Addis Ababa University
College of Health Science

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Eastern Africa Countries Need and Readiness for Implementation of Harmonized Clinical Trials Regulation and National Ethics Review System: A Qualitative Study

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SIGNATURE FORM

This thesis entitled **Eastern Africa Countries Need and Readiness for Implementation of Harmonized Clinical Trials Regulation and National Ethics Review** is prepared by **Assefa Ejamo:** A Qualitative Study Submitted in partial fulfillment of the requirement of the degree of Masters of Science (MSc) in Clinical trials.

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Abbreviation/Acronyms

AMA: African Medicine Agency

AMRHI: African Medicine regulatory harmonization initiative

AU: African Union

AVAREF: African Vaccine Regulatory Forum

CDT-Africa: Center for Innovative Drug Development and Therapeutic Trials for Africa

CTA: Clinical Trial Authorization

DNDi: Drugs for neglected disease initiative

EAC: East African Community

EFDA: Ethiopian Food and Drug Authority

GCP: Good clinical Practice

ICDRA: International Conference of Drug Regulatory Authorities

ICH: International Conference on Harmonization

IDP: Institutional Development Plan

IEC: Independent Ethics Committee

IGAD: Intergovernmental Authority for Development

LMIC: Low and middle Income Countries

NEPAD: The New Partnership for Africa's Development

NMRA: National Medicine Regulatory Authority

NRERC: National Research Ethics Review Committee

NTD: Neglected Tropical Diseases

PMS: Post-marketing surveillance

PV: Pharmacovigilance

RBEC: Regional Bioequivalence Center

RECs: Regional Economic Communities

USFDA: United States Food and Drug Administration

USP: United States Pharmacopeia

WHO: World Health Organization

Abstract

Background: Medical products are regulated from premarket clinical trials to post marketing surveillance and phase IV clinical trials. Research organizations have responsibilities to conduct clinical trials subject to regulatory and national ethics review process before putting products on the market. Harmonized approaches for regulation of clinical trials and national ethics review are practiced globally including in Eastern Africa countries under regional economic communities. However, there are gaps in medicine regulatory in general and clinical trials regulatory and national ethics review harmonization in particular. **Objective:** The aim of this study was to assess the need and readiness for implementation of harmonized clinical trial regulation and national ethics review in Eastern Africa.

Methodology: A qualitative study was conducted in selected Eastern Africa countries focusing on regional economic communities (RECs). Data were collected through semi structured questionnaire from National Regulatory Authorities, National Ethics Review Committee, development partners, sponsor and research institutions through email by assigning facilitators in each country, and were analyzed thematically using QDA Miner Lite qualitative data analysis software. Specific countries regulatory and ethics review system components were analyzed according to the nature of questions and responses.

Results: It was noted that 5 Eastern Africa countries involved (Ethiopia, Kenya, Sudan, Uganda and Tanzania) in the present study had national legislations for medicines and clinical trials regulations. Shortage, lack of experience, lack of appropriate expertise and poor professional mix were staff related problems identified in this study. It was noted that clinical trial structures were established at directorate level in one country, at team level in three countries and none in one. These findings reflect countries readiness for implementation of harmonization initiative. Capacity building, utilizing limited resources in the region and ensuring quality were some of need related findings for implementation of harmonized approach. Existence of platforms like RECs, partners support and enabling conditions were identified opportunities for implementation of harmonized regulation and national ethics review. Challenges identified were lack of awareness, difference in administrative procedures, lack of commitment, resource limitation, and requiring long time for implementation of harmonization. Differences were also noted among countries and RECs (IGAD and EAC) in regulatory system and progress in implementation of harmonization initiative respectively.

Conclusion: The readiness of most of the countries in regulating clinical trials is not adequate to implement harmonized clinical trials regulation and national ethics review. However, there is remarkable need for harmonization in the region. Countries need to strengthen their clinical trial regulatory and national ethics review system in consideration of harmonization.

Key Words

Harmonized Clinical Trials Regulation, National Ethics Review, Eastern Africa Countries

2. Background

Medical products are regulated from premarket clinical trials to post marketing surveillance, i.e., phase IV clinical trials(1). Medical products which need to be regulated include medicines, medical devices, biological/herbal medicines and other related products (2–5). Clinical trial is a study that tests a new medical treatment or new way of using of an existing treatment to see if it will be a better way to prevent and screen for diagnosis or treat a disease(6). In another way, International Conference on Harmonization tripartite guideline defines clinical trials as 'any investigation on human beings to discover or verify the clinical, pharmacological and/or other phamracodynamic effect of investigational products, and/or to identify any adverse reaction to an investigational products, and/or study of the absorption, distribution ,metabolism and excretion with object of ascertaining its safety and/or efficacy(7).

Data generated on safety and efficacy for the specific medical products in various phases of clinical trials have to be made available for market authorization, while safety and right protection should be reviewed by an independent ethics committee (IEC) and competent regulatory authority(8,9).

Product development from animal model to clinical trials intended for use in human beings requires robust and well organized regulation and ethics review to protect participants from any unnecessary harm(10).Research organizations have responsibilities to conduct clinical trials before putting their products on market to confirm the tolerable level of safety and promising efficacy data. Unless there is adequate regulatory oversight; clinical trial participants will be at risk, and it diminishes generation of appropriate information to weigh balance between risk and benefits of the products(11).

There are various regulatory challenges on clinical trials conduct. Such challenges include limited resources, lack of technical competency, inappropriate informed consent, ability to cope up with evolving complex technology, shortage of staff, inadequate legal framework, poor compliance and difficulty in developing commonly accepted standards of clinical trials regulation(12–15). Regulatory and ethics reviews are not easy tasks; they require a well-organized regulatory structure, technical competency of reviewers/inspectors and commonly acceptable standards (16).

Medicines regulatory harmonization is taking place in various regions globally. Some of the regions where regulatory harmonization initiatives have been taken include Asia-Pacific economic cooperation(APEC),East African Community(EAC) and Pan American Network for Regulatory Harmonization(PANDRH) (13,26).

Many efforts are being made by various regions in different continents to implement harmonized approaches considered to be the way for facilitation with exiting minor cultural difference among regions of the countries(33,34). In medical products developments, harmonization has paramount importance to facilitate for problem solving (reducing barriers) to improve access to medicines by reducing time taken for regulation and with reasonable cost of medical products (20).

As there are challenges to comply to the globally accepted good clinical practice or ICH GCP due to limited resources and lack of technical competency, there is a continuous need of support from various organizations for regulatory body but the sustainability of the support is a concern for clinical trials regulations(21). Protection of human participants with appropriately delivered informed consent(22)and ethical consideration along with evolving technology of clinical trials requires well developed system and human power in the area of improvement of conduct of clinical trials. The emerging complexity of data management, monitoring and reporting requires well advanced capability for clinical trials(23).

African vaccine regulators forum (AVAREF) was established by WHO in 2006 for strengthening regulatory capacity for clinical trials conducted in Africa. The forum promoted primarily different standards development and harmonized approaches and standards for accelerating the review of vaccines which have high public importance. There are tools developed by AVAREF which include guide for inspection of clinical trials, guideline for joint review and assisted review of clinical trial application and different templates for assessment of quality, statistical aspect and application forms(24).

Despite the establishment of different initiatives of harmonization approaches in Eastern Africa region, there is limited consideration of the actual set ups of countries regarding the need and readiness of countries for effective implementation of harmonized regulatory and ethics review of clinical trials through support of research findings(25,26). Unless there is acceptable level of readiness which satisfy requirements of conducting clinical trials, there will not be sustainable system and procedure for conducting clinical trials and adequate protection of human participants safety, rights and wellbeing(27,28).

Literature Review

Harmonized clinical trials regulation and national ethics review is believed to be among strategies for minimization of various barriers and disparity in regulation and review process. Concept of harmonization goes back to years with establishment of founding members of EU, USA and JAPAN (29–31).Three years back of establishment; formerly International Conference on Harmonization (ICH) is evolved to International Council for Harmonization with opening the door for other countries under SWISS law. Thus, ICH laid foundations for innovation and clinical development of medical products. Various models of harmonized clinical trials in various regions have different initiatives of regulatory harmonization(32).

The regulation of medicinal products in pre and post authorization phases requires laws, norms and standards required for regulation taking in to consideration for risk minimization activities and risk management. Besides lack of the adequate legal provisions and standards, the common problems observed in regulatory sectors are conditions of fragmentation and uncoordinated delegation(33).

There are various factors that seek common strategies to overcome, and all clinical trial stake holders have to be benefited from regional solutions, and can go to global health related problems in the same manner. There are diseases that specifically affect the Eastern Africa region like neglected tropical disease(34,35). Despite the existence of the problems, the challenges remain unsolved and there need to be initiatives to address. For instance, the concern of chemotherapy for leishmaniasis due to lack of making the area agenda of research, screening for new drugs and standardization of clinical trials is identified (36).

Sharing common borders is also linked with cooperation and collaborative approaches and calls for international collaborations(37,38).The out breaks and public emergency conditions are situations which invite immediate responses at national, regional and global levels. Thus there is a need of solutions with collaborative and cooperative approaches of the countries(39,40). Compared to other African regions, Eastern Africa countries are among the ten top contributing countries for increased population (61%). The high population in the region can be seen as another factor that makes the region appropriate for clinical research as high population, likely increase number of participants to generate generalizable data (41).

The ethical principles need to be rigorous enough for ensuring adequate protection of research participants and data credibility which are expected from independent research ethics committee(42). During conduct of clinical trials the issue of ethics not only about trial design and ensuring willingness of participants or voluntariness but also extends to protection of right, safety and interests of the participants throughout the study (43). Research activities are highly recommended for sustainable health solutions in Eastern Africa (44).

Recently there are various initiatives taking place in different forms (models) of harmonization indifferent regions of the Continents in the world and different forms of regulation of medicinal products. However, most initiatives taking place are not being implemented in the way of sustainable, legally supported and in consideration of acceptable level of countries readiness and based on actual need (45). Guidelines and standards are necessary for facilitation of mutual acceptance of clinical trial data by the regions involved in the harmonized approach of the countries. Both ethical and regulatory standards provide assurance of protection of human participant's safety, rights and wellbeing. The 1947-Nuremburg code, 1964-Declaration of Helsinki,1979-Belmont Report and 1996 ICH-GCP ethical and GCP documents are historical standards and guidelines used for clinical research in different times based on different events that occurred at different times(46).

The challenges associated with conduct of clinical trials in multi countries are more serious than those in a single country. When multi country trials are conducted, investigators and sponsors are expected to fulfill regulatory requirements in all countries to conduct clinical trials. More specifically, limited budget, delay of clinical findings for health of the population and inefficient implementation of multi-country clinical trials are the challenges associated with them(47).

There are various barriers that do not enable the regions to conduct and facilitate development of medical products (48). In addition, non-communicable diseases are becoming a growing concern which call up on high facilitation of medical products development and support of efforts of various research and academic institutions(49).

Despite challenges of regulatory and ethics review, there is increased need of innovation and technology transfer of diagnostics for appropriate test and improvement of treatment for management of infectious diseases. It requires well developed collaborative procedures which

reduce the efforts of time taking, helpful for cost reduction and common use of the regional findings for various regional and global problems(50).

