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Joint reviews and inspections: Strategic forms of collaboration for strengthening the regulatory oversight of vaccine clinical trials in Africa

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ABSTRACT

Vaccine developers are required to submit a clinical trial application to the authorities in each country where a clinical trial will be conducted. The application has to be made both to the relevant Ethics Committees and to the National Regulatory Authorities, and only after appropriate clearance by both can a clinical trial commence.

This paper describes two specific strategies, joint reviews of vaccine clinical trial applications and joint inspections of clinical trial sites by groups of countries, as part of a WHO initiative to strengthen capacity for the regulatory oversight of clinical trials in Africa. Significantly, the joint reviews and inspections contributed to reinforcing the capacities of the regulatory authorities as well as defining an efficient process to maximize the quality of the reviews and minimize undue delays. Finally we will suggest complementary mechanisms to overcome the potential limitations of joint reviews and inspections.

1. Introduction

The promotion of research and development in Africa has the potential to lead to the identification of appropriate medicines to tackle priority diseases, including HIV/AIDS, malaria and tuberculosis [1,2]. A trend reported in recent statistics shows that pharmaceutical companies are moving their sites for clinical trials to developing countries [3,4].

Clinical trials of vaccines are uniquely different from those of drugs. First, the subjects, in vaccine clinical trials, comprise healthy individuals, mostly children or even infants. Secondly, the selected location must be in areas endemic for the relevant disease, and these in most cases are in countries were poverty is high and regulatory oversight is weak or non-existent [5–9].

This constitutes a potential risk, in particular for research subjects, and a threat to the quality and the integrity of the clinical data generated to support the marketing authorization of the product. Consequently the governments of African countries face the challenge to identify and implement suitable mechanisms to ensure oversight of clinical trials, consistent with international guidelines and standards. By doing this, they will ensure the safety of their populations, while promoting the benefits of research for those who will eventually use the new vaccines.

One of the goals of the World Health Organization (WHO) is to ensure global access to the highest possible level of health, achieved in part by helping governments to increase the capacities of their health systems, and providing appropriate technical assistance. WHO has initiated activities for strengthening the National Regulatory Authorities (NRAs) and Ethics Committees (ECs) in Africa to overcome the challenges previously enumerated.

Two main strategies of the initiative developed in the African region are the joint reviews of clinical trial applications and the joint inspections of clinical trial sites.

Using all the documents related to these activities as well as the experiences of those who were directly involved, we present the approach and methodology used by WHO to facilitate the process. Furthermore, we discuss these strategies, by analyzing their successes, weaknesses and limitations and propose means of improvement.

2. Strategic objective and emergence of the joint review and inspection

Very few countries in Africa had the capacity to review clinical trial applications and to inspect clinical trial sites, prior to the introduction of WHO initiatives for strengthening of regulatory oversight of clinical trials. Since in many cases countries host

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multicenter trials [10–13] and face similar challenges of lack of technical expertise and established procedures, it made sense to use the regional approach to build capacity in the countries involved in a given clinical trial.

In contrast to reviews being undertaken by individual countries, the joint review and inspection, respectively, consisted of a joint evaluation by the NRAs and members of ECs of a group of countries, of an application for clinical trial authorization and the clinical trial sites. This was facilitated by WHO and with the agreement of the countries and of the clinical trial sponsor. During a workshop organized by WHO on regulatory procedures for the clinical evaluation of vaccines involving 13 African countries in Addis Ababa in 2005 [14], WHO first proposed the joint review of a clinical trial application as a means to help the selected target countries and to prepare other potential target NRAs and ECs to evaluate future clinical trials. Participating countries agreed that this would be the best approach to strengthen their capacity for oversight of clinical trials in a collaborative manner. Three reviews of clinical trials and two joint inspections were carried out, facilitated by WHO.

