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[See table of contents](#)

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Article abstract

Since 2005, Mali has participated in World Health Organization (WHO) training activities for national regulatory authorities (NRAs) to aid the proper regulation of clinical trials. Despite this participation, there is still very little regulation of trials, a weakness due in part to a lack of integration of oversight mechanism by national authorities. It is thus important to understand what factors actually influence the regulation of clinical trials in Mali. Using an analytical framework based on neo-institutional theory, this exploratory qualitative study involved semi-structured interviews with the Malian NRA, ethics committees, researchers, administrators and hospital practitioners, along with documentary analyses. The results show that the configuration of the organizational field and the position of authorities in this field are essential to understanding the factors that influence the regulation of clinical trials. The preponderance of regulatory barriers to clinical trials, coupled with the inability of the government to strengthen regulation and the weak organizational structure of the field, call for a comprehensive reform rather than partial measures such as, for example, joint reviews and inspections of clinical trials promoted by the WHO.

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Factors influencing the regulation of clinical trials in Mali

By Diadié Maïga, Lise Lamothe, Bryn Williams-Jones and Régis Blais

Introduction

Randomized clinical trials are widely recognized as an essential means of advancing health care knowledge and developing evidence-based guidelines.

They represent the research design favored by the competent regulatory authorities to establish the therapeutic value of drug treatments. This reflects the belief that trials are an important means of ensuring the availability of quality care services for the health of individuals and populations. However,

Without independent and appropriate monitoring of the conduct of clinical trials, there is a lack of reliable information on the effectiveness of drugs, their safety, their quality and the protection of human subjects against abuse in research.

Until recently most African countries had no regulatory system for clinical trials (Maïga et al. 2009). Therefore, many actors in the clinical trials environment in Africa want the implementation of adequate regulatory mechanisms to promote biomedical research leading to real improvements in healthcare delivery.

To help understand this issue, particularly the factors influencing regulation, we study the case of Mali for three main reasons. First, Mali is a developing country and, according to the United Nations Development Program (UNDP), it ranks among the poorest countries (ranking 178th rank out of 182 countries), which makes it particularly vulnerable to abuse in clinical trials (UNDP 2009). Secondly, Mali is home to major research centers experienced in conducting trials and which are sufficiently equipped and staffed with highly qualified personnel. As a result, it has become sufficiently attractive on a continental scale to host numerous trials. As an indication, in April 2010, among the 53 countries of the continent, Mali had 52 active trials and occupied the 6th rank after South Africa (1082 trials), Egypt (178 trials), Uganda (117 trials), Kenya (102 trials) and Tanzania (87 trials) (www.clinicaltrial.gov). Thirdly, Mali participates in a very important way in the activities of reinforcement of the regulation of the African countries initiated by the WHO since

According to the scientific literature, regulation is sometimes perceived as a barrier to carrying out clinical trials (Watson 2003; Hartmann and Hartmann Vareilles 2006; Duley et al. 2008). According to international standards, it is seen as an irreplaceable means of ensuring the quality of biomedical research and protecting the health and well-being of research subjects (World Health Organization 1995). In the literature, the focus is usually on collecting information on regulatory performance and evaluating it against certain standards. In the area of clinical trials, some regulatory information has been accumulated. For example, the weakness of the regulatory framework in developing countries has been highlighted numerous times in recent years

(Kirigia et al. 2005; Brennan et al. 2007; Nyika et al. 2009). To our knowledge, there is still no clear consensus on the factors that influence regulation. Thus, there are limits on the ways to interpret and use the information to make decisions that will effectively redirect regulation. In order to be able to change things, it seems essential to understand which factors influence regulation. Identifying these factors in Mali will provide useful guidance for determining appropriate regulatory mechanisms in Mali and other developing countries with similar contexts. This is the objective pursued in the present study. More specifically, we seek to identify the obstacles and the factors facilitating the establishment of appropriate mechanisms for the regulation of clinical trials in Mali.

