2019 Annual International Bioethics Forum

Study Participants Protection: Translating Principles to Practice

RESEARCH PRACTICE AND REGULATION IN WEST AFRICA: WAHO GUIDELINES

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Introduction-Why the high Incidence of Disease Burden in ECOWAS Region

- **With a population of about 365 million, large market size and the need for quick access of quality essential medicines and Vaccines;**
- **Due to high disease burden- huge incidence of malaria , HIV/AIDS, Tuberculosis, neglected tropical diseases and other newly emerging diseases like Ebola Virus, Dengue, Lassa fever;**
- **Combined with other communicable and non-communicable diseases, poverty and malnutrition, which also impact on the types of medicines required;**
- **And taking cognizance of the porosity of our borders, these factors fuel illegal distribution of counterfeit medical products as well as illicit trade;**
- **Despite efforts by regional and national bodies (ECOWAS/WAHO, National Medicines Regulatory Authorities) the counterfeit situation is still high.**

15 West African Member States

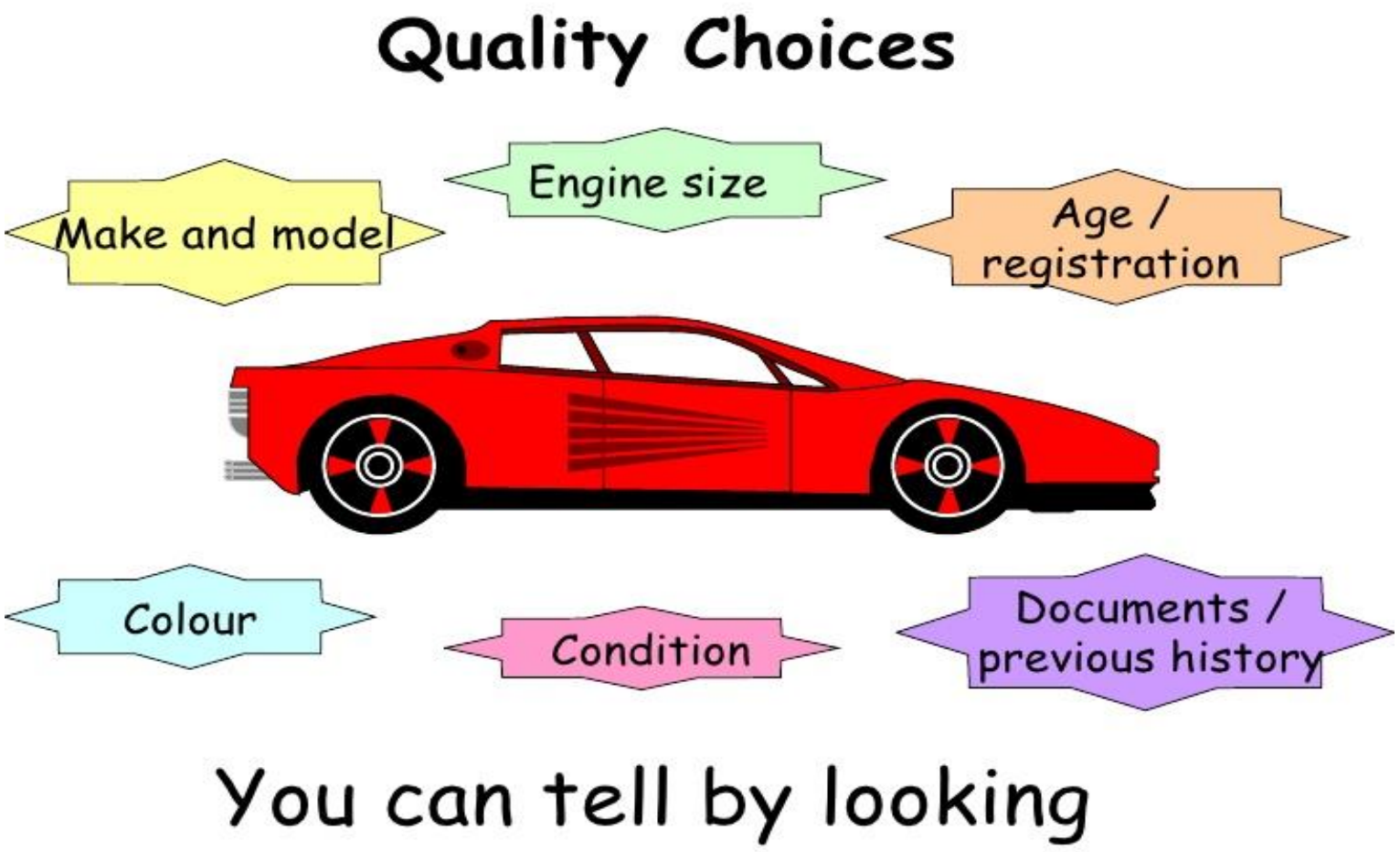
The Vulnerability of the Population

- High demand for medicines and vaccines (other biological products);
- Yet, access to these medical products is low, an issue that affect the healthcare of the population;
- Does it mean that anything goes regardless the quality? **A big NO;**
- **Quality and safety of medicines can be compromised.**
- **Why? – safety of the patient is at risk- many tragedies leading to public outrage that have led to regulations and legislations to control the associated risks;**

History of Tragedies

No	Tragedy/Case	Regulation/Law
1.	12 children died from Diphtheria antitoxin vaccine that was contaminated with live tetanus bacilli	Biologics control act of 1902 which mandated the inspection of manufacturers and sellers of biologics by the FDA
2.	107 died using Sulphanilamide which is usually in powder form but demand for liquid formulation (elixir) increased – A company formulated using diethylene glycol as solvent (aka anti-freeze)	Federal Food Drug & Cosmetics (FD&C) act 1938 – Which meant that companies had to prove that their product are safe before marketing
3.	About 300 people killed or injured by sulfa drug, tainted with Phenobarbitol, a sedative.	Manufacturing and quality control requirements were drastically revised which led to The Public Health Services Act of 1944
4.	A company failed to inactivate Polio virus completely in a single lot of vaccine. About 60 individuals inoculated developed polio and another 89 of their family members contracted polio from them	The Public Service Act of 1955- covers a broad spectrum of concerns including regulation of biological products and control of communicable diseases
