency notification and approval of clinical trials by the ethics committee.

As of the May 1st 2004 in the new system presently there are 27 national approaches with a common minimal regulatory basis as defined by EU directives and guidelines which are implemented in national laws, ordinances, decrees of costs etc of each member

state. The approval remains a national issue, even if the application has been submitted in all European countries in parallel.

Advantages of the new system include:

1. Ethic committee and Competent Authority can work in parallel
2. Core Dossier and application form are valid / defined for all countries
3. Guidance on content of dossier, forms, SUSAR-reporting, etc
4. Defined CTA processing time lines (average 14-60 days)
5. Transparency through EudraCT data base of all Clinical Trials in Europe for NRAs

A disadvantage may be that there are still many national regulations

For Non-EU countries the following advice options in the EU may be considerable:

1. According to Regulation 726/2004/EC Art. 58 the EMEA may give a scientific opinion, in the context of cooperation with the World Health Organization, for the evaluation of certain medicinal products for human use intended exclusively for markets outside the Community. Articles 6-9 specify a submission to the EMEA.
2. Furthermore a new framework for Scientific Advice and Protocol Assistance was established by the EMEA. Further details may be retrieved from the EMEA homepage <http://www.emea.europa.eu/pdfs/human/sciadvise/426001en.pdf> under
3. As far as EU national regulatory agencies are concerned, scientific advice may facilitate advantages for the pharmaceutical developer (optimization of the development programme, learning on national requirements, agencies experience, early identification of problems) as well as advantages for the agency (experience, internal planning, triggering new guidelines, etc). Pre-submission advice meetings tend to be more effective than ad hoc meetings during the review process

Some of the relevant EU-Documents:

- Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use
- ENTR/CT 1 Revision 2: Detailed guidance for the request for authorisation of a clinical trial on a medicinal product for human use to the competent authorities, notification of substantial amendments and declaration of the end of the trial
- ENTR/CT 2 Revision 1: Detailed guidance on the application format and documentation to be submitted in an application for an Ethics Committee opinion on the clinical trial on medicinal products for human use

-
- ENTR/CT 5 Detailed guidance on the European clinical trials database (EUDRACT Database)
 - ENTR/CT 3 Detailed guidance on the European database of Suspected Unexpected Serious Adverse Reactions (SUSAR) (Eudravigilance - Clinical Trial Module)
 - And others on the web sites:
 - http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/eudralex_en.htm
 - <http://ec.europa.eu/enterprise/pharmaceuticals/pharmacos/new.htm>
 - Directive **2005/28/EC** laying down principles and detailed guidelines for good clinical practice as regards investigational medicinal products for human use, as well as the requirements for authorisation of the manufacturing or importation of such products

5.4 Harmonization of drugs and vaccine trials regulation and good regulatory practice from the point of view of sponsors (Mrs Marie-Chantal Uwamwezi, GSK Biologicals delegate for IFPMA)

The purpose of the presentation was to bring the perspective of clinical trials sponsors, who are often from research-based pharmaceutical companies, on the regulation of clinical trials in Sub-Saharan Africa.

The International Federation of Pharmaceutical Manufacturers & Associations (IFPMA) is a global non-for-profit and non-governmental organisation representing research-based pharmaceutical, biotech and vaccine manufacturers. Its main objectives include;

- to encourage a global policy environment that is conducive to innovation in human medicinal products (drugs and vaccines, therapeutic or preventive) for the benefit of patients around the world;
- to contribute industry expertise and foster collaborative relationships and partnerships with international organizations, national institutions,... dedicated to the improvement of public health, especially in developing and emerging countries.

In relation with the above objective, IFPMA ensures the secretariat for the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) which promotes harmonisation in the interpretation and application of technical guidelines and requirements for medicinal product registration in order to expedite research and development of new medicines.

With respect to clinical trials, the responsibilities of sponsors as delineated in ICH guidelines for Good Clinical Practices (ICH E6) were reminded. The challenges in selecting sites for the more and more frequent multi-national multi-centre trials were summarized, with emphasis on those encountered for trials in Sub-Saharan Africa.

Regarding the regulatory oversight of such trials, two aspects were further discussed, the process for their regulatory approval and the requirements for safety reporting. Currently; the main problem sponsors face relating to NRA authorization of clinical trials is the lack of defined timelines for application review which hinders planning. In addition, documents on regulatory requirements for clinical trials are not easily accessible to the public (e.g. no or very limited publication on Internet) which brings about a risk of non-compliance.

Concerning safety reporting, sponsors face divergent requirements from Sub-Saharan African countries with respect to the scope of SAEs requiring expedited reporting and with respect to reporting timeframe, which can lead to confusion and non-compliance.

Most countries request reporting of all domestic SAEs regardless of causality assessment which is not in line with ICH E2 recommendations. Because the international standardized form (CIOMS I) for expedited reporting of SAEs was not designed for that, there is also divergence in the format of the initial reports which are often amended by follow-up reports leading to poor quality of information and lack of perspective on meaningful safety signals for a given medicinal product.

Research-based pharmaceutical industries invest significantly in the development of new medicinal products and in doing so, have at heart the preservation of patient's safety and rights. In the area of clinical trials regulation, it would be a good practice for small NRAs to learn from the experience, particularly for guidelines development, from other larger and more resourced agencies such as the European Medicines Agency (EMA) Committee for Human Medicinal products (CHMP) or the US Food and Drugs Agency (FDA).

From the sponsors' viewpoint, clinical trials would be greatly facilitated if the following were in place:

- A clearly defined regulatory procedure for clinical trial authorizations & easily accessible to sponsors with :
 - 1) Defined procedural timelines for application review
 - 2) Clearly described regulatory requirements including for regulatory documentation appropriate to the type of product and its development phase,
 - 3) Core document gathering requirements for both vaccines and drugs or any other medicinal product
- Opportunities for interaction, communication with sponsor on general requirements for clinical trials as well as opportunities for consultations/advice prior to the conduct of specific trials (for example pre-submission meetings).

With respect to safety reporting, African NRAs should consider alignment with internationally recognized practices (ICH E2 and CIOMS). This would ensure, for sponsors, better compliance and improved clinical trial planning while ensuring that medicinal product development meets NRAs expectations. Ultimately, this would expedite patients access to potentially life-saving new medical interventions as their development is a long and complex process.

With more and more clinical trials to be conducted in Africa, this is a unique opportunity for countries to make regulatory environment more conducive to such trials. IFPMA is ready to partner with African NRAs and contribute its expertise to capacity building in the area of medicines regulation; in collaboration with WHO.

The following points were raised during the discussion:

- It was commented that the general principles presented with respect to best practices and harmonization of regulatory processes made sense, however such endeavours are difficult to put in practice. Nevertheless, it was agreed that NRAs should avoid unnecessary barriers to drugs development. NRAs, sponsors and other stakeholders in medicinal product development have as a common goal to ensure access to drugs and vaccines particularly for vulnerable populations.
- With respect to SAEs reporting, some NRAs and ECs representative stated that they could not completely trust the investigators ability to establish in a totally independent fashion, the potential for causal relationship with medicinal products. Hence by receiving all SAEs regardless of investigators assessment, signals and trends could be picked up. It was also asked if it could be considered to have a 3rd party to assess causality of SAEs.

Answer:

SAEs monitoring and reporting during clinical trials is not entirely the responsibility of investigators, there are local independent safety monitors often appointed to oversee all aspects of safety monitoring. In addition, more and more trials have an independent Data Safety Monitoring Board (DSMB) or Independent Data Monitoring Committee (IDMC) , that review safety information on an unblinded fashion during trials and help detect potential safety signals. These 3rd parties do not have potential conflicts of interest like investigators.

- Lastly, it was commented that the contribution/participation of developing countries NRAs to the ICH process should be enhanced. SADC is currently a member of the Global Coordination Group of ICH however because of its rotating chairmanship, it was difficult for SADC countries to make the most of harmonization initiatives.

The IFPMA delegate agreed to convey this message for a need to consider ways to better integrate African NRAs in ICH/GCG processes.