EAC and IGAD member countries are lower(Ethiopia, Sudan and Uganda) and lower middle income(Kenya and Tanzania) countries in which there is a growing need to conduct clinical trials which require well-functioning and established harmonized trials regulatory and national regulatory approaches(51). Common standards use can make acceptance of data generated for marketing authorization and implementation in clinical practice effective and easy, increased access to safe and effective medicines and advanced set up for clinical trials (52).

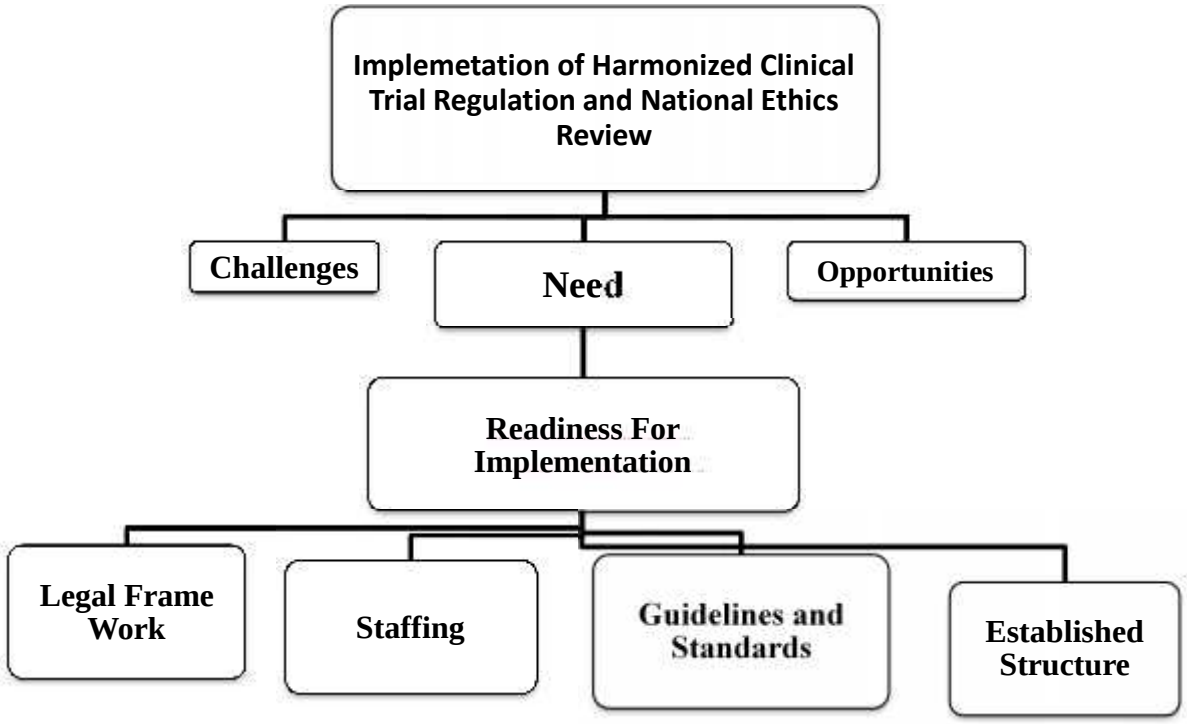

Figure 1: Conceptual Frame Work

4. Statement of problem

Clinical trials conducted at different phases are normally reviewed and approved by independent national ethics committee and competent regulatory authority before commencement of the conduct of trials on human participants. All approval processes by both stake holders take time and require resources or become reason for requiring more resources and sometimes can be barrier for innovation and solution for burden of various health related problems.

Harmonized clinical trials regulatory approaches among different regions of continents will have impact on reducing overall barriers of conduct of clinical trials. For implementation of harmonized clinical trials regulatory procedure there should be adequate readiness in respective countries with respect to commonly accepted and adopted regulatory standards, competent and adequate number of regulatory staffs and appropriate legal framework to support and follow the results of review, inspection and approval. Unless there is readiness in staff competency with adequate number, making clinical trials one of the regulatory priority area, adopting and developing commonly accepted regulatory standards; implementation of regulatory and ethics review harmonization may not be possible and problem solving and have sustainable system for innovation of new medical products. In addition, there is limitation in consideration of situations at ground in LMICs by various development partners and high income countries.

Globalization in various areas including clinical trial is increasing. In globalization of clinical trials, regulatory and ethics harmonization procedures cannot be neglected. So that without appropriate readiness and need of the countries with commonly accepted standards, procedures and system; implementation and generating both safety and efficacy data may not be acceptable and difficult to grant marketing authorization and making accessible for patients based on fragmented approaches and system of countries in the region.

Regional differences in various aspects of drug regulatory and ethical review procedures are different contributing factors for inefficient drug accessibility and approval procedures and highly affect product innovation and technology transfer including cost and delay in time of developing the medical products. The likely existence of gaps in Eastern Africa countries regarding readiness and need is believed and is required to be bridged. This helps bring solution for various challenges for conducting clinical trials and important to improve access to

medicines, technology transfer, and innovation and building capacity of regulators and ethics committee.

Regulatory compliance and ethical conduct of clinical trial has paramount importance for ensuring safety, wellbeing and right of participants of clinical trial. Based on its importance, having appropriate regulatory and ethical procedures including ethics committee, important standards, competent staff, and regulatory structures need to be there for clinical trials regulation and ethics review. Unethically conducted research has many consequences that the results may not be acceptable, safety of patients may be compromised, and dignity of participants might be diminished. In addition, unless the appropriate regulatory and ethics procedures are met in the countries of the region, the benefits of effective harmonization; such as system sustainability, strategy development, minimization of barriers for innovation, cost reduction and acceleration of access to medical products cannot be ensured. Therefore, to implement the initiative of effective harmonization of the regulatory and ethical procedures, personnel and standards should be well established in the countries of the regions.

5. Significance of Study

As one of the stakeholders of clinical trials, a regulatory body will use the study findings to identify the existing gaps, to take appropriate action regarding clinical trials authorization (oversight) and contribute for readiness to implement GCP standard clinical trials. Furthermore, the findings will contribute to fill the gap and serve as experience sharing. Harmonizing regulatory and ethics review system saves time and finance to ensure governments efforts on safety and efficacy of medicines.

These findings will help investigators conduct their clinical trials with reduced barriers like delay approval and increased cost. They will be able to start the study early and make ready for policy makers with established and facilitated regulatory and ethical system of clinical trials.

Clinical trials are conducted primarily to solve public health problems so that the facilitation of the conduct of clinical trials with the maximum safety and confirmed efficacy will ultimately make the public beneficiary by increasing access to medicine with ensured efficacy and safety. As a region, there are health problems specifically affecting the Eastern Africa and necessitate to attract more clinical trials. Therefore, the findings will be helpful for government, policy makers and researchers to strengthen the system, develop guidelines and fill the gaps identified. Furthermore, the experiences will be extended to researching on other core regulatory functions under medicine regulatory harmonization initiatives.

6. Objectives

6.1. General Objective

- To assess the readiness and need for implementation of harmonized clinical trial regulation and national ethics review system in Eastern Africa

6.2. Specific Objective

- To assess the readiness of countries in terms of adequacy and competency of staff
- To assess the readiness of the countries in developing legal framework and having structure to implement harmonized clinical trials regulatory and national ethics review approach
- To assess the harmonized guidelines and standards of clinical trials regulation and national ethics review
- To assess the need for implementation of harmonized clinical trials regulation and national ethics review
- To assess opportunities and challenges in the implementation of regulatory harmonization initiatives and member countries of RECs adopting (compliance to) AVAREF tools

7. Methodology

7.1. Study Area and Period

The study was conducted in selected Eastern Africa countries focusing on regional economic communities, i.e. EAC and IGAD regional economic communities (Ethiopia, Kenya, Sudan, Tanzania and Uganda). The selected countries were from 8 EAC member countries (Kenya, Uganda, Tanzania, Burundi, Rwanda and South Sudan) and 8 IGAD member countries (Djibouti, Ethiopia, Eritrea, Kenya, Somalia, the Sudan, South Sudan and Uganda) based on the experience of clinical trials conducted and accessibility of key informants. The experience of conduct of clinical trials was determined based on information obtained from WHO international clinical trial registries platform, U.S. National Library of Medicine, ClinicalTrials.gov (https://apps. who.int /trial search/ and https://www.clinicaltrials.gov/ct2/home) and NRAs joint review, different forums of capacity building activities in the region. The study was conducted starting from March/2020 to September/ 2020.

7.2 Study Population

Regulatory experts of all included Eastern Africa countries' National Medicine Regulatory Authorities (NMRA); National medicine and Poison Board (NMPB) of Sudan, Ethiopian Food and Drug Authority (EFDA), Pharmacy and Poison Board (KPPB) of Kenya, Tanzania Medicine and Medical Devices Authority (TMDA), National Drug Authority (NDA) of Uganda, National Ethics Committee Members of participating countries, IGAD Health Expert, DNDi staff, USP technical advisor, and research institutions were participated in the study. A total of 24 participants participated in this study. Considering the relevance of clinical trials with other core regulatory functions, Pharmacovigilance, Medicine Registration and experience of harmonization experts dealing other than clinical trial were also involved from NMRA.

7.3. Study Design

Study design was qualitative. Semi-structured questionnaires were developed based on the specific area of the participants in qualitative approaches; the opinions collected through semi-structured questionnaire were analyzed. All participants were contacted through their email address by facilitators of data collection. The address of participants was obtained through request of collaboration through the use of information found during joint training, assessment and GCP inspection activities.

The existing legal frameworks, inclusion and compliance to AVAREF tools in the regulatory framework, gaps regarding regulatory capacity, existing structure, development of harmonized

standards and tools were assessed. The need, challenges, and opportunities for harmonized regulation of clinical trial and national ethics review system were analyzed thematically.

The questionnaires were grouped in to five major parts: for regulators, national ethics review committee, sponsors, and development partners and for selected investigators in selected research institutions. Appropriate questions directly related with or addressing missions of NMRA, national ethics review committee and development partners together with their contribution for regulatory system strengthening of the countries were included into the questionnaires.

Prior to administering the questionnaire, the study participants were provided with general information about the study by providing an information sheet which includes the importance, aim of study and requesting their consent before answering the questions.

7.4. Operational Definitions

Readiness: Readiness is acceptable level that enables Eastern Africa countries to implement harmonized clinical trial regulation and national ethics review of clinical trials through having legal provisions, harmonized guidelines and standards, competent and adequate staff and appropriate structure(53).

Need: Need is the difference between currently available clinical trials regulatory and national ethics review system in Eastern Africa countries and the desired conditions through harmonized clinical trials regulation and national ethics review(54,55).

Regulatory and National Ethics Review Harmonization: Bringing together Eastern Africa countries NMRAs and national ethics committee into agreement or harmony to develop common guidelines and standards, communicate and collaborate in aim of building capacity, improve public health, facilitate access to essential medicines and improve regulatory and ethics committee performance, sharing of scarce resources and reduce duplication of efforts(56).

7.5. Eligibility Criteria

7.5.1. Inclusion Criteria

1. NRAs staff involved in harmonization activities of Eastern Africa countries having at least experience of regulation of clinical trials, Pharmacovigilance and medicine registration
2. Sponsors involved in at least one clinical trial in the region

3. Research institutions having experience of conducting clinical trials in the region
4. National research ethics committee member having direct involvement in clinical trials application review process
5. Development partiers having participation in facilitation and capacity development activities in the region.
6. Participants willing to participate

7.6. Sampling procedure

The nature of research question and objectives were taken into consideration where the key role players were few in number. However, the representation was considered by taking into consideration of both economic communities of Eastern Africa in which involved countries have remarkable experience of conducting clinical trials in the region.