5.	Thalidomide marketed as sleeping pill and to treat morning sickness in pregnant women. Side effect caused teratogenicity. An estimated	Clinical trials amendment required drugs to be tested on animals before man 1950-1960 (Phase 1-4 of the clinical trials)

Why Regulate?



Quality Choices

Make and model
Right product

Engine size
Right strength

Age / registration
Right expiry date

Colour
right appearance

Documents / previous history
Batch Record

Condition
No contamination

You can't tell just by looking

Purpose for Clinical Trials

To assess the benefit/risk for the patient/volunteer participants and society at large

The assessment is a judgement call based on:

- Extrinsic factors:
  - Morbidity and mortality of the disease
  - Extent of the unmet medical need
  - Availability of validated safety and efficacy measures
  - Knowledge about the drug target and drug class
  - Marketing requirements
- Factors related to the drug and the trial:
  - All accumulated data on the drug product
  - The proposed trial, eg design, population, dose regimen, safety and efficacy measures, risk mitigation measures
  - Adequate risk communication to trial participants

Source: The concept of benefit/risk by Celia Lourenco, Health Canada. Presented at the APEC Preliminary Workshop on Review of Drug Development in Clinical Trials

Proposed Clinical Trial

- Rationale
  - Consider what is new in the trial, the clinical relevance, and the medical need that the trial aims to address
  - Is it properly justified and applicable to the local context?

- Primary objective(s) and endpoint(s)
  - Are they clearly defined, measurable, and acceptable?
  - Are there primary endpoints for this type of study/indication, do they match the goals?

Proposed Clinical Trial

- Secondary objective(s) and endpoint(s)
  - Are they clearly defined, measurable, and acceptable?

- Study population
  - Healthy volunteers/patients
  - Age range
  - Gender
  - Women of childbearing potential

Proposed Clinical Trial

- Vulnerable populations and clinical trials in emergency situations
  - Pregnant and breast-feeding women
  - Women of child bearing age not on contraception
  - Incapacitated participants unable to give informed consent

Are any of these groups included in the trial? And if so, is their inclusion clearly justified?

In case of emergencies, does the trial provide clinically relevant direct benefit to the participants?

Proposed Clinical Trial

- Inclusion criteria
  - Are they clearly defined, representative of the target population and acceptable?

- Exclusion criteria
  - Are they clearly defined and in accordance with the comparator's safety profile?

Does the sponsor justify the exclusion or underrepresentation of a specific group in the in/exclusion criteria?