5.5 Recommendations from Discussion Group 3 (Satellite 3)

5.5.1 Key elements

The key elements to optimize the use of resources at the national level for the oversight of clinical trials of drugs and vaccine are:

-
- Legislation: baseline law specific in each country/ Guidelines documents on regulation
 - Common technical requirements and application procedures
 - Development of National Database with key elements and limited access to ensure confidentiality and password
 - Capacity in each country
 - One common entry point for applications
 - Information sharing and networking: in country and at regional level– need of website
 - Model MoU template document on information sharing

5.5.2 Advantages of harmonized regulatory guidance documents for all processes relevant to oversight of clinical trials

- Learning from each other;
- Best compliance (harmonized regulatory guidance improve compliance)
- Prevent shopping issue
- Help health system perspectives : enhance access to medicines
- Cost effectiveness for regulatory
- Standardized procedures (No ad hoc decision)
- Recognition of the basis of approval to enhance decision making process.
- Exchange of information between regulatory agencies
- Improve (Facilitate) capacity building
- Improve efficiency
- Promote transparency
- Better utilization of resources

5.5.3 Disadvantages/threats/challenges

In fact, no disadvantages were found, but challenges:

- Loss of local identity(some specific issues are not addressed)
- Existing of national regulations
- Financial issues: it is a costly exercise (Harmonization can increase cost for some countries).
- Inadequacy in capacity

5.5.4 List of documents that can be proposed for common use in the region

1. Common guidelines on:
 - submission of CT
 - content of application
 - database
2. Common Evaluation documents on: screening form and evaluation of application
3. Process flow chart
4. Model template approval for CT

-
5. Pre submission meeting
 6. Common documents on CT inspection (GCP inspection documents)
 7. Safety monitoring of CT (SAEs reporting document)
 8. Guidance on information needed for IMPD
 9. Prequalification for application
 10. Model MoU
 11. Model legislation

5.5.5 Plan for optimization of resources in the region with regards to evaluation of clinical trial applications and inspections

1. Identify resources in the region (in each country) and share information in terms of:
 - *Human resources*
 - *Expertise*
 - *Sharing information for a common understanding*
2. To create a structure for sharing information and expertise(VPN)
 - Joint review/Joint assessment of application
 - Intercountry evaluation committee coordinated by WHO
3. Framework for consultation and MoU

5.5.6 Types of capacity building activities sponsored by WHO that should be done in common for drug and vaccine trials and those that should be done separately

- Joint inspection
- Training

5.5.7 List of required training

1. GCP training on CT
2. CT Evaluation
3. CT Inspection
4. GMP on IMP
5. Safety monitoring/Pharmacovigilance
6. Medical devices
7. Safety monitoring/Pharmacovigilance
8. Quality management of CT oversight
9. Database development and use
10. Development of CT regulations
11. Ethics training

PLAN OF ACTION/ RECOMMENDATIONS FOR COUNTRIES AND FOR WHO

Action point	Activities	Timeline	Responsibility	Remarks
1. Baseline survey for all AVAREF countries	1.1. Develop assessment tool	Short term	WHO	
	1.2. Conduct survey on regulatory framework	Short term	WHO	
	1.3. Survey on capacity and availability of expertise within AVAREF Countries	Medium term	Countries/WHO	
2. Information sharing and networking	2.1. Each country to develop or improve on their webpage with link to WHO	Short term	Countries	At national level
	2.2. Formalize information sharing /MoU between countries within AVAREF	Long term	Countries/ WHO	At Regional level
	2.3. Shared network platform (VPN= <i>Virtual Private Network</i>)	Short term	WHO to coordinate	
	2.4. Sharing information among NRAs where CT are on going	Medium term	Countries	
3. NRAs to establish timelines for CT process	3.1. identify processes that requires timeline	Short term	Countries	
	3.2. Validate timeline and publish	Medium /Long term	Countries	
4. List the common technical doc	4.1. Formalize a task team (WHO, IFPMA, EMEA, Canada, AVAREF countries)	Short term	WHO/ Countries	
	4.2. Complete/revise the List of common technical doc	Short term	Task team	
	4.3. To Develop/ adapt docs	Medium /Long term	Task team /countries	
5. Training	1. GCP training on CT 2. CT Evaluation 3. CT Inspection 4. GMP on IMP 5. Safety monitoring/ Pharmacovigilance 6. Medical devices 7. Q. Manag. of CT oversight 8. Database dvpt and use 9. Ethics training 10. Dvlpt of CT regulations	Short term	WHO/Countries with capacity should offer training e.g. SA	
6. Joint review and inspection	6.1. Countries with applications to join review	Short to Medium term	- WHO to coordinate - Sponsors to facilitate - Countries to facilitate - WHO provide secretariat	
	6.2. Intercountry evaluation committee	Long term		

6. Country Progress reports

6.1 Burkina Faso (Amadou Koumare)

Current status

A National Ethics Committee for health research has been created by presidential decree. The composition of this Committee is under review.

The National Regulatory Authority, in collaboration with the Ethics Committee, develops guidelines and procedures relevant to the authorization and oversight of clinical trials.

Prior to this, in September 2007, a coordination meeting among the different parties involved in the application and regulation of clinical trials has considered the following points:

- Draft text for the regulation of clinical trials
- Content of the application for clinical trial authorization
- Order of submission of dossiers
- Delay in the response after the recommendation by the Ethics Committee
- Application fees

The following parties were present: NRA, research centers, Direction of Prevention by immunization, Direction of studies and planning, Legal Counsel of the Minister of Health.

Capacity Strengthening

A course on good practices (clinical, laboratories and manufacturing) has been organized in February 2008.

Un cours national sur les bonnes pratiques (cliniques, de laboratoires et de fabrication) a été organisé en février 2008. The participants were:

- 5 persons from the NRA
- 3 persons from the Ethics Committee for health research
- le comité nationale d'éthique pour la recherche en santé
- 1 person from the Direction of Prevention by immunization
- 1 person from the Direction of studies and planning
- 2 representatives from the research centers

Pharmacovigilance

A workshop has been organized in May 2008 to prepare a biennial plan 2008-2010 for the implementation of pharmacovigilance

Plans for 2009

It is expected that the regulations relevant to clinical trials will be adopted and we hope to implement a program of coordination of inspections. The main tool to be used is the inspection checklist prepared by WHO

The inspections will include general health inspection services, the NRA and the Ethics committee.

6.2 USFDA (Dr. Rosemary Tiernan, Division of Vaccines and Related Product Applications Office of Vaccines Research and Review (OVR), Center for Biologics Evaluation and Research (CBER), FDA)

Dr. Tiernan reviewed the following topics:

- 1) The new FDA Guidance for Industry dated September 2008, entitled “General Principles for the Development of Vaccines to Protect Against Global Infectious Diseases” is now “Ready for Implementation”. This guidance outlines regulatory pathways for development of vaccines to treat diseases or conditions in endemic areas outside the U.S. Highlights of the guidance include that FDA will accept foreign clinical trial data, FDA encourages trials overseas to be conducted under the US IND process, however, if studies overseas are not conducted under US IND then evidence of Good Clinical Practice and an Ethics Committee should be demonstrated.
- 2) New US Legislation was passed in September 2007 which is called the FDA Amendments Act (FDAAA 2007). Congress includes section 524 in this new law which encourages development of products to prevent and treat certain tropical diseases affecting millions of people throughout the world. Consequently, FDA has released a Draft Guidance for Industry dated October 2008: “Tropical Disease Priority Review Vouchers” outlining waiver eligibility for a product that includes:
 - Must be listed for tropical disease
 - Must be submitted under section 505 (b)(1) of the Act
 - Must contain no active ingredient (including any ester or salt of the active ingredient) that has been approved in any other application under section 505(b)(1)
 - Must be submitted after the enactment of FDAAA (September 2007)
 - Must qualify for a priority review (see below)

More details regarding the Tropical Disease Priority Waiver are addressed in the October 2008 draft guidance:

- User fees also apply to tropical disease applications but some of these drugs may qualify as “orphan drugs”(rare disease or condition) and may qualify for exemptions from application fee
- Products regulated by CBER are eligible for priority review if they provide a significant improvement compared to marketed products in the treatment, diagnosis or prevention of a serious life-threatening disease.
- Priority review is a 6 month review of an entire BLA from the time the last section is submitted (instead of usual review time of 10 months).

