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GOOD CLINICAL PRACTICE IN EAST AFRICA: A REVIEW

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ABSTRACT

Objective: To call for harmonisation of good clinical practice guidelines in East Africa as one of the necessary precedents to enhancing their quality and quantity in the region.

Data sources: There were two main sources of background information for this review. The first was a series of articles discussing and documenting the harmonisation process in East Asia and in Latin America. The other was a short survey conducted in Kenya in July 2000.

Study area selection: Most of the survey participants were drawn from the Kenya Medical Research Institute (KEMRI) in Nairobi, Kisumu and Kilifi with a few coming from the vicinity of these areas.

Data processing and analysis: The survey tool was a fourteen page questionnaire seeking information in various areas. These were: personal information, general clinical research information, medical practitioners, clinical research experience, human subject participation, sponsors, clinical trial supplies, investigator sites and general comments. Data entry was performed in Microsoft Access®. Forty four researchers participated in a period of three weeks. Data summaries and reports were performed in SAS®.

Conclusion: The advancing capacity for clinical research in East Africa will be accelerated by harmonising clinical research requirements and guidelines.

INTRODUCTION

Need for more clinical trials in sub-Saharan Africa:

There is a case to be made for increasing the number of clinical trials performed in sub-Saharan Africa. Firstly, many of the medicinal products that are used in this region were developed and tested elsewhere. Because of inevitable variants in the prevailing conditions in the region compared to those under which the trials were done, the outcome measures may significantly be dissimilar to those observed in the experimental studies. Variability may be due to demographic, physiologic, cultural differences in compliance, among many others. This is especially true for drug products intended for indigenous diseases since these factors may all have an effect on the efficacy and toxicity of the drug in question. Secondly, local clinical trials are crucial for capacity building and institutional strengthening. Any of these studies involve scientific, regulatory, industry components and their interrelations. Scientists involved in such trials therefore gain exposure and experience in conducting clinical studies especially those that form part of a multi-national global drug development program. Thirdly, conducting global clinical trials locally will highlight both local and international regulatory issues. Chief among these are the quality and efficacy of drugs in general and as they pertain to local public health needs.

In the current climate of globalisation and market liberalisation, it is counter-productive to regulate clinical studies in complete isolation from other regions of the

world. This is one of the primary reasons why Japan, the United States and the European Community invested substantial financial resources and approximately ten years to derive harmonised guidelines for conducting studies in those countries. The goal of this effort was to ensure that a clinical study performed in a member country would be acceptable, by and large, in any other member country thereby reducing cost, increasing efficiency and ensuring faster access to drug products for patients while maintaining clinical research standards that are acceptable to each country. Many other regions of the world such as Latin America(1), East Asia(2-9) are adapting this process.

Objective: The objective of this article is to argue that regional harmonisation of good clinical practice guidelines in East Africa will help to increase the number of clinical trials in the region. It is also suggested that adapting the International Conference of Harmonisation guidelines, especially that of good clinical practice would help to accelerate the regional harmonisation process.

International guidelines for good clinical practice:

The Declaration of Helsinki, the Council for International Organisations of Medical Sciences Ethical Guidelines for Biomedical Research involving Human Subjects (CIOMS), World Health Organisation (WHO) and International Conference for Harmonisation (ICH), Guideline for Good Clinical Practice (GCP) are examples of international technical and scientific guidelines that have been established for carrying out biomedical research on human subjects. These guidelines provide a welcome common platform of regulatory requirements that facilitate and

support ethical review of biomedical research in all countries around the world. An objective in adapting these guidelines locally is to enhance existing regulatory procedures to be both compliant with the ICH GCP guideline and at the same time locally relevant, practical and culturally sensitive. Compliance, thus defined, is a two step procedure of adapting the guideline practice and putting regulatory systems in place that will ensure adherence. Relevant academic and industrial institutions and government authorities in all countries that participate in global drug development must demonstrate compliance and a commitment to the maintenance and updating of the guidelines as the conduct of clinical trial evolves in response to progress in science among other factors.