2.1. Conjugate Meningitis A vaccine clinical trials

The first two joint reviews were for clinical trial applications of phase II and II–III studies of a conjugate meningitis A vaccine, produced by the Serum Institute of India and sponsored by PATH/MVP (Meningitis Vaccine Project).[1] The first clinical trial took place in Mali and The Gambia. Both countries had participated in the workshop in Addis Ababa in September 2005 that resulted in the development of regulatory procedures for submission and review of clinical trial applications and for importation and release of clinical batches. These model procedures were used to inform the sponsor on the documentation required by the NRAs. A joint review of the clinical trial application was done in Banjul, The Gambia in June 2006. The participants were from the NRAs and ECs from the two target countries and representatives from other countries where clinical trials were planned in the future (Senegal, Ghana, Ethiopia and Burkina Faso). The joint inspection of a clinical trial site was done in Mali in January 2007 with the same participants. Independent experts were recruited by WHO to support the processes of review and inspection. Invited countries (those invited to learn from the process but had not received the application) as well as the consulting experts signed confidentiality agreements.

The second joint review of a clinical trial application for a subsequent study of the same vaccine was done in Dakar, Senegal in June 2007 and the second joint inspection in two clinical trial sites in Senegal, following a similar format. A third clinical trial site involved in this particular vaccine development plan was in The Gambia. The country participants from the regulatory authority and the ethics committee of The Gambia were encouraged to conduct their own inspection following the same procedure, without the presence of an external expert. However, WHO provided support by facilitating a consultation with the lead expert who provided support for the inspection in Senegal, before and after the visit to the clinical trial site. This allowed country inspectors to validate their preparations for the inspection and the interpretation of the observations.

Representatives from the countries that participated in the joint reviews and the inspections, reported to WHO to have successfully applied the knowledge and methodology to other clinical trial applications and for the inspections of sites in their territories.

[1] The MVP is a partnership between WHO and Program for Appropriate Technology in Health (PATH) aiming at preventing epidemics of meningitis in the sub-Saharan Africa after the epidemic of 1996–1997.

2.2. RTS, S Malaria vaccine clinical trial

A third joint review of a phase III clinical trial application of the RTS, S Malaria vaccine manufactured by GSK Biologicals, in Belgium was undertaken. In this case the clinical trial involved 11 sites in seven countries (Burkina Faso, Malawi, Tanzania, Ghana, Kenya, Mozambique, and Gabon). The complexity of the arrangements due to the number of countries involved required a lengthy process of preparation to seek agreement from all participating countries, reach consensus on the use of a harmonized format for the dossier to be submitted by the manufacturer and to design the review process in a way that would build on the already existing capacities in the target countries.

The first stage was the presentation of the project by the vaccine manufacturer (GSK) and the vaccine development partner, Program for Appropriate Technology in Health, Malaria Vaccine Initiative (PATH/MVI) during the second meeting of the African Vaccine Regulatory Forum (AVAREF) in September 2007 [15]. Countries agreed that a joint review would be a good opportunity to enhance the quality of the evaluation process. They also agreed that the model procedure developed by WHO would be used so the manufacturer would prepare one single dossier for all target countries, and on the minimum information that should be presented in each of the sections of the application. In April 2008, a timeline was agreed upon by the manufacturer, and four of the seven target countries. NRAs requested that a period of 2 months be given to them to perform their own review in preparation for the joint review. This was a significant difference from the first two experiences, where no individual country review was done prior to the joint review. Another difference was that in this instance, expert reviewers from the NRA of the country of manufacture provided technical support to the seven African countries.

In October 2008, the joint review was conducted. A joint report with observations from all reviewers was prepared, and presented to the manufacturer. The outcome of the review was a joint report of observations, which were either clarified or became a commitment for submission of additional information to each of the countries, to allow them to complete the evaluation process and issue approvals of the application independently.

3. Key stakeholders in joint reviews and inspections

All the joint reviews and inspections have been facilitated by WHO with the intention of creating a mechanism that countries could follow in the future, if the format proved efficient in enhancing the quality of the review and reducing undue delays in the process between submission of the applications and the issuance of an approval (or rejection), while at the same time the experience served as a unique leaning opportunity for the participating countries.

Based on the experience gained, there are a few elements that must be in place:

(a) Agreement from the manufacturer and sponsors as owners of the information.
(b) A neutral partner to support WHO with funding and/or with negotiations with the owner of the information to ensure that the clinical trials would go through the highest possible level of regulatory oversight.
(c) Consensus from the countries involved to review the application together, and to use the common report as the basis for their national decision.
(d) Focal persons for the NRA and the EC in each participating country, to communicate with.