Tropical Diseases that would qualify for a priority disease review voucher include:

- Blinding trachoma
- Buruli ulcer
- Cholera
- Dengue/Dengue Hemorrhagic Fever
- Dracunculiasis
- Fascioliasis
- Human African trypanosomiasis
- Leishmaniasis
- Leprosy
- Lymphatic filariasis
- Malaria
- Onchocerciasis
- Schistosomiasis
- Soil transmitted helminthiasis
- Tuberculosis
- Yaws
- Any other infectious disease if no developed nation market and affecting poor or marginalized populations

- 3) Dr. Tiernan discussed that US FDA is participating in the WHO prequalification process where vaccines approved by FDA e.g. RotaTeq® (rotavirus) and Gardasil® (human papillomavirus vaccine) can be procured and distributed through the WHO.
- 4) Dr. Tiernan described an FDA training initiative that took place recently in Rockville, Maryland in October 2008. This was an FDA Training Program for International Regulators in which the Center for Drug Development (CDER) and Center for Biologics (CBER) participated.

6.3 Belgian regulatory Authority/EMEA (Pieter Neels)

Action Points promised at the 2nd AVAREF meeting in Burkina Faso Ouagadougou:

EMEA will look at the following:

-
1. Assess possible ways to help AVAREF countries with capacity building
 2. Harmonize procedures for European products with trials in Africa to exert better control
 3. Possible ways to help with CT evaluation

Point one and three are the same. Since AVAREF II, two joint WHO -EU initiatives have been planned and started: the joint review of an anti-malaria MA application with 7 African countries in Geneva and a joint review of an anti-malaria vaccine CTA with again 7 (not all the same) African countries during the AVAREF III meeting.

Some organisational hurdles have been taken: it is not evident to convince management of these initiatives: budget, work floor, back-log,

The EU participants however do consider these initiatives as very positive, as it is a win-win situation: discussions on dossier content is enriching as there is often more than one way to look at a given data set.

1. Paediatric Regulation in the EU: A success or a nightmare?

The last year a new legislation came into force at the EU, in order to oblige industry to develop the use of new medicines in paediatrics.

For new products the Applicants are invited (practical joke, it is an obligation) to submit very early –after finalising phase 1 of the development- a PIP (Paediatric Development Plan). This PIP is judged by the new PDCO (Paediatric Committee) and should be approved. The paediatric development should start after the data are available that the new medicinal product is safe in adults. Also the PIP should not delay the development of the product in adults.

The company can ask for a waiver for certain or all age categories if it is felt that a paediatric development in these age categories is useless (e.g. an Alzheimer product) or the company can ask for a deferral: postponement of the research in certain age categories.

Within this new legislation the Applicants are obliged to fully elucidate all planned clinical trials in the PIP, wherever the trials will be executed.

It is felt that this new legislation is a significant step forward, however the additional work this legislation brings to the regulatory bodies in the EU is substantial and many issues are still under debate.

6.4 Update on Health Canada's Initiatives in support of AVAREF (Mr. Kwasi Nyarko, Centre for Policy and Regulatory Affairs, Biologics and Genetic Therapies Directorate, Health)

This presentation provided an overview of Health Canada's mission for Canadians, the legal basis for regulatory oversight on food and drugs, clinical trial in general and specifically clinical trials involving vaccines.

Following the AVAREF-2 meeting in September 2007 in which Health Canada committed to the following: reviewing existing regulations to identify and address gaps areas that refer to vaccines manufactured in Canada indented solely for export; to advocate for regulatory capacity building initiatives such as AVAREF; and to review existing regulatory procedures and share with African National Regulatory Authorities, training manuals and courses, assess possible opportunities for exchange programs, mentorship programs that can help AVAREF countries.

At this meeting, Health Canada reported on the Progressive Licensing Project which includes a proposal to address the limitations in the section 37 of the Food and Drug Act (by providing a potential for exemptions to the provision). Health Canada also urged AVAREF members for destination countries (i.e., the African NRA) to work collaboratively with manufacturing countries to address the continuing issue of effective regulatory oversight for products manufactured elsewhere for use in clinical trials in Africa. It was suggested that the destination countries should have requirements that prohibit the use of products not approved in their country of manufacture from their markets or for products to have an acceptable level of oversight such as the IND process in the USA or CTA application in Canada. It was suggested to the AVAREF members that addressing this gap should be prioritized and efforts should be made to address the issue comprehensively. Health Canada mentioned the application for BGTD to be a WHO Collaborating Centre, and the recent training of the NRA in India.

Health Canada also promised to continue exploring meaning and effective ways of contributing to regulatory capacity building and to support AVAREF, urged AVAREF to be formalized into a network to enable effective interaction between the African Regulators and also with regulators from manufacturing countries. A formalized network would enable members to have confidentiality agreements, strengthen informal linkages, and provide a springboard for harmonization with the region, training, and effective sharing resources and hence contribute to providing access to save vaccines for Africa.

7. New TB vaccines

7.1 The New Generation of TB Vaccines (U. Fruth, WHO Initiative for Vaccine Research)

A number of new TB vaccine candidates have been developed that show promise for the control of TB disease in endemic countries. Several of these are being tested in early clinical trials in South Africa and soon in other African nations. The AVAREF provides the regulatory expertise and the innovative “joint review” approach to facilitate the development of a safe and effective vaccines in Africa. The objective of this session was to introduce the TB vaccine candidates and provide case studies of clinical trials that have occurred in Africa, to the AVAREF group in preparation for a future joint review of a multicenter TB vaccine study within Africa that would be sponsored by the Aeras Global TB Vaccine Foundation.

While BCG is quite effective against extrapulmonary TB in young children, its effectiveness of the BCG vaccine against pulmonary disease can at best be described as very variable. This justifies the need for an new and effective vaccine to help control the global epidemic of tuberculosis. However, what is needed is probably not one, but more likely two or even three new TB vaccines with different profiles: one to replace or 'amplify' BCG early in life and before exposure to *Mtb*, another one to boost anti-mycobacterial immune responses later in life when latent TB is installed, and possibly a therapeutic vaccine against active TB. All of these vaccine types would potentially be of enormous benefit to African, in particular sub-Saharan populations and all vaccine candidates are being or will likely be tested in human trials on this continent.

Pre-exposure TB vaccines: This type of TB vaccine, of which BCG is the prime example, is intended for use in newborns or young infants, i.e. at a timepoint when the individual's immune system has not yet been exposed to natural infection with *Mtb* or other mycobacteria. Improved BCG or rationally attenuated *Mtb* are currently being proposed and tested as 'first contact' pre-exposure vaccines, with or without additional infancy booster doses of one of the new non-living products under development, e.g. adjuvanted protein subunit vaccines or vaccines based on replication-deficient viruses.

Post-exposure TB vaccines: 'Post-exposure vaccines' are vaccines that can be given to school children, adolescents or adults, when the individual has been latently infected with *Mtb* or other mycobacteria. Availability of an efficient post -exposure vaccine would allow to help those estimated two billion individuals in the world who are thought to be carrying *Mtb* and where a post-exposure vaccine could make a huge impact. Some of the above-mentioned booster-vaccines based on purified proteins or genetically modified, replication-deficient viruses are also being tested clinically as post-exposure vaccines.

Therapeutic TB vaccines: Therapeutic vaccines, i.e. those that are to be given to individuals with active TB, represent a special case of the above-mentioned post-exposure vaccines. The general idea is not to use these vaccines as stand-alone agents, but rather as adjunct to antibiotic treatment, with the aim of shortening the duration of

anti-TB chemotherapy. Two preparations of inactivated mycobacteria are currently being tested in clinical trials for this purpose: a preparation based on fragmented *Mtb* (RUTI) and another based on inactivated *M. vaccae*. The latter has just completed, as the first of all new TB vaccine candidates, a clinical phase III trial in Tanzania, where it has shown a certain therapeutic effect in HIV-infected individuals.

- The Dar Dar Clinical trial in Dar es Salaam
- Clinical Trials in Uganda
- TB Vaccine Trials in South Africa

7.2 TB Vaccine Trials in Africa

7.2.1 Introduction

A number of new TB vaccine candidates have been developed that show promise for the control of TB disease in endemic countries. Several of these are being tested in early clinical trials in South Africa and soon in other African nations. The AVAREF provides the regulatory expertise and the innovative “joint review” approach to facilitate the development of a safe and effective vaccines in Africa. The objective of this session was to introduce the TB vaccine candidates and provide case studies of clinical trials that have occurred in Africa, to the AVAREF group in preparation for a future joint review of a multicenter TB vaccine study within Africa that would be sponsored by the Aeras Global TB Vaccine Foundation.