Purposeful sampling with criterion and maximum variation sampling design was implemented. As important stake holders, regulators, researchers, national ethics committee members and sponsor were involved in the study. In addition, because of their important role in organizing and being involved in capacity building activities, development partners like IGAD, WHO and USP were involved. Among selected countries of Eastern Africa, there were one EAC member country (Tanzania), two both EAC and IGAD member countries (Uganda and Kenya) and two IGAD member countries (Ethiopia and Sudan). The sampling procedure is schematically presented in Figure 2.

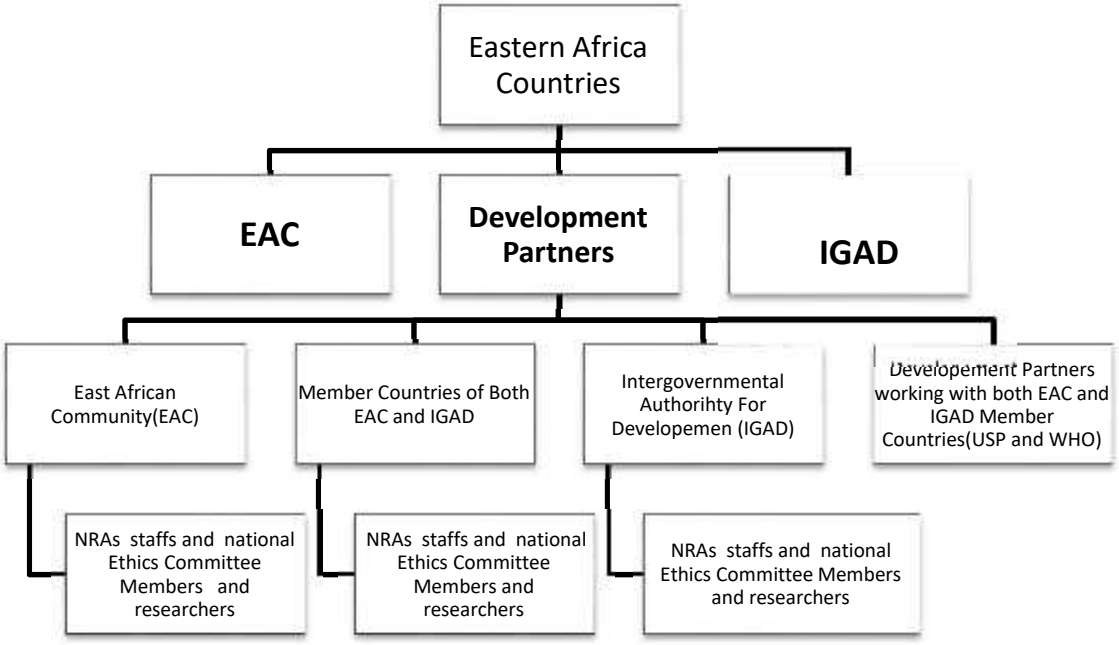

Figure 2: Schematic Presentation of sampling procedure

7.7. Data Collection

The data collection tool (semi-structured questionnaire) was prepared by considering the general harmonization approach of core regulatory functions. In addition, international organizations guidelines including adoption of AVAREF tools and WHO (Global bench marking tool) were considered.

7. 8. Quality Assurance

The actions taken to ensure quality of the research were re-administering the analyzed part of the research for some of the selected study participants, re-reading (re-checking) and iterative processes were followed during coding and thematic analysis. Two researchers other than principal investigator were involved independently in coding of qualitative data to avoid researcher bias.

The questionnaire was administered part by part to participants as their relevance to the respondents: regulators, national ethics review committee, development organizations, research institutions and sponsors. To address the right participants, the questionnaires were delivered by data collection facilitators in each country.

7.9. Data Analysis

The responses related to legal framework, organizational structure, staffing and standards were analyzed as specific countries system components of study. Responses related to need, opportunities, challenges, and specific opinions relevant to harmonization were analyzed qualitatively using QDA Miner Lite software. In the QDA Miner Lite software coding texts from participant's opinion, retrieving and reviewing coded data was undertaken. Thematic analysis was done following developing codes required to be given through identification of ideas and patterns of meaning that come up repeatedly. During thematic analysis both sub themes and themes were drawn. During coding, familiarization, coding, generating sub theme and themes with reviewing were undertaken. Themes and sub themes were presented in tables.

7.10. Ethical Consideration

Ensuring the right to participate (give information), the importance or benefit of participation for system improvement and protection of participant's information are relevant ethical issues of the study. Therefore, the protocol was submitted to Scientific and Ethics committee of CDT-Africa under College of Health Sciences in Addis Ababa University before commencement of the study. After delivering the information, consent was obtained from participants before involving them in the study. The basic research ethical principles were ensured by protecting confidentiality, obtaining informed consent, and disclosing the information on potential risk/ benefit due to their participation.

8. Result

8.1. Participants Characteristics

In total24 individuals participated in the study, of 9 were from NRAs, 3 from National Ethics Review Committees,5 from development partners, 3 from sponsor and 4 from research institutions. The age groups of participants were between >30(1), 30-39(12) and 40-49(10) and >50(1) with Males (16) and Females (8) of the 24 participants. Their highest level of education was first degree (7) and MSc (16) and PhD (1). Regarding professional mix Pharmacists were the highest number (12) followed by Physicians (5). Other disciplines account for 7participantsas indicated in Table 1.

Table 1: Participants Characteristics

Characteristics		Number (%)
Age Group	18-29	1(4.16%)
	30-39	12(50%)
	40-49	10(41.6%)
	>50	1(4.16%)
Sex	Male	16(66.7%)
	Female	8(33.3%)
Highest Level of Education	First Degree including MD	7(29.17%)
	MSc	16(66.7%)
	PhD	1(4.16%)
Year of Experience in Years	1-5	8(33.33%)
	6-10	7(29.16%)
	11-15	5(20.83%)
	16-20	2(8.33%)
	21-25	2(8.33%)
Profession	Pharmacist	12(50%)
	Physicians	5(20.83%)
	Pharmacologist	2(8.33)
	Bioethicist	1(4.16%)
	Immunologist	1(4.16%)
	Medical Manager	1(4.16%)
	Clinical Trialist	1(4.16%)
	Chemist(environmentalist)	1(4.16%)

8.2. Countries, Institutions and Responsibilities of Participants

Ethiopia, Kenya, Sudan, Tanzania and Uganda were included in the study. Within clinical trial related activities, the participants had different responsibilities and roles such as project management, leadership, review of applications, secretary role and principal investigators. The other core regulatory activities like Pharmacovigilance (Post marketing surveillance) and medicines registration were also merged in to one directorate in 4 of the included countries. Countries, institutions and responsibilities of participants are presented in Table 2.

Table 2: Countries, Institutions and Responsibilities of Participants

Countries	Institutions	Responsibility of Participants
⁾ Ethiopia ⁾ Kenya ⁾ Sudan ⁾ Tanzania ⁾ Uganda	⁾ Research Institutions for researchers ⁾ National Regulatory Authorities ⁾ Ministry of Science and Higher Education in Ethiopia, National Institute for medical research in Tanzania and Kenya Medical Research Institute (KEMRI) for ethics review ⁾ Development Partners ⁾ Sponsor	⁾ National Ethics Committee Secretary ⁾ Clinical trial unit leader ⁾ Researchers ⁾ Reviewing clinical trial protocols ⁾ Conducting GCP inspection ⁾ Pharmacovigilance activities ⁾ Technical Consultancy ⁾ Head of Scientific and Ethics Review Unit ⁾ Regulatory Officers ⁾ QA Manager ⁾ Quality Control ⁾ Medicine Registration, ⁾ Project Management (coordination), ⁾ Head, Clinical Trials ⁾ National professional officer for essential medicine and drug

8.3. Legal Framework and Clinical Trial Regulatory Structure

All involved countries have legislations in place incorporating the clinical trial authorization (CTA) as part of the regulation. Clinical trial regulatory system was organized at team level in all countries except Tanzania and Sudan. In Sudan, there was no clinical trial regulatory organizational structure. At team level clinical trial regulatory functions were merged with other activities such as Pharmacovigilance, post marketing surveillance and medicine registration at national NRA. In Sudan both technical and ethical issues were handled by the same ethics committee. Therefore, there was no direct involvement of staff although the regulatory role was vested within the national regulatory activity. The legal framework and structure status are indicated in Table 3

Table 3: Legal framework and clinical trial regulatory organizational structure

S.no	Legal Framework	Ethiopia	Kenya	Sudan	Tanzania	Uganda
1.	Existence of legal Framework for medicines	✓	✓	✓	✓	✓
2.	Inclusion of Clinical Trials in to medicine legal framework	✓	✓	✓	✓	✓
3.	Status of clinical trial regulatory structure	At team level under another department	At team level under another department	No established structure	Established at directorate Level	Established at Team Level

Key:

✓ ***Exists***

Team: *Section in particular directorate (within department) responsible for more than one or more regulatory functions such as PV, PMS and Clinical trials*

Directorate: *Department responsible for one or more particular regulatory activity in NRA such as clinical trial, medicine registration and Pharmcovgilance having budget, staff and infrastructure*

8.4. Guidelines and Standards

Guidelines, standards and other relevant tools for regulatory and ethics review system on clinical trials and source documents used in the participating countries.

8.4.1. Guidelines and standards in Ethiopia

Good clinical practice (GCP) and Clinical Trial Authorization (CTA) guidelines, Checklists for review of applications, and procedures for sites inspection were available at NRA of Ethiopia. The National Ethics review guideline is used by the National Health Research Ethics Review Committee. Incompleteness and loose clarity on conduct & regulation of clinical trials were identified problems related to standards and guidelines, e.g. clinical trials on medical devices, data sharing and scope of clinical trial in general. Harmonized national ethics review of clinical trial application was not supported by National Ethics Review guideline and standards. Clinical trial related activities were review of clinical trials applications, authorization, GCP inspection and approval of amendments. ICH guidelines, EMA guidelines and WHO clinical trial

handbook/ manual were used as source documents for the preparation of the standards and guidelines. CTA and GCP guidelines were posted on website ***(http://www.fmhaca.gov.et/)***

8.4.2. Harmonized guidelines and standards in Kenya

National ethics review guidelines did not have adequate and clear legal provisions, and they were not as clear as regulatory guidelines. Activities being accomplished were review of clinical trials application, approval of amendments and GCP site inspection. The accepted AVAREF guidance by KPPB, approved clinical trials and FAQs were posted on the website (*http://www.nmpb.gov.sd/en/)*

8.4.3. Guidelines and standards in Sudan

NRA was not directly involved in clinical trial regulatory activities but facilitated for committee responsible for review of clinical trials applications to approve and good clinical practice (GCP) inspection. There were no guidelines and standards for regulation of clinical trials found during study (posted) on website (http://www.nmpb.gov.sd/en/). However, there was guideline for ethical conduct of research involving human subjects (http://snrec.sd/wp-content/uploads/2017/05/Sudan-National-Ethics-Guidelines.pdf). In addition, there were no supporting guidelines for harmonization in Sudan.