Proposed Clinical Trial

- Study plan and design
  - Discuss the expected duration of the participants' inclusion and a description of the sequence and duration of all the clinical trial periods, including the follow-up
  - Does the protocol provide enough information on the overall study plan and design (configuration) of the study, eg parallel, cross-over?
  - Highly desirable but not a deal breaker: Diagram/flow chart because it provides a snapshot of the trial

Documents [most commonly] reviewed

- Clinical study protocol:
  - Describes the objective(s), design, methodology, statistical considerations, and organization of a trial
  - Provides the background and rationale for the trial

(adapted from ICHE6R2 section 1.44)

- Investigator's brochure:
  - Compilation of the clinical and nonclinical data on the investigational medical product(s)

(adapted from ICHE6R2 section 1.36)

Documents [most commonly] reviewed

- Informed consent:
  - Documents the process by which participants ***voluntarily*** confirm their willingness to take part in a particular trial
  - ***after been informed*** of all the aspects of the trial that can affect their decision to participate
  - Signed and dated form

(adapted from ICHE6R2 section 1.28)

- Summary of product characteristics (for registered products)
- Scientific publications

Overview of the Clinical Assessment Template

Scope: All types of investigational medical products, e.g. vaccines, new chemical entities, and biotech products, and trial phases.

[Medical devices are out of scope]

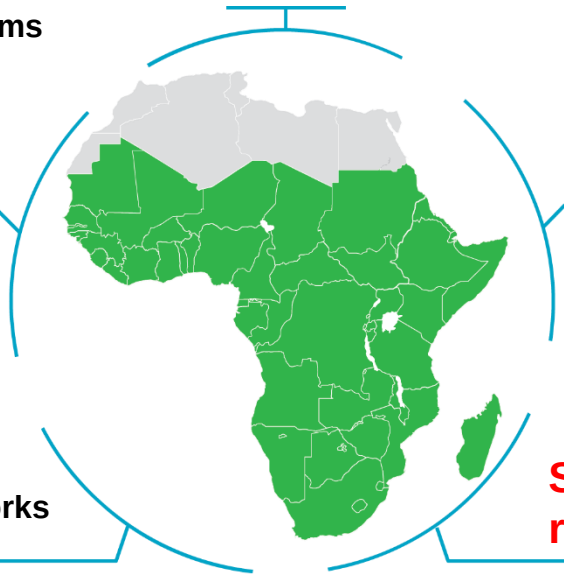
The template leads assessors in a systematic review of the clinical information provided in a clinical trial application. It is a dynamic document subject to improvement.

European and Developing Countries Clinical Trials Partnership (EDCTP) - Strategy for Clinical Capacity Development

Site preparation for conducting clinical research

Strengthening product-focused health systems research
- Pharmacovigilance
- National Health Research Systems (NHRS)

Comprehensive **fellowship programme**
- Preparatory Fellowship
- R&D Fellowship
- Career Development Fellowship
- Senior Fellowship



Regional Networks of Excellence

Strengthening ethics and regulatory capacity

How Prepared is West Africa?

- **Under the West Africa Medicines Regulatory Harmonization Initiative launched in February 2015 in Accra, includes all 15 Heads of Regulatory Authorities:**

  - Steering Committee;
  - 7 Experts Working Groups;
    - Medical Products Dossier Evaluation and Registration
    - Good Manufacturing Practices and Inspection
    - Quality Control
    - Quality Management Systems
    - **Clinical trials and Pharmacovigilance**
    - Information Management Systems
    - Policy, Regulation and Legislation

Documents Developed

- **Developed Clinical Trials guidelines clinical trial submission and assessment**
  - Quality
  - Nonclinical
  - Clinical
- **Standard Operating Procedures;**
- **Application forms and Checklists-** screening or verification
- **Inspections**
  - Guide for the inspections of clinical trials
  - Checklist for the inspections of clinical trials

ECOWAS/WAHO & WHO-AFRO Collaboration -AVAREF

- **25 to 27 February 2019, Addis Ababa align Guidelines and Tools**
- Chair of the TCC, members of the Technical working groups, members of the WAHO Expert Working Group, 2 representatives from each of the 15 ECOWAS countries (Regulators and Ethics), 1 AVAREF, 2 representatives from WAHO Secretariat, 1 representative of UEMOA

Background

- AVAREF, network of national ECs and NRAs established in 2006 by WHO to build their capacity, and improve harmonization of practices in support of product development;

- WAHO-WA-MRH in 2018 developed and validated regional guidelines and tools to improve harmonization of practices and build capacity across region;

- WAHO –WHO/AFRO signed a collaborative MOU to work together on common areas between the two institutions to support member states-
  - Global Programme of Work, to prevent deaths, reduce risk of epidemics, promote health and ensure universal health coverage;

- Since AVAREF was working in the some domain we decided to align are tools to strengthen the continent interest to prevent the other RECs re-inventing the wheel.