7.2.1 MVA85 Vaccine in the Gambia (Jenny Mueller, MRC/The Gambia)

Approval of the MVA85 vaccine trial

The Scientific Coordinating Committee (SCC) located at the MRC (UK) Unit in The Gambia approved the trial and forwarded the documents to the local Gambia Government/MRC Joint Ethics Committee for approval. The Gambian Government was involved in this approval procedure through membership in both committees. In addition the sponsor’s Oxford Tropical Research Ethics Committee (OXTREC) approved the trial.

Informed Consent

As about 80% of the participants are illiterate and do not speak English, the approved English version of the Informed Consent Form (ICF) was translated into the 3 main languages and back-translated into English. The ICF is read and explained to participant’s parent/guardian by nurses/field workers in the local languages in the presence of a literate impartial witness. The ICF is signed or thumb printed (and dated) by participant’s parent/guardian, signed and dated by the person obtaining consent and the witness.

Investigational Products

The participants get vaccinated in accordance with the Gambian Expanded Programme on Immunisation (EPI) that includes BCG at birth or at least within the first 4 weeks of life. Immunogenicity is tested by ELISPOT in the research laboratory in The Gambia.

Safety Oversight and Quality Assurance

Participants are observed by nurses for 1 hour after vaccination and reactogenicity and Adverse Events (AEs) are recorded, as well as by field workers at home visits for 2 days and further at each site visit. Observed AEs are assessed by the trial physician for severity, seriousness, and causal relationship. Serious Adverse Events (SAEs) are reported within 24 hours to the Local Safety Monitor and the Sponsor.

The local trial monitor visits the site in addition to the sponsor's monitor.

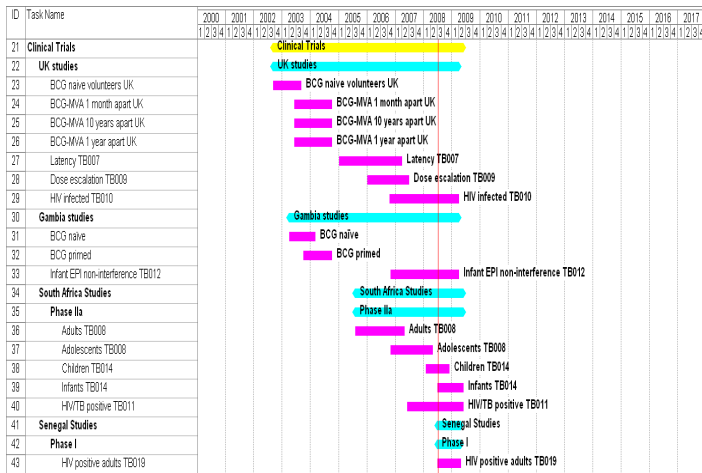
7.2.2 MVA85 Vaccine in the Gambia (Presented by Alison Lawrie)

There is an urgent need to produce an effective vaccine against TB. The currently available vaccine, *M. bovis* BCG, is ineffective at protecting against adult pulmonary disease in endemic areas and it is widely agreed that a new more effective tuberculosis vaccine is a major global public health priority. BCG does confer protection against disseminated disease in children, and it may be unethical and impractical to test and deploy a vaccine strategy that does not include BCG. An immunisation strategy that includes BCG is attractive because the populations in which this vaccine candidate will need to be tested will already have been immunised with BCG.

MVA85A was developed in Helen McShane's group at the University of Oxford as a booster vaccine to BCG. The vaccine is based on modified vaccinia Ankara which has an excellent safety record, as it was used to vaccinate more than 120,000 people at the end of the smallpox eradication campaign, with no serious adverse events.

Although the target populations reside in Africa (infants, adolescents and HIV +), due to lack of regulatory capacity we conducted the initial phase I trials in the UK.

We chose a stepwise approach by gradually increasing the M.tb exposure (to avoid the possibility of a Koch reaction) firstly assessing the safety and immunogenicity in BCG naive adults, BCG+, a safety and dose finding study, latent TB and HIV+ subjects prior to conducting trials in Africa. Trials in Africa for dose finding and age de-escalation from adults, adolescents to children and infants have been conducted. Additionally, MVA85A has also been assessed in HIV and latently infected subjects. There were no severe adverse events related to the vaccine and was shown to be both safe and immunogenic in all of these populations. Safety profiles were also similar between the groups tested in the UK and also in the African trials. We are currently conducting a phase II dose finding and non interference study to test if MVA85A interferes with the immunogenicity of EPI vaccines and vice versa in 4 month old infants. The results of this will be obtained by the end of the year. The following gantt summarizes our trials to date.



We will be conducting a IIB proof of concept trial in the first Q of 2009 in infants in South Africa. This trial is in collaboration with SATVI and Oxford / Emergent TB consortium (OETC) where Aeras is the sponsor, co-funded by Aeras and the Wellcome Trust.

7.2.3 Case Study: Dar~Dar Health Study (Lillian Mtei-Mbowe)

The Dar~Dar Health study recently concluded a clinical trial for the inactivated *Mycobacterium vaccae* vaccine (MV) as a prime-boost strategy in preventing tuberculosis in HIV positive adults in Tanzania. It was a randomised double blind placebo controlled trial conducted to GCP and funded by the Division of AIDS (DAIDS) of the NIH. The study ran from 2001 to 2008 and concluded that a five dose series of MV given to BCG-primed adults is safe and confers significant protection against definite tuberculosis.

The US approval body of DAIDS – Clinical Research Section Committee and the Tanzanian National Institute for Medical Research (NIMR) consented to the study initiation and have been getting progress reports as required. A different Data Safety and Monitoring Board (DSMB) from the NIH DSMB was formed and consisted of six persons with extensive TB vaccine experience but with only one in-country representative.

Institutional Review Boards (IRBs) from the two institutions which collaborate on the study (Dartmouth Medical School and Muhimbili University of Health and Allied Sciences) gave initial and follow-up approvals. Issues with translations, ethical and cultural differences caused delays between the two IRB approvals ranging from one to six months. The approval that led to a protocol acceptance and change was that given by the local IRB.

The US FDA did not review the study for inception (in the year 2000) as the product was of no use in the US, hence the then inexperienced Tanzanian Food and Drug Authority (TFDA) did a vigorous review following US guidelines with one conditionality being

approval of the product in the manufacturing country (UK). The initial review took six months and TFDA has been closely following the study. This had been the first vaccine trial in Tanzania and the TFDA has grown with experience since then.

A community advisory board (CAB) was formed six months into the study with eight members covering a range of cadre that included two independent physicians, a local politician, HIV activist, a journalist and two study participants. The CAB met quarterly to review progress and provided appropriate advise on recruitment and retention to the study staff. It also helped to inform the community about various aspects of the study.

7.3 Clinical regulatory challenges

7.3.1 Sponsor's perspective ((Tony Hawkrige, The Aeras Global TB Vaccine Foundation)

The Aeras Global TB Vaccine Foundation is a non-profit Product Development Partnership (PDP) dedicated to the development of effective TB vaccine regimens that will prevent TB infection in all age groups and will be affordable, available and adopted worldwide. The goal of the Aeras Global TB Vaccine Foundation is to develop, test, characterize, license, manufacture and distribute at least one new TB vaccine regimen for infants and another for adolescents by 2016 and ensure their availability to all who need them. Aeras has 3 main objectives - to advance the world's leading TB vaccine candidates forward towards licensure and availability by reviewing data from clinical trials and selecting only the most promising candidates for large-scale Phase III trials, to rationalize the TB vaccine development process by attempting to validate animal models and immunologic markers capable of predicting vaccine induced protection in humans which will make possible rapid and rational development of more effective vaccines in the future, and to maintain a robust TB vaccine pipeline so that subsequent generations of vaccines that have better performance and/or potential to prevent reactivation of latent infection will be brought forward.