8.4.4. Guidelines and standards in Tanzania

The available guidelines were GCP guidelines**,** Clinical Trial Authorization (CTA) guidelines**,** Standards and procedures for GCP inspection of clinical trials sites**,** Special SOPs for different activities**;** National Ethics review guideline**,** Checklists for review of applications, guideline for inspection of sites and checklist for inspection of trial sites. Identified standards related problems were failure to maximize the potential for new therapies originating from the rich biodiversity in the local environment, lack of regulations governing implementation of trials involving human tissues and specimens like blood and breast milk samples and issues of harmonization was not clearly supported(indicated) by the guidelines. Existing activities were approval of amendments, GCP site inspection and review of clinical trials application. The source documents used for preparing guidelines were from ICH, USFDA and EMA guidelines of clinical trials. There were no guidelines aligned or adopted from AVAREF guidelines except AVAREF Strategy and Guidance for Emergency Preparedness (https://www.tmda.go.tz/)

8.4.5. Guidelines and standards in Uganda

GCP guidelines, CTA, Special SOPs for different activities, Standards procedures for GCP inspection of clinical trials sites and National Ethics review guideline are available. Activities and existing guidance are Approval of amendments, GCP site inspection and Review of clinical trials application. ICH guidelines were identified as source (reference) documents. https://www.nda.or.ug/. In addition, registered clinical trials are found on website https://www.nda.or.ug/human-medicine-guidelines/

8.5. Staff Adequacy, Competency and Related Problems

The average number of staff involved in clinical trial team was 4 in the region. There were internal arrangements to use staff from other sections within the Authority whenever there was a need. The staff related problems mentioned were not taking actions on identified gaps and not considering capacity building activities as one of the priority areas of regulatory authority in planned and regular manner. However, it was noted that there were some attempts such as giving opportunities for education, attending clinical trials forums and hands on trainings in some countries of the region.

It was noted that expertise and competency were available for regulatory review and oversight. However, there were contrasting findings among the participant's responses from different institutions.

The participant's different opinions are quoted as below:

"…staff adequacy can refer all forms competence such as number, qualification, professional diversification, competence by training &/or experience, discipline and diligence. To my assessment, our regulators may be deficient in all aspects but particularly no professional diversification at all." AARI07.

The other participant said that *"…..from the comments we got for our protocols except few most are reviewed by expert comments." GORI09*

The staff related problems identified were no training opportunities nationally and internationally, gap in staff qualification and competency by experience, shortage of staff and no

professional diversification, no gap identification in 3 countries and involvement in more than one regulatory functions.

Table 4: Staff Adequacy, Competence and Related Problems

Staff Related Problems	Promising Findings Related to Staff	Staff capacity Building Activities
Not taking actions on identified gaps and plan ✓ It is not one of priority area of regulatory authority to allocate budget for capacity building activities ✓ No training opportunities nationally and internationally. ✓ There is gap in Staff qualification and competency by training and experience respectively ✓ Shortage of staff ✓ There is gap in adequacy of staff as it can be confirmed from the time taken to give feedback ✓ No gap identification in three of countries ✓ Involvement in more than one regulatory function ✓ No professional mix	✓ There is expertise as can be seen from the feedbacks ✓ Staff are qualified and competent for regulatory review and oversight ✓ There is gap identification experience.	✓ Education Opportunities ✓ Participation in hands on activities ✓ Participation in international and national trainings ✓ Oversee short- and long-term training for the staff ✓ Attending different clinical trial forum and workshop ✓ Ensuring the staff adherence to the established clinical trials standard operating procedures ✓ Regular training and exposure ✓ Mentoring and in house training

8.6. Focus to CTA, Precondition and Actions Need to Be Taken

Allocation of budget, having adequate and competent staff in place, ensuring that awareness of all stakeholders on harmonization has been created, developing and implementation of clear

regulatory standards and attracting funds to increase number of clinical trial applications were identified ways for giving focus to CTA. It was also noted that sustainability related problems need to be solved. How to give focus to CTA, Pre-conditions and actions need to be taken are presented in the table 5.

"*…most regulatory harmonization started with support of development partners with inadequate ownership and empowerment of member states, and hence sustainability is still an issue.*" *AAPA25*

"…developing a regional / national institutional development plan or strategy, Capacity building of technical experts, Promote/Sensitize the process and guidelines to stakeholders" (KERE24)

Table 5: Giving Focus to CTA, Precondition for Harmonization and Actions to Be Taken

S.N.	How to give Focus to CTA at country level	Precondition for Implementation of Harmonization	Actions to be taken
1.	Having Clear Legal Framework	Inclusion of harmonization in legal framework	Development of harmonized standards
2.	Having adequate and competent staff	Ensuring technical Capacity (competency) and adequacy of experts	Develop a regional / national institutional development plan (IDP) or strategy
3.	Allocation of Adequate Budget	Understanding the importance of harmonized clinical trial regulation and national ethics review	Ensuring that there is awareness on the importance of harmonization
4.	Facilitation for the conduct of clinical trials	Ensuring sustainable system and procedures regionally	Promote/sensitize the process and guidelines to stakeholders

8.7. Monitoring System of Harmonization

Strengthening of the initiative should not be considered as one time event rather it should be a continuous process. Regarding the process of strengthening of the system the following quote is taken:

"…the roadmap for harmonization should be started today but with step by step and clear action points over years (framed timeline) with political will plus financial commitments for continuous capacity building investments. It is also worthy to learn from other regional initiatives in this regard for the pros & cons of harmonization so that can be re-purposed in the context". (AARI07)

In the opinion of participants, monitoring system of the harmonized regulatory and national ethics review system further strengthened through complementing activities in the regions of Eastern Africa countries as indicated in the Fig. 3.

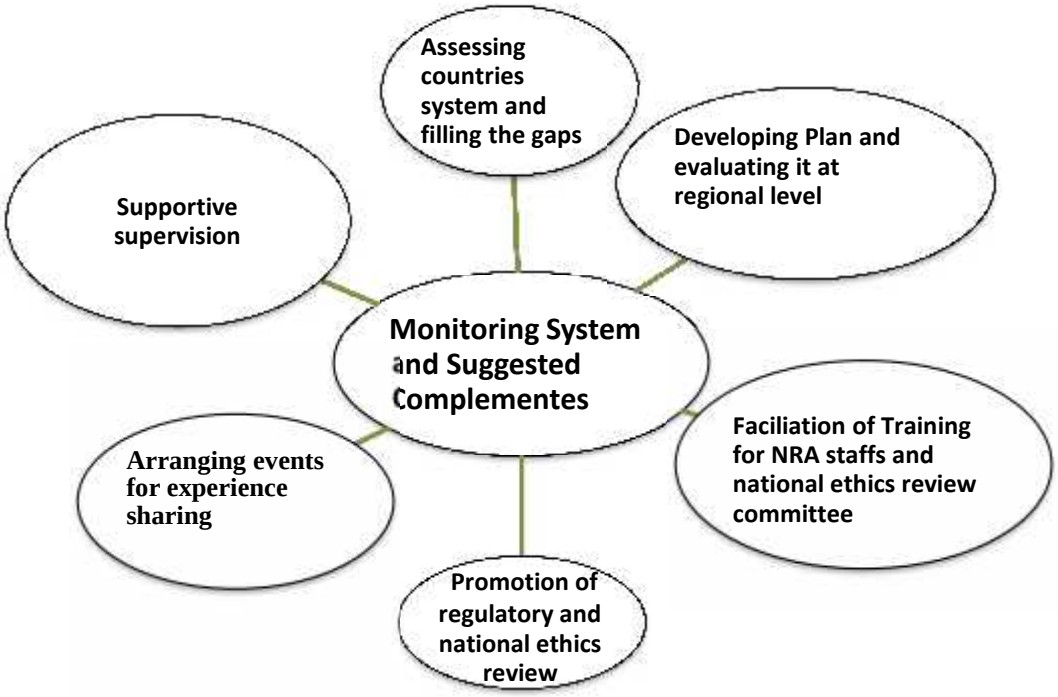

Figure 3.Monitoring System of the harmonization initiative and suggested Complements

8.8. The Need for Harmonization

Totally 3 themes and 13 sub-themes were identified on need for harmonization at regional level and related with capacity building, utilization of limited resources in the region, facilitation for

bringing sponsors and researchers to involvement, increased regulatory and ethics compliance, to ensure efficiency and quality of review process. Themes and sub-themes are indicated in Table 6. The need related findings from specific participants of the study were quoted as below:

"…we need to review the clinical trial in harmonized ways because it important to reduce the time required approving protocols, attract funding from researchers and funding agencies; providing stakeholders with timely information and progress status of the various research projects, enhance sharing of experiences and gain knowledge (Promote the efficiency of the ethics review committees". (AAEC04)

"Harmonization fastens the review process which eventually ensures increased accessibility of medicines to the public reduction of cost for manufacturers as it reduces the need of compiling different applications and sometimes in different languages to suit individual countries".(AANRA19)

"…Particularly the growing local Pharmaceutical industry that wills surely seeking for regional marketing may be an immediate pressing demand for harmonization. However, it might be long to go to have common vision and clear goal among member countries". AARI07

"…epidemic outbreaks, increased interest of many African Countries including East Africa are promoting local production and attracting direct foreign investment in medical product manufacturing, various solidarity in promoting access to essential medicines is demanding harmonization regulation and ethical review of clinical trials". AAPA25

Table 6: Themes and Sub Themes Related To Need

S .no	***Themes***	***Sub Themes***
1.	Capacity Building and Limited Resources in the region	Capacity Building
		Save Time and Cost of NRAs
		Facilitate Experience Sharing

2.	Increase Sponsors and Researchers Involvement and Regulatory/Ethics Compliance	Improve Regulatory Compliance of stake holders
		Safeguard Safety and wellbeing of participants
		Attraction of Funding
		Increases conduct of Clinical Trials(encourage innovation) and access to medicines
		Encourage local production
		Decrease number of amendments
3.	Ensuring Quality and Efficiency of Review Process	Improve quality of review
		Timely feedback delivery
		Easy conduct of multi country trials

8.9. Opportunity for Implementation

Totally 3 themes and 11 sub-themes were identified on opportunity. Opportunities for implementation of harmonized clinical trial regulation and national ethics review was identified as desire expectation to have strong regulatory and ethics review system in the region, presence of initiatives and platforms and enabling situation as indicated in the table 6.Some quotes related to the existing opportunities are presented as below:

"…existence of huge number of population within the member states countries promotes researchers and CRO, the pandemic COVID looks for new drugs and vaccine for development, the existence of common WHO/GBT/ tools for NRA function which approaches different regulatory function of variety countries..." (AANRA19)

"…*the interest of sponsors, pharmaceutical manufactures toward Africa which will increase clinical trial request and regional BE center if accredited by WHO"*. (AANRA21)

Table 7: Themes and Sub Themes Related to Opportunity

S.No.	Themes	Sub Themes
1.	Stake holders expectation to have strong regulatory and ethics review system in the region	Desire to share data and other information easily
		Desire to strengthen System through the process
		To have harmonized guidelines and standards
		To enhance and improve regulation and national ethics review
2.	Presence of initiatives and platforms	Availability of global tools to follow and evaluate system as IDP
		RBEC based on its accreditation status
		Presence of RECs for facilitation
3.	Enabling situation	Increased interest of stake holders
		Large number of population
		Public health emergencies(outbreaks)
		Presence of support from partner institutions and platforms

8.10. Challenges for Implementation

Challenges for effective implementation of harmonized regulation and national ethics review were identified as stakeholders' awareness gap, difference in administrative actions of individual countries, lack of commitment, difference in set up and resources, requirement of long time for making fully established and functional system. Both themes and sub-themes are presented in Table 8. Among responses related with challenges one of the responders is quoted as below:

"Most east African countries are facing with inadequate budget which is allocated in NRA, shortage of staffs and lack of competency to carry the assessment and inspections of clinical trial applications in the region. The researchers have low awareness on the laws and rules on regulations of clinical trials in the region. Different levels of regulatory activities among the countries obstruct the smooth execution of harmonized activities. Other countries have advanced in term of regulatory function and other they don't have even regulatory framework such as laws and regulation of clinical trials" TANRA14

Table 8: Themes and Sub Themes Related to Challenges

S.N	Themes	Sub-Themes
1.	Presence of stake holder's awareness gap	Investigators awareness gap
		Partners awareness gap
		Sponsors awareness gap
2.	Difference in administrative processes and interest of individual countries	Difference in countries preferences
		Difference in legal frameworks
		Lack of mutual recognition for regulatory decisions
		Mistrust among member states
		Lack of government and others stake holders commitment
3.	Difference in set up and resources	Staff Shortage and gaps in competence
		Organizational structure difference
		Difficulty of coordination
		Difficulty to establish the same standards
		Lack of sufficient funding
		Shortage of infrastructure
		Different level of expertise and experience
		Lack of ethics and regulatory legislation
		Lack of clarity of process between review boards and regulatory authorities.
4.	Long time to establish functional system	Ensuring clinical trial stake holders awareness about harmonization
		Ensure readiness of member countries
		Time for developing governing guidelines
		Establishment of validation system for shared information among member countries

8.11. Regional and Individual Countries Differences

Differences were noted among individual countries in structure, approach of review, capacity building activities and development of harmonized guidelines. Progress in Implementation of harmonized clinical trial regulatory and national ethics review initiative was not the same in both EAC and IGAD regional economic communities.

"I think regulators in the region are not at same or comparable maturity level and hence there is a need to create awareness to the NRAs in the region so that all will be on the same page..." AAPA22

…there is progress as individual countries but there are gaps as a regions and difference in IGAD and EAC regions of the initiatives … KERE24

8. Discussion

The study explored various relevant issues related to readiness and need for harmonized clinical trials regulation and national ethics review system. For effective implementation and satisfying the actual need of the initiative, effort and readiness of individual countries would have direct impact and reflection at regional level for the implementation of harmonization initiative. Regulatory framework is the crucial part of any functional regulatory authority established to ensure safety, efficacy and quality of medical products. Our study findings show that there was legal framework in all participating countries for regulation of medicines in general and clinical trials in particular. The legal frame work for medicine regulation in general and inclusion of clinical trial regulation in particular were found to be consistent with WHO Drug Information report, review article and review of international documents(57–59). Following legislation, countries develop guidelines and standards to interpret and put direction on how to comply to the regulatory legislation(58).

Clinical trials regulatory activities of the participating countries were found to be structured at team level except one which has been organized at directorate level showing that not all countries have given equal focus on regulatory functions of clinical trials.

Our assessment revealed that there were attempts to have national guidelines and standards in all participating countries. However, significant guidelines related problems have been identified. Such problems include failure to address specific areas of clinical trials, incompleteness, lack of

clarity to differentiate among clinical trials, behavioral studies, observational studies… etc. Furthermore, the standards did not address harmonized clinical trials regulation and national ethics review. These findings were in contrast to ICDRA 14th report which addressed countries need to take the initiatives to their legislation (60).

The basic issues which need to be addressed to implement harmonization issue are harmonizing important standards, inclusion of initiative in medicine legislation of individual countries (55), staff capacity building and improvement of organizational structure. Unless addressed, system sustainability and collaborative approach may not be effective; as harmonization needs agreement to work together in different model of implementation (26,25). In the present study, we found that there were gaps in standards adequacy, clarity on how to address the specific areas of clinical trials like maximization of biodiversity, data sharing and distinction of clinical trials from other observational studies. There are structures for regulating clinical trial at team level merged with other regulatory activities.

Competency, professional mix and shortage of staff were identified staff related problems in our study. These findings are inconsistent with the indicators related to staff on WHO bench marking tool for countries institutional development(IDP) for clinical trials oversight (53), and in addition, regulation of clinical trials require qualified, competent and experienced staff (61).

We found that the average number of staff for regulatory activities within NRA was four in all participating countries. This number of staff was not only for clinical trials regulation but also for other regulatory functions such as pharmacovigilance and post marketing surveillance. To attain the two common goods of GCP, i.e., participants protection and data credibility, availability of qualified, experienced and committed staff in all stakeholders including regulatory authorities and ethics review committees is crucial. The growing need and attraction of clinical trials is demanding all the required resources including appropriate staffing and functional institutional structure. These resources were found to be scanty in all participating countries in our study. Though there were some weakness with regard to clinical trial regulation and ethical review system in all participating countries, strength was also observed in some countries. In Tanzania, clinical trial regulatory functions have been organized at directorate level and the practice of using staff from another directorate as per need have been noted. In Kenya, the AVAREF guidelines and other tools were adopted and posted at KPPB website which can be taken as

important example of actions for harmonization. In Ethiopia, there were plans to develop SOPs for specific clinical trial regulatory activities and staff capacity building by giving opportunity for education. This gives confidence for investigators conducting clinical trials as the decision to be made by the regulatory authority studies will be appropriate. Countries focus to CTA has connection with improving the regulatory system structurally, materially, and financially in addition to human resource. The staff related problems in the region have impact on harmonized clinical trial regulation and national ethics review system such as delay of feedback to applicants of clinical trial protocol. Incompetency and poor experience are associated with deficiency in the safeguard of clinical trial participants, ensuring the quality of data generated from clinical trial site through GCP inspection and progress report evaluation. Similarly, staff related problems identified in our study can be also source of mistrust and problem for mutual recognition of regulatory decisions.

The standards available at countries level reflects the readiness for implementation of harmonized regulatory and national ethics review system. The few standards available in individual countries are more general. Clinical trial regulatory areas require further specific standards and guidelines at regional level to implement harmonized clinical trials regulatory and ethics review system. As our findings indicate harmonized regulatory and national ethics review system establishment require long time as existing challenges for development of strategies and capacity building activities require solution. Differences at country level have been observed; some countries have good initial steps and some require efforts to make the initiative part of countries regulatory system.

RECs are considered to be opportunity for harmonized clinical trials regulation and national ethics review facilitation. In addition to the gaps observed in harmonizing or adopting AVAREF guidelines, our study findings showed that there was no harmonization on the regulatory framework and ethics review system. Lack of clarity also negatively affects the conduct of clinical trials. Even though there were gaps in specificity and clarity, almost all the available documents found in our study were adopted from one or more globally accepted and harmonized documents such as ICH, AVAREF and USFDA (https://www.ich.org/) (62).

Desire for capacity building, limited resources in the region, to increase sponsors and researcher's involvement, to maximize regulatory/ethics compliance to standards and ensuring quality and efficiency of review process were found to be the reasons for the need for

implementation of harmonized clinical trials regulation and national ethics review system. Complexity of implementation and benefits of standardization were similarly reported in United Kingdom on standard harmonization and cultural difference for multi-national clinical trials by Christine et al. (63) .

From the opportunities perspective our study showed; stakeholder's expectation to have strong regulatory and ethics review system in the region, presence of different initiatives and platforms and enabling conditions as existing opportunity to further strengthen the harmonized regulatory and national ethics review system of the regions. CTA as one of the important areas as innovation and solution for various public health problems such as already existing diseases, emergencies , and outbreaks, NRAs and National Ethics Review system need to give it more focus. The detail of opportunities related to enabling situations are large number of population, interest of partners to support and the availability of existing initiatives, global bench marking tools for evaluation of the system for countries institutional development plan and assessment by WHO's NRA evaluations system (53).

Collectively as a region the challenges for effective implementation of harmonized clinical trial regulation and national ethics review of the initiative are explored. The anticipated challenges to implement the initiative effectively are presence of awareness gap, difference in administrative processes and preferences of individual countries, differences in setup and resources and lengthy process of establishing functional system which agrees with finding reported by Paul Ndebele et al., on regulatory challenges associated with conducting multi-country clinical trials in resource-limited settings and S. Atzor et al., from Switzerland and United States of America reported on whether EU clinical trials regulation support the innovative industry respectively (47,64). In addition, it is indicated that multi-country clinical trial is difficult to conduct even having advanced procedures in place (5,50).

9. Limitation

It was not possible to collect data by physical contact of participants due the lock down of travel to different countries due to COVID 19 global pandemic. Some potential partners for the initiative were not included in the study (NEPAD, AVAREF and Pharmaceutical Companies)

10. Conclusion

Efforts and strengths of individual country are the foundation for effective implementation of regional harmonized clinical trial and national ethics review system. Generally, there are gaps of structural, staffing and standards and integration of harmonization to national regulatory framework. The results showed that some individual countries are ready to implement. However, looking at the insufficient focus given on organizational structure, standards development and staffing. Readiness to implement the initiatives does not seem realistic. However, there are efforts made to support and change clinical trials landscape as individual countries and regions.

Our findings suggest that there is strong need for implementation of harmonized clinical trial regulation and national research ethics review system.

11. Recommendations

- Member countries need to improve their own regulatory system in staffing, establishing appropriate structure and putting important standards in place
- All partners need to develop plan and strategies to support RECs to have timely monitoring system of the initiative
- Countries should use of the available tools effectively for implementation of harmonized procedures
- The need for harmonization and challenge needs be answered in aligned or integrated manner for harmonized clinical trial and national ethics review of clinical trial in Eastern Africa.
- Countries lacking NRAs and functional system of regulation shall develop legal frameworks, standards and perform capacity building activities.
- RECs need to play leading role in countries system improvement at regional and individual countries level
- Further researches need to be conducted at individuals, institutional , and regional level on specific areas of harmonization
- There should also be experience sharing activities in between the two RECs

