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Short communication

Regulatory oversight of clinical trials in Africa: Progress over the past 5 years

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ABSTRACT

Randomized controlled clinical trials represent the best way to establish the therapeutic or preventive value of medicines. This decade has seen a strong shift in the location of clinical trials from industrialized countries to developing countries, including many in Africa. However, without independent strong regulatory and ethical oversight of clinical trials the safety of research subjects, and scientific integrity of clinical data cannot be verified. This article draws up a portrait of clinical trials regulation in Africa in support of development of priority medicines, highlights challenges and presents the progress made by countries under WHO guidance over the past 5 years.

1. Introduction

Rousseau and Cazale define regulation as a means aimed at ensuring a good functioning of a system and keeping its balance [1]. Within the framework of this study we understand by regulation a legal framework properly implemented, that gives mandate to defined bodies to exert the oversight over clinical trials, including the authorization of applications submitted for their approval, effective follow-up of their execution, and their termination if necessary.

Recent statistics show that pharmaceutical companies are changing their strategies by moving their sites of clinical trials to developing countries. For example, out of all clinical trials sponsored by American companies, the proportion of the clinical trials sites within the United States regressed from 90% in 1999 to 47% in 2007 [2]. The European medicines agency (EMEA) estimates that a quarter of the subjects recruited as participants for pivotal clinical trials conducted to build evidence of safety and efficacy of medicines, to support an application for marketing authorization for the period 2005–2008 came from developing countries, many of them in Africa [3].

Two publications in 1999 by WHO, specifying the mandates of national regulatory authorities (NRAs) for vaccine regulation [4,5] marked the need for a change to ensure that there is full regulatory oversight of all clinical trials in Africa. However, this change could not occur without the implementation of initiatives of WHO to support the regulatory authorities of these countries in the process of establishing a regulatory framework.

Indeed before 2005, with exception of very few countries, legislation on regulation of clinical trials was quasi-non-existent in Africa [6]. The same report showed that, where legislation existed, it did not specify who had the mandate to authorize the clinical trials, carry out inspections and to terminate them if found non-compliant with GCP standards and with the approved protocol. Consequently, when an authority authorized the trials, it seldom carried out their follow-up and inspection; the monitoring of their implementation was always limited [6]. In September 2005, WHO organized a workshop on regulatory procedures for clinical evaluation of vaccines in Addis Ababa. This meeting revealed that out of 13 participating African countries, 10 had an ethics committee which examined clinical trial applications, 4 had national regulatory authorities (NRAs) which were involved in the process of clinical trials review and/or authorized the importation of the clinical batches, and/or carried out the inspection of the clinical trial sites. These roles were not always clearly defined in the national legislation. Regulatory structures and review processes varied significantly among countries, in most cases they were less than optimal and they lacked the necessary expertise to conduct the activities involved in the regulation of clinical trials. The NRAs and the ethics committees (ECs), except in 2 cases, acted in parallel and no interaction existed between them [6]. Where NRAs existed there were no proper and complete guidelines for the relevant activities.

This article seeks to draw up a portrait of clinical trials regulation in Africa and presents the progress made by African countries in this regard, under WHO guidance over the past 5 years.

2. Method

We have identified, gathered and analyzed data sources including documents related to the regulation of clinical trials as well

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as relevant documents from health systems in Africa, and those describing the activities of the services involved in the regulation of clinical research. The review of documents including meeting reports made it possible to analyze the changes in regulation in African countries as reported by representatives from NRAs and ECs. Progress was assessed by comparing the situation before 2005 and in 2009, almost 5 years after the introduction of the WHO initiatives to support NRAs for the oversight of clinical trials.