Tuberculosis, tuberculosis vaccines and tuberculosis vaccine trials

In most developing countries where Aeras works TB is a declared priority disease / national emergency. There is a lack of regulatory experience (worldwide) with regard to reviewing novel TB vaccine trial protocols and registering new TB vaccines. The reasons for this include the fact that most BCG trials occurred a long time ago and there have been no trials of new TB vaccines until comparatively recently. There were no new TB vaccines for almost 100 years and then there has been a flurry of activity in the last 20 years with trials being conducted in a number of developed (Europe, N America) and developing (sub Saharan Africa, India) countries. There is little experience and little relevant literature and the result is that the assessment and registration of these new products constitutes somewhat uncharted territory.

On the other hand, we now have experience with recent malaria and HIV vaccine trials with many overlapping issues.

Some practical issues facing tuberculosis vaccine developers

Here follows a list of some practical issues and suggestions which relate to the development of new TB vaccines and the obstacles faced by developers.

a) Time delays

One of the major challenges in the pursuit of a new and better TB vaccine is **time delays**, some of which are for regulatory approval. All developers/sponsors have limited and time-bound funding – the degree varies. A long approval process is thus a problem, since time is funding. Obvious contributors to delays include the number of committees which must be negotiated, unrealistic meeting schedule (e.g. only every 2 months), a lack of enough experienced people to staff these committees which must be filled on a volunteer basis leading to backlogs.

The cost in lives and \$ of delay may be considerable. If a new TB vaccine is 70% effective and there are 1.7 million deaths / year, or 4 658 deaths/day, it means 3620 preventable deaths for every day's delay. If there are 9 million cases of TB / year or 24 658 cases / day, it means 17 260 preventable cases for every day's delay.

Aeras hopes to make new products available at \$1-2 per dose (i.e. at cost) in high burden countries, but to generate some revenue in low burden countries in order to cross subsidize. Every day delayed eats into this cross subsidy.

b) Protocol Amendments

We need to ask whether the approval of protocol amendments needs to take as long as the approval of protocols. The investigational agent is the same and these risks have already been evaluated. Could the amendment approval pathway be different to (and shorter than) the protocol approval pathway?

Long approval times means that amendments are more likely. Long approval times make it more likely that an amendment will occur since data from other sources is coming in all the time and thinking about the most advantageous protocol changes.

Outsourcing some aspects of protocol review

Might it be possible to charge a user fee and contract out some aspects of review? Commercial IRBs generally conservative. Might regulatory agencies consider contracting out some aspects of protocol review so that they can concentrate on the issues which cannot be contracted out? They could pay for this by charging a non-refundable user fee to sponsors, paid in advance. These fees would only guarantee that an answer would be given within a given period of time. They would not guarantee a favorable answer.

Individual product managers

Could regulatory agencies consider assigning an individual product manager to each product under trial? Discussions and correspondence on the product can then have continuity. A product manager might manage more than one product. This would provide a single person with whom safety issues could be discussed, for example.

Area specialists

Might regulatory agencies develop human resources with particular competencies for particular fields? This way a sponsor could be confident that there is relevant expertise on the other side of the regulatory divide.

Genetically Modified Organisms (GMO's)

Might it be possible to have GMO oversight capacity within the regulatory authority and not involving other Departments (e.g. Agriculture) which may not be familiar with clinical research? These departments tend to use the same expert reviewers in any case. Could the need for a new GMO review for the same product before each trial of that product be dispensed with? The product has not changed between reviews.

In summary

Sponsors are not all for-profit, but even not-for-profit sponsors have to meet timelines and produce results or they don't get re-funded. Approval delays are amongst the biggest obstacles facing developers of new tools to fight TB. Delays cost money, health and ultimately lives. Responsible and ethical sponsors do not ask for shortcuts but do ask for some flexibility in order to attain greater efficiency. Communication between regulators, sponsors and investigators is all important.

7.4 Challenges in the clinical evaluation of new TB vaccines: regulator's perspectives

7.4.1 FDA perspective (Dr. Rose Tiernan, USFDA)

Clinical development challenges for tuberculosis (TB) vaccines may include product-specific issues and/or more general issues related to clinical trial design.

Product:

Live TB vaccines may cause disseminated disease with potential for increased risk if the vaccine recipient is immunocompromised e.g HIV-infected. Adjuvanted vaccines may enhance and stimulate the immune response to vaccine antigen but may also have potential to produce reactions such as autoimmune disease. At an early stage of development, the added value of the adjuvanted vaccine formulation should be demonstrated while safety of the adjuvanted product should be compared to a saline placebo comparator. Use of novel viral vectored vaccines may raise questions related to persistence, integration, distribution and shedding that will need to be addressed.

Clinical Trial Design:

Issues related to clinical trial logistics include 1) local standards of care may differ regarding the diagnosis and treatment of TB cases 2) need to reach consensus on the tests that will be used to diagnose TB infection and TB disease during the clinical trial and discuss the challenges of using these tests in immunocompetent vs immunocompromised populations 3) need to standardize case definitions for TB infection and disease and consider the challenges of also doing this for the pediatric and immunocompromised populations 4) initial study population usually includes healthy immunocompetent adults with no evidence of latent or active TB but target population is ultimately the child who has already received BCG in the neonatal period

(“prime boost” approach) 5) issues related to type of safety and efficacy data required prior to enrolling immunocompromised patients with HIV 6) HIV patients may have atypical presentations for TB disease 7) if the study subject is latently infected with TB and has HIV and then is initiated on highly active anti-retroviral therapy (HAART) the patient will need to be monitored for immune reconstitution inflammatory syndrome “IRIS” 8) need to demonstrate there is no interference if concomitant vaccines are administered with the study TB vaccine 9) in multi-center and/or multi-country clinical trials, the BCG comparator or “prime” may be different and impact on licensure path 10) when is the most immunologically feasible and yet practical time to boost with study vaccine 11) need to validate assays that test humoral and cell mediated immunity recognizing there is no correlate of protection 12) response to PPD after vaccination also does not correlate with other parameters of TB immunogenicity and efficacy 13) efficacy endpoints could include decrease in incidence of TB infection and/or decrease in incidence of TB disease so need to standardize case definitions and field efficacy trials will be required with options to discuss the e.g endpoint issues at an Advisory Committee 14) immunogenicity and efficacy differences between populations may result from differences in factors such as genetics, nutritional status and background infections 15) safety endpoints will be product-specific and important to monitor for dissemination of vaccine strain vs acquisition of new TB infection or disease and challenges of evaluation of fever in patients who may have co-morbid infections such as dengue, malaria and HIV 16) potential vaccine indications could include administering vaccine to prevent infection “pre-infection” or administering vaccine “after/post- infection” as a means to modify established infection trying to prevent progression from latency to active disease. In summary, although TB vaccine development has some unique challenges, the Overall clinical development approach is similar to that of other vaccines with a goal that early phase studies support the safety and efficacy of the product recognizing that the path to licensure may be different depending on the epidemiology of TB in the country of interest. Field efficacy trials for TB vaccines will be required and prior to conduct of the phase 3 trials, the safety and efficacy endpoint issues could be discussed with the Advisory Committee

7.5 How AVAREF can contribute to the TB Vaccine Solution (Michael Brennan, The Aeras Global TB Vaccine Foundation)

Regulators are often seen just as “gatekeepers” to review product and clinical trial submissions, to assure the safety of licensed products, to inspect facilities and to enforce actions to protect the consumer. In the new paradigm, regulators should be seen as “facilitators” by constructing understandable and transparent regulatory pathways for new products, by assisting product developers in troubleshooting and problem solving, by contributing to assay development and by initiating concrete timelines for review and responses. Previous global meetings of regulators have indicated that there is no clear global regulatory pathway for TB vaccines as this time but has provided recommendations for improving the regulatory environment for the clinical study and licensure of TB vaccines in endemic nations (Brennan, MJ, et al. 2007. PLoS Medicine.

4:1299-1302). Vaccine developers recognize that the choice of a regulatory pathway is a critical part of the vaccine development strategy. Regulators recognize that it is important to provide a pathway that provides timely responses without compromising the quality of the review and that early interactions with product sponsors can improve submissions by identifying areas that will need attention. The “joint review” process pioneered by AVAREF is an innovative strategy that has great potential for improving the quality and efficiency of regulatory reviews particularly for products entering multinational clinical trials.