References

1. Alqahtani S, Seoane-vazquez E, Rodriguez-monguio R, Eguale T. Priority review drugs approved by the FDA and the EMA : time for international regulatory harmonization of pharmaceuticals ? 2015;(October 2017).
2. Sen S, Chakraborty R. Revival, modernization and integration of Indian traditional herbal medicine in clinical practice: Importance, challenges and future. J Tradit Complement Med [Internet]. 2017;7(2):234–44. Available from: http://dx.doi.org/10.1016/j.jtcme.2016.05.006
3. Medical WHO. WHO Global Model Regulatory Framework for Medical Devices including in vitro diagnostic medical devices.
4. Jones DR, Mcblane JW, Mcnaughton G, Rajakumaraswamy N, Wydenbach K. A regulatory perspective of clinical trial applications for biological products with particular emphasis on Advanced Therapy Medicinal Products (ATMPs). 2012;203–9.
5. Services H. Enrichment Strategies for Clinical Trials to Support Determination of Effectiveness of Human Drugs and Biological Products Guidance for Industry Enrichment Strategies for Clinical Trials to Support Determination of Effectiveness of Human Drugs and Biologi. 2019;(March).
6. Thorat SB, Banarjee SK, Gaikwad DD, Jadhav SL, Thorat RM. CLINICAL TRIAL : A REVIEW. 2010;1(2):101–6.
7. Conference I, Harmonisation ON, Technical OF, For R, Of R, For P, et al. E6(r1). 1996;1996(June).
8. Ndomondo-Sigonda M, Miot J, Naidoo S, Dodoo A, Kaale E. Medicines Regulation in Africa: Current State and Opportunities. Pharmaceut Med. 2017;31(6):383–97.
9. Vitezić D, Lovrek M, Tomić S. Centralized national ethical review of clinical trials in Croatia. Croat Med J. 2009;50(2):111–6.
10. Vannice KS, Wilder-Smith A, Barrett ADT, Carrijo K, Cavaleri M, de Silva A, et al. Clinical development and regulatory points for consideration for second-generation live attenuated dengue vaccines. Vaccine [Internet]. 2018;36(24):3411–7. Available from: https://doi.org/10.1016/j.vaccine.2018.02.062
11. Maïga D, Akanmori BD, Chocarro L. Regulatory oversight of clinical trials in Africa: Progress over the past 5 years. Vaccine. 2009;27(52):7249–52.
12. Dansie LS, Odoch WD, Årdal C. Industrial perceptions of medicines regulatory harmonization in the East African Community. PLoS One. 2019;14(6):1–15.
13. Grover S, Xu M, Jhingran A, Mahantshetty U, Chuang L, Small W, et al. Gynecologic Oncology Reports Clinical trials in low and middle-income countries — Successes and challenges. Gynecol Oncol Reports [Internet]. 2017;19:5–9. Available from: http://dx.doi.org/10.1016/j.gore.2016.11.007
14. Teo HS, Foerg-Wimmer C, Chew P-LM. Medicines Regulatory Systems and Scope for Regulatory Harmonization in Southeast Asiahttps://www.facebook.com/messages/t/100000588810776. Med Regul Syst Scope Regul Harmon Southeast Asia. 2016;
15. Collins JF, Sather MR. Regulatory Issues for Clinical Trials in Humans. 2018;24(1).

16. Milstien J, Belgharbi L, Milstien J. Regulatory pathways for vaccines for developing countries. 2004;003046(03).
17. Pombo ML, Porrás A, Saidon PC, Cascio SM. Regulatory convergence and harmonization: Barriers to effective use and adoption of common standards. Rev Panam Salud Publica/Pan Am J Public Heal. 2016;39(5):217–25.
18. Guidance D. Rare Diseases : Common Issues in Drug Development Guidance for Industry Rare Diseases : Common Issues in Drug Development Guidance for Industry. 2019;(February).
19. Training of Regulators. 2017;(November).
20. Tamura A, Kutsumi H. Multiregional medical device development: Regulatory perspective. Clin J Gastroenterol. 2014;7(2):108–16.
21. Marchetti E, Mazarin-Diop V, Chaumont J, Martellet L, Makadi MF, Viviani S, et al. Conducting vaccine clinical trials in sub-Saharan Africa: Operational challenges and lessons learned from the Meningitis Vaccine Project. Vaccine. 2012;30(48):6859–63.
22. Lema VM, Mbondo M, Kamau EM. Informed consent for clinical trials: A review. East Afr Med J. 2009;86(3):133–42.
23. Moodley J, Naidoo S, Morar NS, Govender V, Charls P, Ramjee G. Ethical considerations in implementing a biometric co-enrolment prevention system in clinical trials in South Africa. South African J Bioeth Law. 2016;9(1):39.
24. Document History Code AVAREF2017-JRCTA History Original document Date Endorsed by AVAREF Steering Committee. :1–18.
25. Maïga D, Akanmori BD, Chocarro L. Joint reviews and inspections: Strategic forms of collaboration for strengthening the regulatory oversight of vaccine clinical trials in Africa. Vaccine. 2009;28(2):571–5.
26. Vannice K, Chocarro L, Pfleiderer M, Bellah A, Ward M, Yoon IK, et al. The value of multi-country joint regulatory reviews: The experience of a WHO joint technical consultation on the CYD-TDV (Dengvaxia®) dossier. Vaccine [Internet]. 2017;35(43):5731–3. Available from: http://dx.doi.org/10.1016/j.vaccine.2017.07.044
27. Li G, Wu Q, Jin Y, Vanniyasingam T, Thabane L. Key factors of clinical research network capacity building. 2018;1–7.
28. Sleeboom-faulkner M, Chen H, Rosemann A. Regulatory capacity building and the governance of clinical stem cell research in China. 2018;45(November 2017):416–27.
29. Evangeline, L; Mounica, NVN; Reddy, VS; Ngabhushanam, MV; Reddy, DN; Bonthagarala B. Regulatory process and ethics for clinical trials in India (CDSCO). Pharma Innov J. 2017;6(4 Part C):165–9.
30. Guerra SÁ. Harmonization of quality standards for clinical trials. ISO-9001 standard and guide of good clinical practice. Rev Cuba Farm. 2011;45(3):380–8.
31. Lourenco C, Orphanos N, Parker C. The International Council for Harmonisation : Positioning for the future with its recent reform and over 25 years of harmonisation work. 2016;18:79–89.
32. Coalition COE. APEC LSIF RHSC Training Centers of Excellence for Regulatory Science Operating Model and Guidelines APEC LSIF RHSC Training Centers of

Excellence for Regulatory Science - Operating Model and Guidelines. 2018;(January).

33. Series RS. Practical Guidance for Conducting a Review (based on the WHO Data Collection Tool for the Review of Drug Regulatory Systems). 2007;(12).
34. Wissmann B, Welburn SC, Lutumba P, Fe EM. The Burden of Human African Trypanosomiasis. 2008;2(12).
35. Bern C, Maguire JH, Alvar J. Complexities of Assessing the Disease Burden Attributable to Leishmaniasis. 2008;2(10).
36. Croft SL, Olliaro P. Leishmaniasis chemotherapy — challenges and opportunities. 2011;
37. Cain KP, Marano N, Kamene M, Sitienei J, Mukherjee S. The Movement of Multidrug-Resistant Tuberculosis across Borders in East Africa Needs a Regional and Global Solution. 2015;1–7.
38. Preston C, Chahal HS, Porrás A, Cargill L, Hinds M, Olowokure B, et al. Regionalization as an approach to regulatory systems strengthening : a case study in CARICOM member states. 2016;39(5):262–8.
39. Himeidan YE, Kweka EJ, Mahgoub MM, Amin E, Rayah E, Ouma JO. Recent outbreaks of Rift Valley fever in East Africa and the Middle East. 2014;2(October):1–11.
40. Nishioka SA. CARTAS LETTERS Cooperation between regulatory authorities from developing countries in the evaluation of vaccine clinical trials Cooperação entre agências reguladoras de países em desenvolvimento para avaliação de ensaios clínicos de vacinas. 2008;24(9):2191–2.
41. Africana U. STATE OF AFRICA ’ S POPULATION 2017 Keeping Rights of Girls , Adolescents and. 2017;(March).
42. Dove ES, Townend D, Meslin EM, Bobrow M, Littler K, Nicol D, et al. Europe PMC Funders Group Ethics review for international data-intensive research *. 2016;351(6280):1399–400.
43. Silverman H. Ethical Issues during the Conduct of Clinical Trials. 2007;4:180–4.
44. Macdonald NE, Bortolussi R, Kabakyenga J, Pemba S. MicroResearch : Finding sustainable local health solutions in East Africa through small local research studies. J Epidemiol Glob Health [Internet]. 2014;4(3):185–93. Available from: http://dx.doi.org/10.1016/j.jegh.2014.01.002
45. Zerhouni E. The need for global regulatory harmonization : A public health imperative. 2016;8(338):11–3.
46. Report C, Wandile P, Ghooi R. Bioethics A Role of ICH- GCP in Clinical Trial Conduct. 2017;8(1):1–5.
47. Paul Ndebele, Christina Blanchard-Horan, MA, CCRP†, Akbar Shahkolahi, PhD†, and Ian Sanne, MBBCH, FCP, DTMandH. Regulatory challenges associated with conducting multi-country clinical trials in resource-limited settings: Manuscript A. NIH Public Access. 2015;65(0 1):1–6. doi:10.1097/QAI.0000000000000037.
48. Nair SC, Ibrahim H, Celentano DD. Clinical trials in the Middle East and North Africa (MENA) Region: Grandstanding or Grandeur? Contemp Clin Trials [Internet]. 2013;36(2):704–10. Available from: http://dx.doi.org/10.1016/j.cct.2013.05.009
49. Unachukwu CN, Agomuoh DI, Alasia DD. Pattern of non-communicable diseases among

medical admissions in Port Harcourt, Nigeria. Niger J Clin Pract. 2008;11(1):14–7.

50. Hauskeller C, Baur N, Harrington J. Standards, Harmonization and Cultural Differences: Examining the Implementation of a European Stem Cell Clinical Trial. Sci Cult (Lond). 2017;5431:1–26.

51 World Bank Country and Lending Groups (https://datahelpdesk.world bank.org/knowledgebase/ articles/906519-world-bank-country-and-lending-groups)

52. Directions F. Perspectives on Metastasis.Pdf. 2007;14(6):687–96.

53. WHO GLOBAL BENCHMARKING TOOL (GBT) FOR EVALUATION OF NATIONAL REGULATORY SYSTEM OF MEDICAL PRODUCTS CLINICAL TRIALS OVERSIGHT (CT): INDICATORS AND FACT SHEETS. 2018;(November):1–50.

54. Concept of Need(https://www.joe.org/joe/1964summer/1964-2-a4.pdf)

55. Poc MA, Reggi V. Medicines regulatory harmonization: international collaboration as a key to improve public health. 2017;1(1):10–3.

56. Akanmori BD, Mukanga D, Bellah A, Traore T, Ward M, Mihigo R. The Role of The African Vaccine Regulatory Forum (AVAREF) in The Ac- celerated Clinical Evaluation of Ebola Vaccine Candidates During the Large West Africa Epidemic. 2018;75–9.

57. Article R. Legal and ethical issues in research. 2016;(76):684–8.

58. African S. Regulatory Harmonization. 2010;24(1):6–20.

59. Patr M. International Documents. 2017;(August).

60. Conference I, Authori- DR, Authority HS, Conference T. 14th International Conference of Drug Regulatory Authorities. :1–16.

61. Preston C, Chahal HS, Porrás A, Cargill L, Hinds M, Olowokure B, et al. Regionalization as an approach to regulatory systems strengthening : a case study in CARICOM member states. 2016;(December).

62. African T, Regulatory V. Regulatory collaboration. 2015;29(2):127–32.

63. Hauskeller C, Baur N, Harrington J. Science as Culture Standards , Harmonization and Cultural Differences : Examining the Implementation of a European Stem Cell Clinical Trial Standards , Harmonization and Cultural Di ff erences : Examining the Implementation of a European Stem Cell Clinical Trial. 2019;5431.

64. Atzor S, Gokhale S, Doherty M. Will the EU Clinical Trials Regulation Support the Innovative Industry in Bringing New Medicines Faster to Patients ? 2013;75–82.

Annex: QUESTIONNAIRES (1)

QUESTIONNAIRES (1)

You are cordially invited to respond on the questions which are raised on readiness and need for harmonized clinical trials regulation and ethics review in Eastern African countries and to contribute for advancement of the clinical trial regulation and national ethics review. Thank you in advance for your cooperation by taking your time. All of your responses are entirely used for the research purpose with appropriate protection of confidentiality. The questionnaires are prepared in five main parts for the whole study. This is one of the five parts and you are administered with more of clinical trials regulation related questions.