In their discussions on prospects for regional harmonisation in Latin America, Bergamo *et al* (1) listed some of the obstacles that are experienced in that region as insufficiency in: legislative and regulatory frame, knowledge and training at all levels, commitment and implementation procedures and systems at the health authorities level, the understanding and commitment to good GCP training programmes in general.

Similarly, Tsutani(2,3), Tominanga(4), Shin(5), Becker(6), Chern(7), Teoh(8) and Guo-Wei(9) presented these and various others as obstacles to the local adaptation of the ICH GCP guidelines in East Asia. As may be expected, cultural differences were noted by these authors as being top among the key issues to be considered. The challenge in the adaptation process for the countries facing those obstacles is how to overcome them in view of insufficient infrastructure, technical and financial resources. These issues are discussed with respect to the East African region.

CURRENT STATUS OF CLINICAL RESEARCH IN EAST AFRICA

East African Cooperation: The commonality in the objectives of socio-economic development of the peoples of Kenya, Tanzania and Uganda has led to the formation of the East African Cooperation (EAC) with a common development strategy. The EAC existed previously as the East African Community since the late sixties but failed in the late seventies due to irreconcilable ideological differences between the then three heads of state which included the former Ugandan dictator Idi Amin. The current effort to revive the EAC hopes to recapture the momentum in economic growth which got derailed and which the three countries have been separately struggling to revive. The EAC is intended as a catalytic mechanism in the general socio-economic development of the people in the region. Their commonality in linguistics, demographics and post-colonial culture can only enhance and facilitate this economic alliance.

In spite of these and other similarities, it is well understood that each country operates independently and is therefore not entirely representative of the whole region. Nevertheless, clinical research in any of the three countries

is a relatively good reflection of the practice in the whole region. Hence, the status of clinical research in the region in general and of GCP in particular will be discussed based on a short survey that was done in Kenya in July 2000.

Clinical research survey: The survey is documented in detail elsewhere(10). Briefly, the objectives of the survey were to find out who does clinical studies, to document the regulatory and ethical review procedures and to assess the level of pharmaceutical industry activity. The results indicated that the availability of excellent health professionals and clinical investigators was perhaps the biggest clinical trial asset in the area. However, only thirteen per cent of the studies are pharmaceutical clinical trials. This estimate is quite reliable given that most of the respondents were from the Kenya Medical Research Institute (KEMRI) which is the main clinical research institution in the country. Traditionally, clinical research in this region has followed an academic model. Most of the clinical research has been epidemiological or pharmacoepidemiological.

The need for and shift towards pharmaceutical trials is the search for ways to deal with health challenges that are common and increasing in sub-Saharan Africa. Increasing population densities and deterioration of the environment, prevalence and evolution of old diseases, cultural evolution, increased levels of immunosuppression, increasing levels of epidemics and non-communicable diseases of the more affluent societies(11) are some of the many interrelated factors that are causing a major strain on medical facilities and resources. The public is increasingly subscribing to drug products that were tested elsewhere with very little if any local testing or validation. One may be concerned that this may cause bigger health problems than they solve and hence the need for more local and regulated drug trials. At the same time, the availability of innovative drug products and the improvement in general medical care during clinical trials have been witnessed as real benefits of clinical trials by the general public.

Regulatory procedures: The national drug regulatory agency in Kenya is the Pharmacy and Poisons Board (PPB) which is under the Director of Medical Services in the Ministry of Health. This agency is mandated to regulate drug registration, quality control in drug prescription and the conduct of all clinical trials in the country. A concerted collaboration by members of the Kenya Pharmaceutical Society, Kenya Medical Association, Federation of Kenya Pharmaceutical Manufacturers, other professional bodies, medical training institutions, members of the research community especially those from academia and the government is committed to revising the PPB mandate to adapt the ICH GCP guideline and bring it to par with regulatory standards in the international clinical trial community. The result of these efforts is the Kenya National Drug policy. Uganda and Tanzania have their own regulatory bodies. What is needed now is a more harmonised EAC policy.