3. Results

3.1. Limitations of the regulatory framework for clinical trials before 2005

3.1.1. Legal and regulatory framework for clinical trials

The various stages of development of a drug or vaccine are: (i) discovery and development, including testing in animals; (ii) evaluation in human subjects through clinical trials (phases 1–3); (iii) obtaining the marketing authorization; (iv) post-marketing surveillance through phase 4 clinical trials [7]. In the industrialized countries, these stages of development of a drug or vaccine, including the clinical trials, are governed by many legislative and regulatory measures. In general, to exert regulation these countries refer to a competent authority in charge of the regulation of the pharmaceutical sector. All clinical trials must be declared to this authority which is legally entitled to give the authorization to start a clinical trial. The WHO GCP guideline mention that the "*The role of governments is to provide the legal framework for clinical trials*" [8]. The European directive 2001/20/CE is the legal document for clinical trials of medicines for human use in European countries [9]. One of the objectives of this directive which is to harmonize the legal and administrative framework of the Member States, stipulates that "*before commencing any clinical trial, the sponsor shall be required to submit a valid request for authorisation to the competent authority of the Member State in which the sponsor plans to conduct the clinical trial*" (European directive 2001/20/CE, article 9, paragraph 2). For example, in France, the competent authority to give this authorization to start a clinical trial on any medicine is AFSSAPS (Agence Française de Sécurité Sanitaire des Produits de Santé) [10].

In Canada, the Health Products and Food Branch (HPFB) represents the regulatory body within Health Canada (Ministry for Health) responsible for approval or rejection of an application for a clinical trial.

In addition to the authorization to start a clinical trial, the administrative procedures include obtaining proof of the authorization by the EC. The involvement of the bioethics community in the establishment of these ethics committees have come in part from the adoption of several international provisions or guidelines governing clinical experimentation in humans. Three of these are the Code of Nuremberg, the declaration of Helsinki and the CIOMS guidelines for biomedical research involving human beings [11]. These documents do not constitute an exhaustive list of international regulations or guidelines but represent the principal ethical standards required for clinical research. For the application of these standards, the ECs play an important role in guaranteeing the protection of human research subjects. In Africa these guidelines or principles are yet to be fully translated into national laws in order to protect research participants.

3.1.2. Regulatory capacity of African countries and the operation of the ECs

The various studies carried out on the existence and the capacities of ethics committees reveal a disparity between countries [12,13]. A study led by the WHO Regional Office for Africa (WHO/AFRO) highlighted the absence of national ECs for medical research in 36% of its member states [14]. The same source indicated that only one of these countries ensured that the clinical trials financed by either external governmental or private sponsors were subject to an ethical evaluation and received approval in the country of origin. The recurring results underline failures which relate to the absence of ECs, directives, staff, procedures and other resources [14,15]. It is also noted that, when several ethics committees coexist, it is difficult to define the respective roles and responsibilities. Moreover, in certain cases, the investigators were unaware of the existence of the EC. A study conducted in Sudan in 2007 showed that 53 out of the 116 researchers who were interviewed were unaware of the existence of ECs in the country [16]. However, the first EC was established in this country in 1979 [17].

In addition, the method of decision-making within the committees, their independence, the follow-up of the requests for amendments to the protocols and the monitoring of the performance of the clinical trials after ethical approval also constitute elements of concern in many countries in Africa [18]. According to a study conducted in 14 countries in West and Central Africa, "*what should urgently be addressed is the question of countries considered unable to exercise efficient control of research implemented on their territory, and thus obliged to depend on those who finance or conduct such research*" [19].

In short, before 2005 the regulation of clinical trials was, at its best, perceived as, and limited to the ethical function of review for which the responsibility was allocated to the ECs, in most African countries. The framework for regulation of medicines was lacking for clinical trials, including the roles and responsibilities of the various relevant parties. Moreover, the NRAs did not seem to be aware of their responsibility and their authority in the process of approval and inspections. The sponsors and the investigators lacked interlocutors clearly designated by the national legislations. However, South Africa contrasted with this situation in Africa. The NRA of this country, according to an amended legislative act going back to 1965, requires both regulatory and ethical approval and carries out inspections of the clinical trial sites. The sponsors know exactly the requirements and a Web site disseminates the relevant information. However, in spite of the existence of a legal framework in South Africa, some clinical trials without regulatory approval are reported [6].