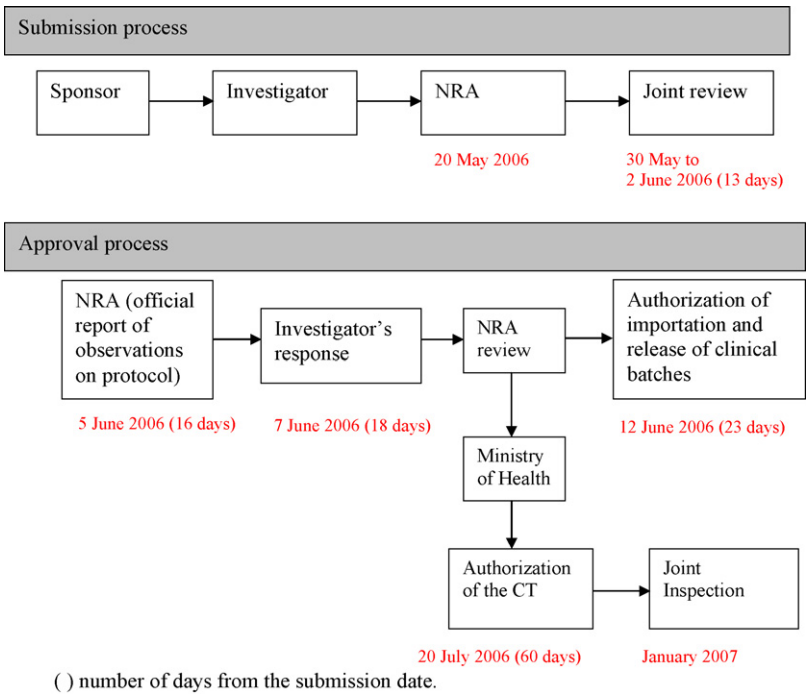

Fig. 1. Submission and approval processes for the conjugate meningitis A vaccine clinical trial: example of Mali. ( ) Number of days from the submission date.

(e) Experts that support the country regulators by sharing their knowledge and experience, but do not have decision-making roles or responsibilities.

The ideal format involves experts from the regulatory authority of the country where the vaccine is manufactured to strengthen the interaction between regulators of manufacturing and trial host countries.

The process must not invade the sovereignty of the participating countries; it helps in the decision-making process by enhancing the quality of the review. The end result is a summation of the expertise and views of all participants in the activity, who in turn bring along the views of their colleagues who have already made a preliminary assessment of the submitted dossier. The final report presents a consolidated list of concerns, which after satisfactory response from the manufacturer should result in the authorization of the clinical trial in each country involved.

4. Advantages of the joint reviews and inspections

Historically, joint activities or common arrangements or various forms of networks have allowed the continuity and the coordination of medical care and services between various stakeholders of a health system [16]. Joint reviews and inspections are an example of this approach to deal with common challenges in the area of regulatory oversight of clinical trials.

From the experiences of the participating countries, the first advantage of the joint review and inspection process was the awareness of the complexities of the review process and the improvement of their knowledge on the methodological, scientific and ethical considerations involved in the evaluation. With regards to the ECs, the joint review provided impetus for national committees to revise existing methods or procedures and to validate activities previously conducted. For example, some participants from ECs reported that they did not previously distinguish ethical approval from the regulatory authorization of the clinical trial. Also, some did not realize that it was their responsibility to consider the scientific aspects of the protocol. Thus, in the past, clinical trials may have started without sufficient scientific evaluation.

Secondly, the benefit for the sponsor is that the whole process follows a pre-determined timeline in these case studies facilitated by WHO, thus avoiding undue delays in the review process itself. Generally the sponsors expect short timelines to avoid delays in the commencement of the clinical trials. From the public health point of view, decisions of the NRAs should be made within a reasonable time to avoid a negative impact on the clinical development of priority drugs and vaccines. On the other hand, sufficient time is required for the evaluation of the dossiers in order not to compromise the quality of the review. For example, a directive of the European Union envisages a period of 60 days for clinical trial applications [17,18]. In Canada the time allowed is 30 days [19]. For many African regulatory authorities it is difficult, if not impossible to carry out the reviews under such demanding timelines without compromising the quality of the review. By pooling their capacities, in collaboration with WHO through these initiatives, the NRAs and ECs were able to finalize the review process within a pre-determined timeframe, considered to be acceptable to the sponsors (Fig. 1).