Ethics review boards: At present, there exist institutional review boards (IRB) at KEMRI, Kenyatta

National Hospital and Moi University. The local IRB is used whenever research is undertaken in any of these institutions. All other sites use either their local IRB if it exists or choose between the KEMRI IRB and the review procedure in the National Science and Technology Office in the Office of the President. The KEMRI review procedure consists of a scientific committee, an ethics review committee and a publication committee. There are considerations for a national ethics committee.

Need for harmonisation: Great efforts are being made in the East African countries towards conducting clinical trials under WHO ICH guidelines. Despite this, the region is yet to position itself to participate in clinical drug development at a capacity that it has the potential for. It is arguable that a limited number of regulators, insufficient training in GCP and clinical trial monitoring continue to hinder progress. Given that the benefits of clinical trials in general outweigh the costs, health authorities and clinical investigators in the region should consider ways to participate in global clinical studies even more intensively. GCP compliance is one way to attract more pharmaceutical clinical trials. Other incentives should be worked out. Less cumbersome and bureaucratic regulatory procedures would be another incentive. Preferential review and registration of drugs for which local clinical studies have been done would be very welcome by industry.

Some of the issues to be considered in the ICH GCP guideline adaptation and harmonisation process are: protocol review and approval, informed consent and ethics committees, investigators brochures, importation of investigational products, study materials, storing, handling, shipping and movement of biological material for clinical studies, investigator and staff qualifications and training, clinical monitoring, safety reporting, data management, clinical/adverse drug reactions reporting, good statistical practice and quality assurance and auditing. Most importantly, a GCP compliance program or accreditation system is needed. At present, each of the countries in the EAC addresses some of these issues independently. However, in the harmonisation process, all must be addressed and adapted to the region in a uniform manner. This process has been successfully followed in East Asia(2-9).

OBSTACLES IN THE IMPLEMENTATION OF ICH-GCP

One can identify five major players in the ICH GCP arena, these being: patients and the public, health authorities, academic and training institutions, clinical investigators and the pharmaceutical industry. The one obstacle that is common across all categories of players is lack of necessary resources.

Patients and the public: Clinical researchers have to assume that the general public from which study participants will be drawn do not comprehend all the constitutes and details of a given research protocol. It is therefore the

responsibility of the sponsor and principal investigator to take such actions and procedures as necessary to ensure that each potential study participant does understand their role in the protocol and is in a position to give informed consent. In most developing countries, the additional problem of extreme poverty and illiteracy of the general public places unique challenges to obtaining genuine informed consent. As this is one of the primary requirements in GCP, intensive trial-specific training and information sessions need to be held prior to recruitment. This takes a large amount of resources that are often not available which then creates the vicious cycle of denying clinical trial advantages to those that arguably need it most. Some of these advantages include generally improved medical care and the availability of highly innovative therapeutic products during the clinical trial period.

Health authorities: To be recognised as a credible drug development partner, the various EAC governments must collectively renew commitment of resources to instituting a well-harmonised regional regulatory policy. Current efforts by the medical community in Kenya are steps in the right direction. Similar efforts may be underway in the Uganda and Tanzania. It is time for a deliberate, transparent and adequately supported regional EAC GCP working group that is driven by the governments of the three countries.

Academic and training institutions: The three EAC universities continue to maintain strong western style schools of medicine albeit with ever diminishing financial resources. In spite of this, universities and medical training colleges have to play an even bigger role in constructing the much needed training courses and workshops for health professionals and other researchers that are expected to conduct clinical trials that meet ICH GCP standards.

Clinical investigators: As has been stated before, one of the main assets that is attractive to clinical trial sponsors is the availability of clinical researchers with excellent training and experience. To enhance this even further, a well formulated and thorough ICH GCP training course perhaps leading to accreditation would be of great benefit. KEMRI, Kenyatta National Hospital and individual investigators in various other institutions have made commendable strides to this end. What is needed now is a harmonised approach within each EAC country and institution and across countries.

Pharmaceutical industry: Local innovator pharmaceutical industry is virtually non-existent in this region. All pharmaceutical activity is generated by big international pharmaceutical companies some with local offices. Since all these companies have well-established clinical trial procedures and requirements and are more familiar and at ease with ICH GCP requirements, there is need to establish some collaborative training opportunities between these companies and the relevant institutions. Concerted care must be taken to avoid conflict of interest situations.