Questions for National Regulatory Authority

1.1 Background Information

Age: _____

Sex:

M **F**

Country:

Institution:

Responsibility:

Profession:

Physician **Pharmacist** **Nurse** **Others, Specify**

Year of Experience and Current Job Title/Position:

Education Level:

Degree **Msc** **PhD** **Others, Specify**

1.2. Part I

1. Is there legal framework for regulation of medicines in the national medicine regulatory authority (NMRA)?

○ Yes ○ No

2. If yes, does legal framework include the regulation of clinical trials?

○ Yes ○ No

3. Is there established structure for regulation of clinical trials in national medicine regulatory authority (NMRA)?

○ Yes ○ No

4. If your answer for question number 3 is yes, what is the division (structure) that the clinical trials regulatory activities are handled in NMRA?

☐ Department Level (as clinical trial department)

☐ Team level under another department. e.g Medicine registration, drug information (PMSPV)

☐ At activity level under other departments

☐ Only focal person assigned for clinical trials

☐ Other,Specify

_____

_____

5. What activities are being done related to clinical trials regulation in your country?

☐ Review of clinical trials application

☐ Good clinical practice (GCP) site inspection

☐ Not directly involved on the review of clinical trials activities but facilitate for national ethics committee review

☐ Approval of amendments

☐ Others, Specify

_____

_____

6. What is number of staff involved in clinical trials activity, if it is at department or team level?

☐ 2

☐ 3

☐ 4

☐ 5

☐ Others,Specify

_____

7. What is the profession of staff involved in regulation of clinical trials?

☐ Physicians

☐ Pharmacists

☐ Nurses

☐ Specialists in clinical Trials

☐ Others, Specify

_____

_____

8. Do you have guidelines and standards for regulation of clinical trials?

☐ Yes ☐ No

9. If your answer for question number 8 is yes, what are the standards you are using for clinical trials regulation?

☐ Good clinical practice(GCP) guidelines

☐ Clinical Trial Authorization (CTA) guidelines

☐ Special SOPs for different activities

☐ Standards or procedures for GCP inspection of clinical trials sites

☐ Others,Specify

_____

_____

10. What are guidelines from which your guidelines and standards were adopted?

☐ From ICH guidelines

☐ From AVAREF guidelines and standards

☐ From USFDA clinical trials guidelines

☐ From EMA guidelines

☐ Others, Specify

_____

_____

11. Are your institution (NMRA) representatives participating in African vaccine regulators forum (AVAREF) meetings?

○ Yes ○ No

12. Do you have information on initiatives and activities of harmonized regulation and national ethics review of clinical trials in Eastern Africa Countries (EAC and IGAD)?

○ Yes ○ No

13. If your answer for question number 12 is yes, does the medicine regulatory legal framework include the harmonized clinical trials regulation?

○ Yes ○ No

14. Do you think that there is importance in harmonized regulatory and national ethics review of clinical trials? ○ Yes ○ No

15. If your answer for question number 14 is yes, what do you think will be importance of following harmonized clinical trials regulatory and national ethics review approach?

☐ **Increase quality of clinical trials and Capacity building**

☐ Facilitation of innovation and Accelerate Access to medicines

☐ Optimize review timeline and Avoid unnecessary delay of approval

☐ Minimize different regulatory and ethics review related barriers

☐ Reduce costs related with clinical development of products

☐ Others,Specify

_____

_____

16. Is there any experience for your institution to use clinical trials related information shared among other countries?

○ Yes ○ No

17. Is there website for your institution in which clinical trials guidelines and tools found?

○ Yes ○ No

18. If the answer for question number 17 is yes, are there any standards posted on the websites?

○ Yes ○ No

2. Part II

1. Is there experience of identification of gaps related with appropriate training needs on clinical trials and filling them for staff involved in clinical trials regulatory activity?

○ Yes ○ No

2. If your response for question number 1 is no, what will be possible reason to not identify gaps and train staff?

☐ Because of small number of yearly clinical trials application

☐ Clinical trials activity can be done by experience

☐ . It is not one of priority area of regulatory authority activities

☐ No budget allocation for training

☐ There is not training opportunities nationally and internationally

☐ Others, Specify

3. Please mention actions taken to ensure competence of clinical trial regulatory staff in national medicine regulatory authority (NMRA) if any.

4. Are there clinical trial standards (guidelines) specifically aligned to African vaccine regulators forum (AVAREF) guidelines and standards in your regulatory authority?

- ○ Yes
- ○ No

5. If your answer for question number 4 is yes, please mention some of the AVAREF standards (guidelines) used or aligned to national standards (guidelines).

6. What challenges do you think are there in your opinion for effective clinical trials regulation and national ethics review in your country?

- ☐ Inadequate allocation of budget
- ☐ Not making regulation of clinical trials one of priority areas of regulatory authority activities
- ☐ Not having common understanding of harmonized regulation
- ☐ Lack of competence for regulation of clinical trials
- ☐ Others, Specify

7. Do you think that there is need for implementations of harmonized national ethics review and regulation of clinical trials in Eastern Africa countries?

○ Yes ○ No

8. If your answer for question number 6 is yes, please mention the rationale for need of harmonized clinical trials regulation and national ethics review?

_____

_____

_____

_____

_____

_____

_____

9. If your response for question number 7 is no, what will be the reason in your opinion?

☐ Low awareness about harmonized approaches

☐ Low level of need for harmonized approaches

☐ Due to regional differences of systems of regulation or commitment

☐ Because of it is agenda of sponsors (other development partners NGOs)

☐ Difference in understanding and accepting its importance

☐ Differences in readiness and strength of systems

☐ Others, Specify

_____

_____

_____

_____

_____

_____

_____

10. What challenges and opportunities are there in your opinion for harmonized national ethics review and regulation of clinical trials in Eastern Africa countries?

11. Please write your general comments on countries appropriate readiness and need of effective implementation of clinical trials regulatory and ethics review harmonization

QUESTIONNAIRE (2)

You are cordially invited to respond on the questions which are raised on readiness and need for harmonized clinical trials regulation and ethics review in Eastern Africa countries and to contribute for advancement of the clinical trial regulation and national ethics review. Thank you in advance for your cooperation by taking your time. All of your responses are entirely used for the research purpose with appropriate protection of confidentiality. The questionnaires are prepared in five main parts for the whole study. This is one of the five parts and you are administered with more of clinical trials national ethics review related questions.

Questions for National Ethics Review Committee

Age: _____

Sex:

☐ M ☐ **F**

Country:

Institution:

Responsibility:

Profession:

☐ **Physician** ☐ **Pharmacist** ☐ Nurse ☐ **Others, Specify**

Year of Experience and Current Job Title/Position:

Education Level:

☐ **Degree** ☐ **Msc** ☐ **PhD** ☐ **Others, Specify**

1.2Part I

1. Is there national independent ethics committee (IEC) for review of clinical trials conducted on human participants in your country

○ Yes ○ No

2. If yes, what is the composition of national ethics review committee members by profession?

- ☐ Physicians
- ☐ Pharmacists
- ☐ Nurses
- ☐ Representative of Community
- ☐ Any relevant scientists
- ☐ Others, Specify

_____

_____

_____

_____

3. If your answer for question number 2 is no, please mention how clinical trials are conducted regarding ethics review?

- ☐ Through IRBs of research institutions or Universities
- ☐ By only regulatory approval
- ☐ It is not mandatory to pass through ethical review
- ☐ Others,Specify

_____

_____

_____

_____

_____

4. What are the tools used by the national ethics review committee for the review of clinical trial application?

- ☐ National Ethics review guideline
- ☐ Checklists for review of applications
- ☐ Guideline for inspection of sites
- ☐ Checklist for inspection of Trial sites

☐ There are no organized tools for ethical review of applications

☐ Others, Specify

5. Do you have information of medicine regulatory harmonization initiatives and national ethics review of clinical trials in Eastern Africa (EAC and IGAD regions)?

○ Yes ○ NO

6. If your answer for question number 5 is yes, is the harmonized national ethics review of clinical trial application supported by national ethics review committee standards (guidelines)?

○ Yes ○ No

7. Do you have any information about African vaccine regulators forum (AVAREF), its activities and tools?

○ Yes ○ No

8. If your answer for no.7 is yes, is there any attempt to incorporate (comply) or adopt AVAREF tools to national guidelines or standards?

○ Yes ○ No

9. Is there any mutual recognition and working together in between Independent Ethics committee and national regulatory authority?

○ Yes ○ No

10. If your answer for question number 9 is yes, how the collaboration and working together is taking place?

☐ By making Prerequisite by national regulatory authority

☐ Joint review at country level

☐ Joint Inspection of clinical sites at Country level

☐ Developing Harmonized Standards

☐ Others, Specify

11. In your opinion do you think that there is importance in following harmonized clinical trials regulations and national ethics review in Eastern Africa countries (EAC and IGAD regions)?

○ Yes ○ No

12. If your answer for question number 11 is yes, what do you think will be importance of following harmonized clinical trials regulatory and national ethics review approach?

☐ Increase quality of clinical trials and Capacity building

☐ Facilitation of innovation and Accelerate Access to medicines

☐ Optimize review timeline and avoid unnecessary delay of approval

☐ Minimize different regulatory and ethics review related barriers

☐ Reduce costs related with clinical development of products

☐ Others,Specify

2. Part II

1. Do you think that there is need for implementations of harmonized national ethics review and regulation of clinical trials in Eastern Africa countries?

○ Yes ○ No

2. If your answer for question number 1 of **Part II** is yes, please mention the rationale for growing need of harmonized clinical trials regulation and national ethics review?

3. If your response for question number 1**part II** is no, what will be the reason in your opinion?

- ☐ Low awareness about harmonized approaches
- ☐ Not believed on need for harmonized approaches
- ☐ Due to regional differences of systems of regulation or commitment
- ☐ Because of it is agenda of sponsors (other development partners NGOs)
- ☐ Difference in understanding and accepting its importance by NMRA
- ☐ Differences in readiness and strength of systems ☐ Others,Specify

4. What challenges and opportunities are there in your opinion for harmonized national ethics review and regulation of clinical trials in Eastern Africa countries?

5. Please write your general comments on countries appropriate readiness and need of effective implementation of clinical trials regulatory and national ethics review harmonization

QUESTIONNAIRE (3)

You are cordially invited to respond on the questions which are raised on readiness and need for harmonized clinical trials regulation and national ethics review in Eastern Africa countries and to contribute for advancement of the clinical trial regulation and national ethics review. Thank you in advance for your cooperation by taking your time. All of your responses are entirely used for the research purpose with appropriate protection of confidentiality. The questionnaires are prepared in five main parts for the whole study. This is one of the five parts and you are administered with more of clinical trials sites (research institution) related questions.

Questions for Research Institutions

1.1**. Background Information**

Age: _____

Sex:

○ **M** ○ **F**

Country:

Institution:

Current Job Title and Responsibility:

Profession:

○ **Physician** ○ **Pharmacist** ○ **Nurse** ○ **Others, Specify**

Year of Experience:

Education Level:

○ **Degree** ○ **Msc** ○ **PhD** ○ **Others, Specify**

1.2. Part I

1. Do you think that there is adequate and competent (qualified) staff for regulation and national ethics review of clinical trials?

○ Yes ○ No

2. If your answer for question **no.1 of Part I** is no, how the problems of clinical trial regulatory staff related with clinical trials regulation?