An additional advantage is that both NRAs and ECs take part in the joint reviews and inspections allowing them to work more closely together in the oversight of clinical trials, which was not the case previously [20]. The case studies also allowed for the discussion of the roles and responsibilities of the NRAs and the ECs so as to avoid duplication of tasks and to promote communication and collaboration between them. Some countries reported that the joint reviews and inspections by the regulatory authority and the ethics committee were adopted as common practice.

In addition, this approach helps build mutual respect to improve the co-operation among African countries and as a step forward towards harmonization of procedures. A further advantage is that alignment of the national procedures to WHO GCP standards will allow the enhancement of the quality of clinical trials and improve the protection of trial participants [21].

Finally, all of these factors, namely the improvement of knowledge of the participating NRAs and ECs, the clarification of their roles and responsibilities, the progress towards harmonization of

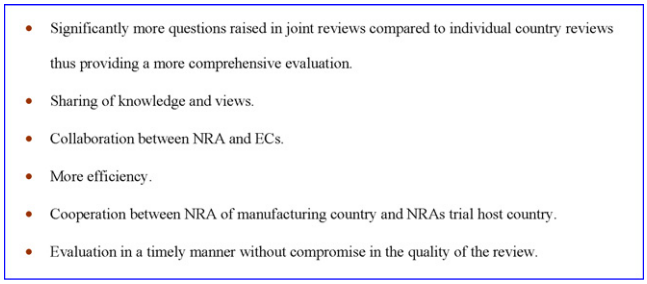

Fig. 2. Advantages of joint reviews and inspections.

procedures consistent with WHO GCP standards contribute to the quality of research and the reinforcement of the protection of the research subjects [18,22]. NRAs and ECs represented at AVAREF reinforced the need for the continued support from WHO to facilitate more joint evaluation activities. They have also suggested that countries should apply the same strategy for multicenter trials through direct coordination among involved countries. Fig. 2 summarizes some advantages of the joint reviews and joint inspections initiative.

5. Limitations of the joint review and inspection and some recommendations

Some of the participating countries transferred the acquired knowledge to other clinical trial applications. However, for some other countries, the experience was taken as a training opportunity without subsequent implementation and application of the learned procedures to other cases. In addition, in some countries there were no changes in the legal framework to include the identification of the roles and responsibilities of the NRAs with regards to regulation of clinical trials. As Denis et al. [23], noted in pluralistic contexts (when many organizations interact), practices and routines are not instantaneously changed. More opportunities for these joint evaluations will increase the impact of the strategy. However, the facilitation of joint reviews and inspections requires a lengthy and careful preparation, including the consensus from the sponsor, and the countries that benefit are limited to those that the sponsor plans to include in their project.

In fact, many countries that are target for clinical trials have not had the opportunity yet, as they were not part of any of the projects cited. WHO continues to seek new arrangements and more opportunities are being considered as more potential neutral partners are approaching WHO with proposals for joint evaluation of vaccines in clinical development. Until countries participating in multicenter studies take the initiative to coordinate among themselves, the joint evaluations will depend solely on the possibility of WHO to reach agreements with neutral partners.

In some countries NRAs must secure the support of the health authorities for investments to implement national initiatives, including legal and regulatory frameworks to grant the NRA the mandate to authorize clinical trials and inspect clinical trial sites, and to recruit and train adequate personnel.

6. Conclusion

Joint reviews and inspections have contributed to the strengthening of regulatory oversight of clinical trials. These activities are intended as a strategic approach to help African countries face challenges related to their constraints with regards to legal/regulatory framework, resources and expertise.

The benefits of these capacity building activities are reflected in the positive response from some countries that have rapidly implemented changes based on the acquired knowledge. However, others have not demonstrated progress after these experiences, and have not applied the lessons learned to clinical trial applications other than that to which the joint evaluation was applied. WHO continues to review the barriers to this aspect of health system strengthening, to seek more opportunities for joint reviews and inspections, and more potential partners are approaching WHO with new proposals as they see the value of these activities in ensuring a quality review in a timely manner. NRAs and ECs represented at AVAREF have expressed their intention to apply the strategy of joint evaluations for multicenter trials in the future, through direct coordination among the countries involved in such studies.

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