SUGGESTIONS FOR THE NEXT STEPS

The production of a comprehensive set of implementation procedures and systems leading to full ICH GCP adaptation involves an extensive number of technical details. A first step in this process would seem to be the formation of a strategic expert EAC GCP working group. Members of the group would be drawn from regulatory authorities, pharmaceutical industries and academic institutions from the three countries to reflect the multidisciplinary scientific, regulatory, ethical and drug development expertise that is needed. Once formed, the group would then be mandated and resourced by the EAC governments to construct an EAC GCP guideline. Below are some suggestions that the group may wish to consider.

Step 1: Will to harmonise: It is important to formally document the will, by the EAC representatives, to adapt the ICH GCP guideline in a regionally harmonised manner. As in the original ICH guideline, one of the primary reasons for harmonisation is the need to efficiently and cost-effectively develop and register good quality, safe and effective medicines in a timely manner. By pooling scientific and regulatory resources, efficiency and cost effectiveness will be greatly enhanced. In addition, the combined population of eighty million inhabitants includes sizable drug-free patient populations with a variety of medical indications that should be part of clinical drug development. Other public health advantages of a regionally harmonised approach include: the prevention of unnecessary duplication of clinical trials, regulatory cost-sharing, shorter time to approvals, less bureaucracy and a more cohesive and stronger clinical investigators group. These issues must be debated, and a consensus reached and documented.

Step 2: General evaluation of existing guidelines: The first assignment for this group may be to evaluate existing guidelines. Some of the issues to work out are: the extent to which current drug registration requirements and guidelines are utilised by clinical researchers and investigators; the level of government and academic commitment and effort to adapt and support these requirements; the disparities and amount of duplication in the guidelines from the member countries; what to retain from each document.

Step 3: Adaptation of ICH GCP: Specific Topics: Most components of the ICH GCP requirements are quite universal and therefore directly transferable. Others, especially those that involve social and cultural issues will need careful evaluation and discussion before a consensus is reached. Examples of these are mentioned below.

Ethics committees (EC) and institutional review boards (IRB): Is there need for a regional EC and how uniform should IRBs be? How should the composition of ECs and IRBs be handled so as to avoid conflicts of interest?

Informed consent issues: In view of the cultural

differences, is "informed consent" by the Western definition feasible? If not, what equivalent procedure should be adapted to still maintain the core values of informed consent especially that of non-coercion and respect for autonomy? In cases where the autonomy of an individual includes some sort of extended family or community, what procedures should be used to ensure that the individual participating in the study is fully aware of their role and the potential risks and benefits?

Investigators delegation of authority: What are the limits of delegation that a principal investigator can give before he or she ceases to be a principal investigator?

Clinical monitoring: Are the current clinical monitoring procedures adequate? If not, what training and other procedures are needed?

Step 4: Maintenance of the EAC GCP requirements: A recommendation should come from the working group as to who shall maintain the guidelines and to whom application for drug registration and or clinical trials should be made. Frequency of review should be stated.

Step 5: Training procedures: Undoubtedly, some training will be required for each step of the process. The biggest issue will be financial resources. Who will pay for training and where will the training be conducted? There are some resources available for ICH training including the Global Cooperation Group (GCG), a subgroup of the ICH steering committees; the WHO is also committed to providing some resources as are some members of the drug industry.

CONCLUSION

Harmonisation of GCP guidelines in East Africa would enhance the clinical research environment and provide incentive to the international drug development community to consider the region in multi-centre clinical studies. It would thus play a catalytic role in increasing the quality and quantity of clinical trials in the region. Fortunately, the ICH guidelines are wide enough in scope that adaptation is viable. However, there must be an appreciation and solid commitment to the process by the governments concerned. The various parties involved such as, government, academic institutions, clinical research institutions, pharmaceutical industries must commit to working together to provide the necessary environment and resources to establish the crucial EAC GCP guideline.

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