☐ Delay in delivery of the results of the review

☐ Low quality of review of the clinical trials

☐ Shortage of the staff for regulation of clinical

☐ Lack of capacity for regulation of clinical trials

☐ Others,Specify

_____

_____

_____

3. Do you have information on initiatives and activities of harmonized regulation and national ethics review of clinical trials in Eastern Africa Countries (EAC and IGAD economic regions)?

○ Yes ○ No

4. In your opinion, do you believe that the harmonized national ethics review and regulation have importance at regional level?

○ Yes ○ No

5. If your answer for question number 4 is yes, what do you think will be importance of following harmonized clinical trials regulatory and national ethics review approach?

☐ **Increase quality of clinical trials and build capacity**

☐ Facilitation of innovation and accelerate access to medicines

☐ Optimize review timeline and avoid unnecessary delay of approval

☐ Minimize different regulatory and ethics review related barriers

☐ Reduce costs related with clinical development of products

☐ Others,Specify

1.2. Part II

1. Do you think that there are adequate and clear legal provisions (legal documents) and standards (regulatory and national ethics review guidelines) of clinical trials in your country?

○ Yes ○ No

2. If your answer for question number 1 **part II** is no, please write your comment on the adequacy and clarity of clinical trials legal frameworks and standards

3. Please, forward your comments regarding the staff adequacy and qualification (competency) for regulation of clinical trials in your country

4. Do you think that there is need for implementation of harmonized national ethics review and regulation of clinical trials in eastern Africa countries?

○ Yes ○ No

5. If your answer for question number 4 is yes, please mention the rationale in your opinion for growing need of harmonized clinical trials regulation and national ethics review?

6. If your response for question number 4 is no, what will be the reason in your opinion?

- ☐ Low awareness about harmonization approaches
- ☐ Due to regional differences of systems of regulation or commitment
- ☐ Because of it is agenda of sponsors (other development partners (NGOs))
- ☐ Difference in understanding and accepting its importance
- ☐ Differences in readiness and strength in countries regulatory systems
- ☐ Others, Specify

7. What challenges and opportunities are there in your opinion for harmonized national ethics review and regulation of clinical trials in Eastern Africa countries?

8. Please forward your general comments on readiness and need of the harmonized national ethics review and regulation in Eastern Africa (EAC and IGAD regional economic communities)

QUESTIONNAIRE (4)

You are cordially invited to respond on the questions which are raised on readiness and need for harmonized clinical trials regulation and national ethics review in Eastern Africa countries and to contribute for advancement of the clinical trial regulation and national ethics review in the region. Thank you in advance for your cooperation by taking your time. All of your responses are entirely used for the research purpose with appropriate protection of confidentiality. The questionnaires are prepared in five main parts for the whole study. This is one of the five parts and you are administered with more of clinical trials sponsorship related questions.

Questions for Sponsor

1.1 Background Information

Age: _____

Sex:

○ **M** ○ **F**

Country:

Organization:

Responsibility:

Profession:

○ **Physician** ○ **Pharmacist** ○ **Nurse** ○ **Others, Specify**

Year of Experience and Current Job Title/Position:

Education Level:

○ **Degree** ○ **MSc** ○ **PhD** ○ **Others, Specify**

---

1. 2. Part I

1. Do you have involvement in any aspect of regulation and national ethics review of clinical trials applications in Eastern Africa countries?

○ Yes ○ No

2. If your answer for question number 1 is yes, in which activities you were involved?

☐ Sponsoring Clinical Trials

☐ Management of Sponsored clinical trials

☐ Establishment of DSMB

☐ Giving training for clinical trials staff

☐ Communicating with regulators and other ethics review committee

☐ Others, Specify

_____

_____

_____

_____

_____

3. Do you have information on initiatives and activities of harmonized regulation and national ethics review of clinical trials in Eastern Africa Countries (EAC and IGAD)?

○ Yes ○ No

4. Do you think that the Eastern Africa countries are ready for implementation of harmonized clinical trials implementation?

○ Yes ○ No

5. If your answer for question number 4 is no, what will be the possible reason?

☐ Not understanding the concept of harmonization

☐ No believing that it has benefit or importance

☐ Thinking of not having large number of trials in the region

☐ Lack of technical competence of regulatory staffs

☐ Others, Specify

_____

_____

6. What do you think will be importance of following harmonized clinical trials regulatory and national ethics review?

- ☐ **Increase quality of clinical trials and capacity building**
- ☐ Facilitation of innovation and accelerate access to medicines
- ☐ Optimize review timeline and Avoid unnecessary delay of approval
- ☐ Minimize different regulatory and ethics review related barriers
- ☐ Reduce costs related with clinical development of products
- ☐ Others, Specify

7. In your opinion, do you think that there is difference between countries in regulation and national ethics review process at Eastern Africa region?

- ☐ There is difference in legal provision of regulation and ethics review
- ☐ There is difference in competency of staffs for regulation and ethics review
- ☐ There is difference in developing guidelines and standards
- ☐ There is difference in timely review and giving approval for applications
- ☐ Others, Specify

2. Part II

1. Do you think that there are adequate and clear legal provision and guidelines (standards) for regulation and ethical review of clinical trials in Eastern Africa countries?

○ Yea ○ No

2. If your answer for question number 1 of **part II** is no, can you comment on the status of the legal frameworks and guidelines

_____

_____

_____

_____

_____

3. Do you think that there is need for implementations of harmonized national ethics review and regulation of clinical trials in Eastern Africa countries?

○ Yea ○ No

4. If your answer for question number 3of **Part II** is yes, please mention the rationale in your opinion for the need of harmonized clinical trials regulation and national ethics review?

_____

_____

_____

_____

_____

5. If your response for question number 3 of **part II** is no, what will be the reason in your opinion?

☐ Low awareness about harmonized approaches

☐ Low level of need for harmonized approaches

☐ Because of it is agenda of sponsors (other development partners NGOs

☐ D. Differences in understanding and accepting its importance

☐ Differences in strength of countries regulatory systems

☐ Others, Specify

_____

_____

6. Do you think that harmonized standards and approaches are well promoted in Eastern Africa countries?

○ Yea ○ No

7. If your answer for question number 6 of **part II** is yes, can you mention practical actions taken regarding harmonized clinical trial regulation and national ethics review.

8. In your opinions what are the possible opportunities and challenges for harmonized clinical trial regulation and national ethics committee

9. Please write your general comments on countries readiness and need for effective implementation of clinical trials regulatory and ethics review harmonization.

QUESTIONNAIRE (5)

You are cordially invited to respond on the questions which are raised on readiness and need for harmonized clinical trials regulation and national review in Eastern Africa countries and to contribute for advancement of the clinical trial regulation and national ethics review. Thank you in advance for your cooperation by taking your time. All of your responses are entirely used for the research purpose with appropriate protection of confidentiality. The questionnaires are prepared in five main parts for the whole study. This is one of the five parts and you are administered with the clinical trials support or organizations related questions.

Questions for Partners

1.2 Background Information

Age: _____

Sex:

M **F**

Country:

Organization:

Responsibility:

Profession:

Physician **Pharmacist** **Nurse** **Others, Specify**

Year of Experience and Job Title/Position:

Education Level:

Degree **Msc** **PhD** **Others, Specify** _____

1.2Part I

1. Are there countries without national regulatory authority (NRA) in Eastern Africa?

○ Yes ○ No ○ No Information

2. Do you think that focus should be given for clinical trial authorization (CTA) or clinical trials regulatory and national ethics review harmonization?

○ Yes ○ No

3. If your answer for question number 2 is yes, how the support or focus should be given in your opinion?

☐ By allocation of adequate budget

.

☐ Having adequate and competent staff of clinical trial regulation

☐ Promoting and ensuring that there is awareness on the importance of harmonization

☐ Developing or having adequate and clear regulatory and national ethics review documents

☐ Others,Specify

_____

_____

_____

_____

_____

4. What preconditions do you think are required for effective implementation of clinical trials harmonized regulation and national ethics review?

☐ Development of harmonized regulatory and national ethics review standards

☐ Technical Capacity (competence) of experts in the regulatory authority

☐ Understanding the importance or benefits of harmonized CT regulation and national ethics review

☐ Having legal provision for clinical trials regulations and national ethics review

☐ Ensuring sustainable system of clinical trials regulatory and national ethics review activities

☐ Others,Specify

_____

_____

5. Is there progress in compliance to AVAREF guidelines and tools in eastern Africa Countries?

☐ There is progress in all countries of East Africa

☐ There is progress in some of the East African countries

☐ There may be countries even without attempt to participate at AVAREF meetings

☐ It needs further effort for implementation or adopting AVAREF tools

☐ Others, Specify

_____

_____

_____

6. Do you think that supporting and monitoring system of progress and timely status of harmonization should be there?

○ Yes ○ No

7. If your answer for question no. 6 is yes, what methods you think need be in place to monitor and support the countries?

☐ Assessing countries system and filling the gaps

☐ Developing plan and evaluating it at regional level

☐ Facilitation of the training for regulatory staffs and national ethics review committee

☐ Arranging the events for experience sharing

☐ Supportive supervision and promotion of regulatory and national ethics review harmonization

☐ Others,Specify

_____

_____

_____

8. What do you think will be importance of following harmonized clinical trials regulatory and national ethics review approach?

☐ **Increase quality of clinical trials and Capacity building**

☐ Facilitation of innovation and Accelerate Access to medicines

☐ Optimize review timeline and avoid unnecessary delay of approval

☐ Minimize different regulatory and ethics review related barriers

☐ Reduce costs related with clinical development of products

☐ Others, Specify

_____

_____

_____

9. What do you think about promotion of importance of the regulatory harmonization and national ethics review of clinical trials?

☐ Well promoted for all of stake holders

☐ Not known about harmonized clinical trial regulation and national ethics review

☐ No need to promote

☐ It needs institution taking responsibility to promote

☐ Others, Specify

_____

_____

_____

2. Part II

1. Do you think that there is need for implementations of harmonized national ethics review and regulation of clinical trials in Eastern Africa countries?

○ Yes ○ No

2. If your answer for question number 1 of **part II** is yes, please mention the rationale in your opinion on need of harmonized clinical trials regulation and national ethics review

_____

_____

_____

_____

_____

3. If your response for question number 1 of **Part II** is no, what will be the reason in your opinion?

☐ Low awareness about harmonized approaches

☐ Because of it is agenda of sponsors (other development partners or NGOs)

☐ Difference in understanding and accepting its importance

☐ Differences in strength of countries regulatory systems

☐ Others, Specify

_____

_____

_____

_____

4. Do you think that there is difference between performance of IGAD and EAC regional economic communities of Eastern Africa Countries regarding progress of harmonized regulation and nation ethics review of clinical trials?

○ Yes ○ No ○ No Information

5. If your answer for question number 4 is yes, what will be the main reason for the difference?

☐ Difference in acceptance of importance of the harmonization approach

☐ Because of difference in technical capacity

☐ Lack or difference of support by NOGs or other development partners

☐ Lack of political commitment

☐ Others, Specify

_____

_____

_____

6. Do you think that there is need for harmonized standards development of clinical trials regulation and national ethics review?

○ Yes ○ No

7. If your answer for question number 6 is yes, can provide some of actions need to be taken for development of harmonized standards for clinical trial regulation and national ethics review?

_____

_____

_____

8. What challenges and opportunities are there in your opinion for harmonized national ethics review and regulation of clinical trials in East African countries?

9. Please write your general comments on countries status on readiness and need for effective implementation of harmonized regulation and national ethics review of clinical trials.