3.2. Progress made in the regulation of clinical trials in Africa in the last 5 years

3.2.1. Objective of WHO strengthening initiatives

The initiatives of WHO to support the African region aims at promoting collaboration among the African countries to enable them to identify and discuss common challenges, share their expertise and to harmonize the procedures for evaluation and regulatory oversight of clinical trials of vaccines.

3.2.2. Implementation

The Department of Immunization, Vaccines and Biologicals of WHO (IVB), Quality, Safety and Standards Team (QSS) initiated activities of strengthening in the field of the regulation of the clinical trials by organizing a meeting in Addis Ababa in September 2005, in collaboration with WHO/AFRO and involving representatives of regulatory authorities from 13 African countries. The workshop reviewed the legal framework of each country, discussed the regulatory procedures for evaluation of vaccines and other common concerns. Following this meeting, model procedures were developed for submission of clinical trial applications and for importation and release of clinical batches. These procedures were used for joint reviews of clinical trial applications and joint inspections of clinical trial sites, facilitated by WHO. These activ-

Table 1
Examples of achievements within the regulatory framework of the initiatives of strengthening of WHO in the field of the clinical trials regulation in Africa.

Field of regulation	Before 2005	Since 2005
Observance of ethical standards.	Diversity of the context (absence of ethics committees, unclear roles and responsibilities, unawareness of their existence). No collaboration between NRAs and ECs.	Awareness of the need to revise or develop the legal/regulatory framework. Clarification of the mandates of the NRAs and ECs. Annual forum for NRAs and ECs since 2006 (AVAREF).
Observance of international scientific standards.	Absence of standards. No harmonization of procedures in the African region.	Training on GCP inspections since 2007. Joint review of 3 clinical trials and joint inspections of 3 clinical trial sites.
Advocacy for regulatory oversight.	Minimal or weak.	Stronger advocacy through annual AVAREF Forum.
Regulatory oversight of clinical trials.	Limited in the best cases to the ethics committees. Few NRAs in existence (4). NRAs not involved. Limited interaction between African NRAs and those of developed (product manufacturing) countries.	Evolution of the roles and the responsibility for the NRAs. Annual forum for interaction between African NRAs and those of developed (product manufacturing) countries since 2006. Better definition of the roles and responsibilities for the intervening parties. Positive interaction between NRAs and ECs. Interlocutors known for sponsors and researchers. Networking between countries and with independent experts through the AVAREF.

ities involving several countries with common challenges, led to the establishment of a platform called the African Vaccine Regulatory Forum (AVAREF). Since its beginning in 2006, AVAREF has met annually, in Accra (Ghana), Ouagadougou (Burkina Faso) and Zanzibar (United Republic of Tanzania), respectively. AVAREF includes representatives of NRAs and ECs from 19 countries and may extend to more African countries.

During the first three meetings, in addition to the NRAs and ECs of represented countries, several experts from strong regulatory authorities like, Food and Drug Administration of the United States, Health Canada and the European medicines evaluation agency (EMEA) as well as other partners like the Program for Appropriate Technology for Health (PATH) and the European and Developing Countries Clinical Trial Partnership (EDCPT) have participated.

The goal of the forum is to build the capacity of the participating countries to implement their full responsibility for the regulation of vaccine trials, it promotes the communication between NRAs and ECs, as well as between NRAs of industrialized countries, which are manufacturers of vaccines and their African counterparts where the clinical trials take place. It has also provided an opportunity for identification of gaps in regulation of clinical trials of vaccines, that require support from WHO. For example, the respective roles and responsibilities of the NRAs and the ECs are discussed and clarified to avoid the duplication of tasks, to optimize the use of resources and to reinforce the communication and collaboration. The process proves to be a stage towards the harmonization of procedures at the regional level, to ensure observance of the Good Clinical Practices enacted in the international guidelines of the ICH adopted in 1996. Table 1 gives some activities carried out within the framework of the initiative since 2005.