Background

- To enable NRAs, ECs and sponsors to achieve a consensus on major ethical and regulatory questions surrounding R&D;

- AVAREF recognized the fact that most African regulatory authorities faced serious resource constraints hence a lack of capacity for adequate review and approval of CTs that is key in ensuring safety of research participants in the process of clinical development of products;

- Accordingly, AVAREF has as its aims the support of NRAs and national ethics committees with a view to ensuring timely regulatory evaluations and decision-making process on CT applications.

Meeting Objective

- The objective of this workshop is to convene the WAHO Expert Working Group on clinical trials and pharmacovigilance and ECOWAS countries to endorse and disseminate the harmonized guidelines and tools.

Expected Outcomes

- Capture the strong desire for harmonization and to use the best means to regulate clinical trials;
- Provided references from ICH guidelines and other sources to explain the rationale for requiring specific tests, standards, limits and to link to all aspects such as safety, concomitant diseases, age, physiological changes, product stability, drug interactions and all other aspects as stated in the template;
- Reinforce case study of evaluation in clinical trial application: eg. polysaccharide-protein conjugate vaccine against meningitis vaccine
  - **to identify the three components, toxin, antigen and agent for conjugation;**
  - **to raise critical issues of assessment of quality of the protocol;**
  - **define all the terminologies, from endpoints to SAEs, DSMBs and in each case providing the justification for reviewing and ensuring that these are addressed as per the template;**
  - **link between non-clinical and clinical assessment;**
  - **scientific review committees could use the templates for assessments.**

Implementation and domestication of harmonized documents 1

- Representatives of countries in the forum should seek the approval of their respective Governments in adopting and domesticating harmonized guidelines and documents within their countries.
- Publishing harmonized guidelines, tools and other documents on the member countries websites should be encouraged to improve awareness and use in countries and RECs.
- Countries should be encouraged to document their experiences, comments and suggestions in the use of the documents as that will help during the revisions.
- The Secretariat to organize a Joint GCP inspection for selected Clinical trials (9 to 12 April 2019, CT Site in Gondar, Ethiopia).

Implementation and domestication of harmonized documents 2

- To facilitate the use of Harmonized documents: guidelines, tools, recommendations.

- As per the TCC and SC the harmonized guidelines and documents are important and critical tools to facilitate the work of NRAs and ECs and therefore should be considered for domestication and implementation at both RECs and country levels as that will help in harmonizing clinical trial activities within Africa.

- It was also highlighted that, in domesticating these important guidelines and documents, the TCC, SC, and the Secretariat must make sure the documents are made available to all the RECs and Heads of ECs and NRAs. Consequently, the secretariat has posted the documents on the following AVAREF page link on the WHO website: http://afro.who.int/about-us/leadership/avaref

Implementation and domestication of Harmonized Documents 3

- The Steering Committee endorses the following guides for use by Member States and RECs and recommends the AVAREF secretariat to support the training/Piloting in member countries:
  - AVAREF GCP Inspection Guide and checklist
  - AVAREF Clinical Trial Application form and Checklist
  - AVAREF Clinical Assessment Guide
  - AVAREF Non-Clinical Assessment Guide
  - AVAREF Quality Assessment Guide
  - AVAREF Joint review guideline

Implementation and domestication of harmonized Documents 4

- Workshop: To discuss the documents, how countries regulatory environment could accommodate these documents and steps taken to use the harmonized guidelines and tools.
- WAHO: 25 to 27 February 2019
- SADC: 14 to 16 May 2019
- EAC: 16 to 18 April 2019
- IGAD: 10 to 12 July 2019

Conclusion

- AVAREF to served as vectors of cooperation and harmonization mechanisms and procedures between countries, NRAs, ECs and the RECs;
- AVAREF activities have contributed to strengthen:
  - capacity of NRAs and ECs,
  - regulation clinical trials, approval, registration, and timelines.
- Engaging RECs is key to success;
- Stronger collaboration AVAREF-RECs improves chances of success
- Country Ownership and decision-making is vital

Thank You

Merci

Obrigada