In order to introduce some of the regulatory challenges that will need to be addressed during the development of TB vaccines, case studies of two TB vaccines currently entering early clinical study were introduced. The AVAREF discussed issues related to characterization of the product, the clinical trial protocol, the target population, endpoints for TB diagnosis and ethical issues. A trial of the MVA85 vaccine highlighted issues such as TB diagnosis in infants, clinical trial protocol strategies for infants, the need for the proper control preparation for the MVA85 vaccine, consent forms in infant populations and the regulatory strategy for licensing a booster vaccine for a BCG prime immunization. Examination of a trial of an adenovectored TB vaccine expressing three Mtb antigens in HIV+ adults included discussion of clinical objectives aimed at assessing safety in HIV+ subjects including CD4 counts and viral load, TB diagnostic endpoints for pulmonary and extrapulmonary TB, the safe use of adenovectors, immune responses in HIV+ subjects and evaluation of results in the presence of the use of ART and anti-TB drugs. The joint review of these case studies identified a number of items of common interest including assurances that subjects are covered by insurance during the studies, the ethics of providing benefits to the subjects particularly infants, how to study non-interference of the investigative vaccine given with other vaccines in the EPI schedule including OPV, clinical registry protocols, how to test for latent TB, and how to obtain consent in infant studies. In the future, an AVAREF workshop will be planned to review the documents submitted for a multinational clinical study of the safety and efficacy of a TB vaccine for use in Africa.

8. Recommendations and action points

The following recommendations were endorsed by AVAREF members at the third plenary meeting held in Zanzibar, 27th to 31st October 2008.

AVAREF members agree that regulation of clinical trials of drugs and vaccines must be considered by WHO as a unique initiative for strengthening purposes. Therefore the recommendations below apply to clinical trials for all medicines (drugs and vaccines).

Satellite 1: Joint review of clinical trial application of a malaria vaccine

1) The model procedure for clinical trial applications should be revised and improved. Reviewers will propose changes to WHO and WHO will facilitate the revision and finalization of the new version for distribution to all AVAREF members.

Satellite 2: Strategy to link ethical review, regulatory oversight and Clinical trial registries in Africa

2) AVAREF members agree that a link between ethics committees, Regulatory Authorities and Clinical Trial Registries will increase transparency, promote communication among bodies involved in regulation of clinical trials and increase efficiency of clinical trial oversight processes.

The ATM registry(*) should be expanded to PACTR (Pan African Clinical Trial Registry and be designated a WHO compliant Primary Clinical Trial Registry for African countries. In addition to the links at the national level between EC's/ IRB's and NRA's, PACRT will be the link among NRAs and EC's of all AFRO countries.

3) A task team has been designated:

- Bocar Kouyate (EC/Burkina Faso)
- Shyamly Mumbodh (NRA/South Africa)
- Charles Wysonge (ATM registry/South Africa)
- Davina Gheri, Liliana Chocarro, Samvel Azatyan, Milan Smid, Bartolomeu Akinmori, Jean Marie Trapsida (WHO)

The task team will:

a) prepare a concept paper on this proposed strategy, for advocacy for the meeting that will take place in BAMAKO Ministerial Summit for Health Research with the Ministers of Health and other decision-makers, to present the project (deadline November 14th 2008)

b) prepare a strategic plan to be endorsed by AVAREF representatives to be adopted by AVAREF (by March 2009) and be submitted as a proposal to potential funding organizations

c) prepare a manuscript on this concept for publication in journal(s) (i.e. PLoS, WHO Bulletin, etc)

4) NRAs will develop databases of clinical trials run in their countries. WHO will formally request the Minister of Health of South Africa, the sharing of their (blank) database system.

5) Two pilot projects will be initiated in Uganda and South Africa to link their clinical trial databases with the PACTR (Q3/2009)

Satellite 3: Harmonization of drug and vaccine clinical trial regulation in AFRO countries

6) A task team will be constituted to move forward the recommendations. A small group will be designated among the following volunteers from AVAREF members: Beno (Nigeria), Amadou Koumare (Burkina Faso), Aaron Sosola (Malawi), Jayesh Pandit (Kenya), Rajen Misra (South Africa). The following will be part of the task team: Kwasi Nyarko (Health Canada), 1 representative from IFPMA (to be nominated). From WHO: Liliana Chocarro, Samvel Azatyan, Bartholomew Akanmori, Jean Marie Trapsida.

The task team will be responsible for the following:

7) A baseline survey for all AVAREF countries will be conducted. Existing assessment tools will be evaluated and improved as required (Q2/2009) to do an inventory of

a) NRA capacity (structure, resources and regulatory framework)

b) Experts of relevant disciplines in each country, to build a roster of regional experts as a resource for all countries

8) Information about regulatory authorities should be easily accessible to facilitate contacts from regional and international bodies. Therefore NRAs will develop websites that will be linked to WHO and other relevant sites.

9) To improve efficiency of the review processes and provide clear information to sponsors submitting applications, NRAs will establish timelines for CT review process in their guidance documents and will make this information available.

11) A list of common technical documents will be compiled and validated and WHO will commission experts to develop the model documents (the list proposed includes (clinical trial application, content of the application, content of CT database, common evaluation documents (screening and evaluation), review process flowcharts, model template approval letter for CTs, guidelines for presubmission meetings, common document for GCP inspections, safety monitoring during CTs, guidance on information for investigational product dossiers, prequalification of experts, model MOU, model legislation)

12) A plan for development and delivery of proposed list of required training will be prepared. (Q1/2009)

13) WHO should continue facilitating joint reviews (i.e. new TB vaccines) and joint inspections (i.e. malaria trials) . Countries will initiate a similar system including countries involved in multicenter trials and will seek consensus from sponsors directly.

14) AVAREF countries will establish an intercountry evaluation committee (long term project) that will optimize the use of regional expertise to serve all countries that need the review outcome for their decision making process

Plenary sessions:

15) Expert regulators from European agencies, USFDA and Health Canada have provided and offered to continue providing expert support to AVAREF countries. To maximize the use of this expertise, AVAREF members will propose topics for consultation with international experts for the next AVAREF plenary meeting.

16) EMEA GCP Inspectors Working Group has requested WHO to provide contact details for all AVAREF countries to facilitate communications when inspections are to take place in Africa. AVAREF members will provide one principal and one alternate contact person details to WHO to be forwarded to EMEA (Nov/2008).

17) Next AVAREF meeting will be held the week of September 21st in Nigeria or Zambia

9. Closing Ceremony

Speech for the Closing of the third meeting of the African Vaccine Regulatory Forum By Dr. Mohammed Jiddawi, The Principal Secretary Ministry Of Health And Social Welfare, Revolutionary Government Of Zanzibar

The Chairman of the meeting

The Coordinators of the meeting

Members of AVAREF

Representatives from National Regulatory Agencies

Staff of WHO HQ and WHO AFRO

Vaccine Manufacturers and companies present

Representatives of Development Partners,

Distinguished Guests,

Ladies and Gentlemen,

It is a pleasure to be invited to participate in the closing ceremony of this very important 3rd AVAREF meeting, the first to be held in Zanzibar, I am very pleased that AVAREF and WHO decided to choose Zanzibar for this 3rd AVAREF meeting and I am sure that you not regretted this choice.

I am reliably informed that AVAREF is a network of regulators and ethical committee members from 19 African countries and was established in 2005 and with the following aims:

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 very safe and effective. To ensure this, very standards of reviews are required by scientific committees, ethical committees and regulatory authorities 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 including Zanzibar. This is very critical in enabling us to attain some of the Millennium Development Goals.

I am informed that during the week you worked very hard and achieved a number of objectives. The objectives include the joint review of dossiers by NRAs and ethics committee members of seven African countries which have been targeted for a phase clinical trial of a malaria vaccine and produced recommendations on how to strengthen the links between ethical committees and NRAs, as well as common guidelines for regulation of vaccines and drugs. I commend you for the hard work and the recommendations you have made and urge you to ensure that these very important recommendations are fully implemented to the benefit of the people of the continent. My advice to you as a network of regulators and ethics committees is that you should not wait for the next meeting of AVAREF but continue to collaborate and communicate with each to share experiences and skills to the benefit of all your countries.

I wish to take this opportunity to thank and congratulate the organizers of this workshop which has enabled the gathering of such distinguished people in the different areas of vaccines management and regulation.

May I take opportunity to welcome you to the United Republic of Tanzania in particular Zanzibar – island of spices.