3.3. Priority clinical trials of vaccines in Africa: challenges of regulation for the different stakeholders

The regulation of clinical trials in developing countries contributes to the development of new products to tackle the myriad of health problems which specifically affect these countries [20,21]. For example, clinical trials are required to test new drugs and vaccines within Africa in the fight against the major endemic diseases, namely malaria, tuberculosis and HIV/AIDS. The Declaration of Helsinki [22] which represents the most quoted ethical framework, recalls in several of its articles that human experimentation constitutes a source of improvement for prophylactic, diagnostic and therapeutic procedures as well as providing better understanding of the aetiology and pathogenesis of diseases, including new and emerging diseases. WHO, by initiating these projects of building capacity of African NRAs perceived well in advance the fundamental obligation for African countries to have effective oversight of all the clinical trials which take place in their territories. It is important to understand that the responsibilities of the countries that will host clinical trials and where new drugs and vaccines will be introduced cannot be replaced by the regulatory approval of the manufacturing countries.

In spite of the regulatory strengthening initiatives of NRAs by WHO, many countries have not succeed yet in the implementation of a regulatory framework. The legislations in place in most African countries do not assign a clear mandate for regulation and oversight of clinical trials to a specific body within the health authorities. The new-institutional theory suggests that any organization should adopt structures in response to external expectations [23]. In addition, constitution and law are crucial factors of context and contents of activities of public organizations, on one hand because their structures and their goals are mainly stipulated in the laws which created them and on the other hand because the roles of the public agencies and their managers, as well as the resources placed at their disposal, are the subject of regulations in these laws. In fact, public administration is subordinate to the law [24,25]. Since the lines of authority in the oversight of the clinical trials are multiple and unclear, each part assumes that it does not have all the necessary levers to take up the challenge of regulation. It is thus essential at the national level to pay important and particular attention to the development of the legal body within a framework of dialogue of all interested parties in order to integrate the whole essential dimensions in a harmonious way.

In addition to the enacted international standards, the legal authorities must take initiatives to implement them because the

partners, including WHO, cannot impose on them a model for the regulatory procedures. That pertinently raises the question of the legal framework of cooperation. It is important to take into consideration such a question to promote collaboration and to encourage the exchange of information and expertise among NRAs and the various partners. The African countries which are selected to host the clinical trials often do not have enough experience with regards to legal framework for the oversight of the clinical trials. It is apparent that from a cognitive point of view, staff from NRAs and members of ECs need a basic academic and professional development level to enable them to make the best possible use of the capacity building opportunities offered by WHO. In this respect it has to be stressed that many countries which are targets for the introduction of new vaccines do not have the full competence and the necessary expertise to evaluate the quality, safety and efficacy of these vaccines for which they have the responsibility of evaluating [26]. That represents a challenge but also an opportunity to take advantage of the support by experts from WHO and partners. It was suggested that WHO serves as a means to facilitate the access to these external resources. Some examples are the participation of international experts in the joint reviews and joint inspections of clinical trials to support the reviewers and inspectors from the African NRAs and ECs, as well as the participation of experts at the AVAREF meetings, and the development of regulatory procedures made available for AVAREF countries to adapt and/adopt into their national regulatory frameworks. This list of documents includes guidelines for sponsors for the submission of clinical trials application, procedures for GCP inspections and models of legislation. This approach indeed makes it possible to optimize the use of international standards, to reinforce the activities of the regulatory authorities of African countries. Moreover, the participating countries are given the chance to develop their own experience from the acquired expertise [27–29].

4. Conclusion

The globalisation of clinical trials and their fast expansion in emerging countries, the lack of a mandate by the regulatory authorities of the industrialized countries to provide regulatory oversight of clinical trials outside of their territories and the weaknesses of the NRAs of the host countries are all factors which contribute to adversely affect the clinical trial environment in Africa. Despite these challenges WHO, through its multiple initiatives including the AVAREF, is resolutely committed to an approach of strengthening of the activities of National Regulatory Authorities in African countries. The success of these initiatives lies on the responsibility of the participating countries to secure the implementation of the activities relevant to their mandate to regulate clinical trials, which will guarantee the protection of research subjects.

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