On this note, Mr Chairman, ladies and Gentlemen, let me once again thank you and wish you safe journeys back to your homes and families. For those who are still here I encourage you to visit the many sites in Zanzibar, enjoy the warm hospitality of the people and sample some of our food. I declare the meeting officially closed

Annex 1

General Agenda

27-31 October 2008

Monday October 27 th	Tuesday October 29 th	Wednesday October 30 th	Thursday October 31 st	Friday November 1 st
8:30-9:00 Registration PLENARY 9:00-10:00 Opening And Introduction	9:00-10:30 Satellite 1 - Joint review Malaria vaccine CTA Satellite 2 and 3 (joint session)	9:00-10:30 Satellite 1- Joint review Malaria vaccine CTA Satellite 2 Integration of ethics, regulation and registration of CTs Satellite 3 Harmonization of drug and vaccine CT regulation	PLENARY 8:30-9:00 Report from Satellite 1 9:00-10:30 Report and discussion Satellite 2	PLENARY 9:00-10:30 New TB Vaccines
10:00-10:30 Coffee	10:30-11:00 COFFEE BREAK			
11:00-13:00 Satellite 1 Joint review Malaria vaccine CTA Satellite 2 and 3 (joint session)	11:00-12:30 Cont. Satellite 1 - Joint review Malaria Satellite 2 and 3 (joint session)	11:00-12:30 Continued	11:00-12:30 PLENARY Report and discussion Satellite 3	11:00-12:30 PLENARY New TB vaccines
13:00-14:00 Lunch	12:30-13:30 LUNCH			
14:00-15:30 Continued Satellite 1 Joint review Malaria vaccine CTA Satellite 2 and 3 (joint session)	13:30-15:00 Satellite 1- Joint review Malaria vaccine CTA Satellite 2 Integration of ethics, regulation and registration of CTs Satellite 3 Harmonization of drug and vaccine CT regulation	11:00-12:30 Continued	13:30-15:00 (Closed session for regulators) Reports from USFDA, Health Canada and EMA on changes in regulation of CTs	13:30-15:00 (Closed session for regulators) Regulatory support for New TB vaccine trials
15:30 Coffee break	15:00-15:30 COFFEE BREAK			
16:00-17:00 Continued as above	15:30-17:00 Continued	15:30-17:00 Continued	15:30-17:00 (Closed session for regulators) AVAREF country progress reports	15:30-17:00 PLENARY Recommendations and action points

Satellite meetings
Integration of Ethical Review, Registration and Regulation of Clinical
Trials in Africa
And
Harmonization of Drug and Vaccine Clinical Trial Regulation
27-29 October 2008

DAY 1

Time	Topic	Speaker
8:30 Registration		
Session 1: Welcome and introduction		
9.00	Welcome address and opening remarks <ul style="list-style-type: none"> Briefing on the aims and working method of the meeting Introduction of the participants Announcement of co-chairpersons and co-rapporteurs 	WHO Representative, Tanzania
9.20	<ul style="list-style-type: none"> Recommendations from AVAREF-2 and implementation Overview of the meeting, format and expected outcomes 	Liliana Chocarro
10:00- 10.30 Coffee/Tea Break		
Session 2: Integration of ethical review, regulation and registration of clinical trials		
10:30	<ul style="list-style-type: none"> Why register clinical trials? Why integrate ethical review, registration and regulation? 	Davina Ghersi
Assessing the situation		
11.00	Status of ethical review of clinical trials in Africa	Bocar Kouyate
11.30	The ATM Registry	Charles Wiysonge
12.00	The South African Clinical Trial Registry	Dr. Rajen Misra
12.20	Linking regulation with ethical review: case studies	Rutendo Kuwana (Zimbabwe) Helen Byomire (Uganda) Markieu Janneh-Kaira (Gambia)
12.50	Discussion	
<i>13.00 Lunch Break</i>		
Session 3: Models for achieving a regional platform for trial registration		
14.00	Developing a common platform for clinical trials registration in Latin America and the Caribbean.	Davina Ghersi on behalf of Renato Murasaki
14.30	The European and Developing Countries Clinical Trials Partnership Programme (EDCTP)	Andrew Kitua
15.00	Brainstorming: What are the critical issues?	

<i>15.30 Coffee/Tea Break</i>		
Session 4: Strategies Goals and Objectives		
16.00	Brainstorming: what should be done about the critical issues (broad approaches / strategies)	
17:00	Conclusions of the first day's presentations and discussions.	

Day 2 (am)

Time	Topic	Speaker
Harmonization of drug and vaccine clinical trial regulation		
9.00	Use of structures, resources and procedures for regulation of medicines and vaccines clinical trials oversight: South African model	Dr. Rajen Misra Department of Health, South Africa
9.45	Existing and planned regional activities concerning clinical trials	Dr Margareth Ndomondo Sigonda, Director General, Tanzania Food and Drug Authority
<i>10.30 Coffee/Tea Break</i>		
11.00	Complex regulatory systems and regulatory harmonization from regulator point of view	Dr. Immanuel Barth
11.45	Harmonization and good regulatory practice from the point of view of sponsors	Marie-Chantal Uwamwezi (IFPMA)
<i>12.30 Lunch Break</i>		

Day 2 (pm)

Participants will divide into two discussion groups:

1. Integration of Ethical Review, Registration and Regulation of Clinical Trials in Africa
2. Harmonization of regulation of clinical trials of medicines and vaccines

The two groups, working during Tuesday afternoon and all Wednesday must achieve the following:

Group 1: Integration of Ethical Review, Registration and Regulation of Clinical Trials in Africa

- Identify the key elements that justify the need to have a regional strategy to link ethical review, regulatory approval and registries of clinical trials
- Prepare a proposed strategy to maximize efficiency and transparency with regards to oversight of clinical trials
- Propose the composition of a task force that will work with WHO to implement the proposed strategy

-
- Prepare a report to be presented in the plenary on Thursday morning that will include:
 - highlights of the discussions
 - proposed strategy
 - recommendations for countries and for WHO and action points

Group 2: Harmonization of regulation of clinical trials of medicines and vaccines

- Identify key elements to optimize the use of resources at the national level for the oversight of clinical trials of drugs and vaccines
- Identify the advantages/disadvantages of harmonized regulatory guidance documents for all processes relevant to oversight of clinical trials
- Prepare a list of documents that can be proposed for common use in the region
- Propose a plan for optimization of resources in the region with regards to evaluation of clinical trial applications and inspections
- Identify types of capacity building activities sponsored by WHO that should be done in common for drug and vaccine trials and those that should be done separately
- Propose a list of required training and tentative timeline
- Prepare a report to be presented at the plenary on Thursday morning that will include:
 - Highlights of the discussions
 - Key elements identified
 - Proposed plan of action and recommendations for countries and for WHO

Regulatory forum on New TB Vaccines 31 October 2008

Agenda

9:00 - 10:30 New TB Vaccines: Clinical trials in Africa

- General overview of the new generation of TB vaccines: a description of TB vaccine candidates in pre-clinical and clinical studies Uli Fruth
- Case studies of TB vaccine trials in Africa
Lillian Mtei - M. vaccae vaccine trials in Tanzania
Alison Lawrie and Jenny Mueller – MVA85 vaccine trials in the Gambia

10:30-11:00 Coffee break

11:00-12:30 Regulatory challenges

- Clinical Regulatory Challenges:
Harriet Mayanja.- TB vaccine trials in Uganda; a PI's perspective:
Tony Hawkridge- TB vaccine trials in S. Africa; a Sponsor's perspective:
- Challenges in the clinical evaluation of new TB vaccines: Regulator's perspectives
Rose Tiernan – TB vaccine challenges from the CBER/FDA perspective
Shyamly Numbodh - Overview of regulation in the Republic of South Africa

12:30-13:30 Lunch

13:30 -15:00 Closed session for regulators

Mike Brennan -Overview of regulatory challenges for TB vaccines

General discussion of future joint reviews of TB vaccines, of trial sites for phase II trials in Africa, of existing regulatory capacity and the identification of regulatory support needs.

ANNEX 2

List of participants

Ghislaine Akerey, Directrice Adjointe ANR Gabon(DMP), Direction du Médicament et de la Pharmacie / MSP, Libreville, **Gabon**

Immanuel Barth, CT-Section, Deputy Head, **Paul Ehrlich Institute**, Langen, 63225 **Germany**

Mr Eric Karikali Boateng, Acting Head Laboratory Services, **Food and Drugs Board**, Accra, **Ghana**

Dr Michael J. Brennan, Senior Advisor, Global Affairs, **Aeras Global TB Vaccine Foundation**, Rockville, 20850 MD, **United States of America**

Dr Nditonda Benno Chukilizo, Acting Manager, Medicine and Cosmetics Evaluation and Registration, **Tanzania Food and Drug Authority**, Dar -es-Salaam, **United Republic of Tanzania**

Dr Adam Mitangu Fimbo, Acting Manager - Clinical Trials, **Tanzania Food & Drug Authority**, Dar-Es Salaam, **United Republic of Tanzania**

Stephen Gyani, Principal Regulatory Officer, **National Agency for Food and Drug Administration and Control**, Yaba-Lagos, **Nigeria**

Dr Mamuye Hadis, Head Dept. (Infections & Other Diseases), **EHNRI**, Addis Ababa, **Ethiopia**

Dr Tony Hawkrige, Head, **Aeras Global TB Vaccine Foundation**, Africa Office, Cape Town, 7700 **South Africa**

Mrs Markieu Janneh Kaira, Acting Chief, Pharmacist/Registrar, Central Medical Stores, **Medicines Board**, Banjul, **Gambia**

Joseph Karashani, Past Chairman, Research Ethics Committee, **University of Zambia**, **Zambia**

Dr Andrew Yona Kitua, General Director, National Malaria Control Program, **National Institute for Medical Research**, Dar Es Salaam, **United Republic of Tanzania**

Amadou Koumare, Directeur, Direction de la Pharmacie et du Médicament, **Ministère de la Santé**, Ouagadougou, **Burkina Faso**

Dr Bocar Kouyate, Directeur, **Centre National de Recherche et de Formation sur le Paludisme**, Ouagadougou, **Burkina Faso**

Mr Rutendo Kuwana, Assistant Director, Pharmacovigilance& Clinical Trial, **Medicines Control Authority of Zimbabwe**, **Zimbabwe**

Alison Lawrie, Senior Coordinator, Project Manager, Badlock Hoe, Old Boars - Oxford,
United States of America

Lamine Nane Mahamadou, Member of Ethics Committee, Health Director, **Ministry of Health, France**

Professor Charles Mgone, Executive Director, **European and Developing Countries Clinical Trials Partnership**, The Hague, 2509 AA **Netherlands**

Rajender Misra, Director, Clinical Evaluations & Trials, **National Health of South Africa**, 2052 **South Africa**

Ms Doreen Anna Sophia Mloka, Department of Pharmaceutical Microbiology, Dar Es Salaam, **United Republic of Tanzania**

Alambo Mssusa, Clinical Trials Control & Pharmacovigilance Officer, **Tanzania Food & Drug Authority**,

Dar-Es-Salaam, **United Republic of Tanzania**

Jenny Mueller, Clinical Trials Support Manager, Berlin, 12307 **Germany**

Shyamli Munbodh, Deputy Director, Medicine Regulatory Authority, **South Africa**

James Munthali, Secretary, University of Zambia, **Biomedical Research Ethics Committee**, Lusaka, **Zambia**

Ms Bernice Mwale, Director-Product Registration, Pharmaceutical Regulatory Authority, **Department of Pharmaceutical Services, Zambia**

Ms Jane Nabbuto, Science Officer - Research Compliance & Ethics, **Uganda National Council for Science and Technology**, Kampala, **Uganda**

Leah Nawegulo, Head, Research Safety & Ethics Unit, **Uganda National Council for Science and Technology**, Kampala, **Uganda**

Mrs Helen Byomire Ndagije, Head Information Development, **Drug Information**, Kampala, **Uganda**

Dr Bagrey Ngwira, Lecturer (Ethics Committee Member), **College Of Medicine, Malawi**

Dr Emmanuel Nkeramihigo, Secretary, **National Ethics Committee**, Kigali, **Rwanda**

Dr Beno Nyam Yakubu, Principal Regulator & Officer, Clinical Trial Unit, **National Agency for Food and Drug Administration and Control**, Lagos, **Nigeria**

Mrs Priscilla Nyambayo, Senior Regulatory Officer, **Medicines Control Authority of Zimbabwe, Zimbabwe**

Dr Kwasi Nyarko, Unit Manager, Policy and Promotion Division, Centre for Policy and Regulatory Affairs, **Biologics and Genetic Therapies Directorate**, Ottawa, K1A 0L2 ON, **Canada**

Jayesh Pandit, Head, Department of Pharmacovigilance, **Pharmacy and Poisons Board**, Nairobi, **Kenya**

Mr Momodou Cheyassin Phall, Acting Executive Director, National Nutrition Agency, Office of the Vice President, **Ministry of Health, Gambia**

Dr Sinah M. Selelo, Principal Pharmacist, Drugs Regulatory Unit, **Ministry of Health**, 300355 **Botswana**

Mr Shija Joseph Shija, Assistant Registrar, **Zanzibar Food, Drug & Cosmetics Board**, Zanzibar, **United Republic of Tanzania**

Dr Shaban Sifuma, Regulatory Pharmacist, **Ministry of Health, Pharmacy & Poisons Board**, Nairobi, **Kenya**

Margareth Ndomondo Sigonda, Directeur General, **Tanzania Food and Drug Authority**, Dar-Es-Salaam, **United Republic of Tanzania**

Mr Aaron Glyn Sosola, Deputy Registrar, **Pharmacy Medicines and Poisons Board**, Lilongwe 3, **Malawi**

Dr Rosemary Tiernan Eshman, **Division of Vaccines and Related Product Applications**, Rockville, 20852 **United States of America**

Dr Geneviève Waeterloos, Head Biological Standard, **Scientific Institute of Public Health, Biological Stand., Pri, Belgium**

Dr Dale Wierenga, Director, Regulatory Affairs, **Aeras Global TB Vaccine Foundation**, Rockville, 20850 MD, **United States of America**

Dr Charles Shey Wiysonge, Senior Scientist, Human Rights, Gender, Best Practice HGP, **Medical Research Council**, Cape Town, **South Africa**

Rutendo Zinyama, Research Officer, **Medical Research Council of Zimbabwe**, Harare, **Zimbabwe**

Dr Pieter Neels, CHMP Member, Environment DG Medicinal Products, **Federal Agency for Medicinal and Health Products**, Brussels, 1060 **Belgium**

Mrs Marie-Chantal Uwamwezi, Scientist -Technical Regulatory Unit Recombinant Vaccines and Adjuvants, Regulatory, Epidemiology & Safety, **GlaxoSmithKline Biologicals**, Wavre 1300, **Belgium**

WHO SECRETARIAT

Dr Bartholomew Akanmori, Research and Development New Vaccines Officer, Immunization and Vaccine Development Programme, **WHO/AFRO**, Brazzaville, **Republic of Congo**

Dr Samvel Azatyan, Technical Officer, Regulatory Support, (PSM/QSM), **WHO**, Geneva, **Switzerland**

Dr Liliana Chocarro, Scientist, Regulatory Pathways, Quality, Safety and Standards (IVB/QSS), **WHO**, Geneva, **Switzerland**

Dr Nora Dellepiane, Group Leader, Vaccine Quality and Regulation, Quality, Safety & Standards (QSS), **WHO**, Geneva, **Switzerland**

Ms Davina Gherzi, Team Leader, (IER/IPC), **WHO**, Geneva, **Switzerland**

Dr Pierre Kandolo, Conseiller PEV de routine & nouveaux vaccins, (IST/IVD), **WHO**, Libreville, **Gabon**

Dr Evariste Mutabaruka, Capacity Building and Training Officer, Immunization Support Group, (VPD), **WHO/AFRO**, Harare, **Zimbabwe**

Dr Femi Oyewole, Medical Officer, Routine Immunization, **WHO**, Ouagadougou, **Burkina Faso**

Ms Rose Shija, EDM/NPO, **WHO**, Dar Es Salaam, **United Republic of Tanzania**

Dr Milan Smid, Technical Officer, Prequalification Team , **WHO**, Geneva, **Switzerland**