The concept of regulation

There are many definitions of regulation to the point that Dubnick and Gitelson called this diversity a conceptual quagmire several years ago (Dubnick and Gitelson 1982). There is, however, a common trait that links most of these definitions. It is a notion that aims to qualify a certain type of State intervention with the aim of regulating the behavior of private companies. A distinctive feature of regulation is that it involves the existence of a government agency charged with the ongoing oversight of the behavior that is being controlled (Reagan 1987; Jordana and Levi-Faur 2004; Permanand 2006).

Depending on the field of application, two types of regulation can be distinguished: economic regulation and social regulation. The first corresponds to the traditional form of regulation and it applies to the economic sphere. Its social counterpart is much more recent and refers to control in the field of health, safety and social practices such as civil rights and discrimination of all kinds (Howlett and Ramesh 2003). The perspective targeted in this study, allowing us to thus define the regulation of clinical trials: a correctly implemented legal framework, which mandates defined public bodies to exercise control over clinical trials, including the authorization of applications submitted to them. approval, effective monitoring of their execution, and if necessary their interruption.

Typical operation of clinical trials

A clinical trial is an experiment using human subjects whose main objective is to estimate the effect of a treatment or health action in a precise and valid manner in human beings. Clinical trials are necessarily accompanied by a certain level of risk for the safety of participants and their community. In the absence of regulation, these risks are potentially greater. The main categories of risks documented in the literature are threats to the health and safety of subjects, the exploitation of research subjects, the risk of stigmatization and social discrimination of certain communities likely to be

victims of “genetic labeling”, the lack of scientific integrity of clinical data and the potential injustice towards certain vulnerable groups (Benatar 2000; Beecher 2001; Corrigan and Williams-Jones 2006).

Therefore, the safety of new drugs and the ability of health authorities to ensure that safety are central concerns surrounding the regulation of clinical trials. However, the responsibility for the development of a new drug rests on an effective partnership between many stakeholders, including sponsors, investigators, national regulatory authorities (ANR), ethics committees (EC). Within this partnership, the NRAs provide a critically important service by ensuring that trials are planned and conducted properly. In accordance with international standards, they must exercise independent oversight of trials, including reviewing protocols, inspecting individual and organizational actors involved in the conduct of the trial to ensure compliance with Good Clinical Practice (GCP) and national guidelines, and if necessary exercise their authority to delay or stop the test. These measures are intended to: (1) ensure that data from clinical trials are valid and accurate; (2) protect the rights and safety of trial subjects, including ensuring that they are not exposed to unnecessary risks given the anticipated benefit of using an experimental therapy and that they give informed consent before being enrolled in the trial.

Theoretical frame

The article is situated in the theoretical framework of neo-institutionalism. The definition of neo-institutionalism that we retain is as follows: “Institutionalism can be represented very simply as a set of arguments that describe higher-order constraints imposed by socially constructed realities ”

(free translation by Jepperson in DiMaggio and Powell 1991: 144). Neo-institutionalism is a renewal of the institutional theory of the 1940s. Unlike the latter which focuses on the institutional character of the organization, neo-institutionalism strives to explain the influence of the institutional environment on organizations. In the neo-institutionalist conception, the environment is assimilated to organizational fields (Scott and Meyer 1991). Local and non-local connections, horizontal and vertical links, cultural and political influences as well as technical exchanges are all included in the institutional environment of an organization (Scott 1991).

Consequently, the perspective of this research proposes to study the regulation of clinical trials by means of the analysis of the institutional context in which the organizations concerned operate. The research approach adopted is based on the postulates that today formal organizations are born in highly institutionalized contexts (Meyer and Rowan 1977) and that organizational behavior is determined by compliance with the rules that must be sought in the institutional environment. A remarkable boom in the scientific literature shows, in fact, that institutional determinants play a decisive role in shaping the strategies of interest groups. Hence, neo-institutional theory emphasizes the constraining role of institutions that impose restrictions because of legal, moral and cultural limits (Scott 2008). The analysis of the institutional context allows

to account for how institutions influence the behavior of individual and organizational actors (Lawrence and Suddaby 2006). Moreover, a reorientation of the institutional work makes it possible to understand the action of the actors and how this affects the institutions. The concept of institutional entrepreneur refers to actors who act intentionally to achieve institutional change. In this perspective, individuals exercise free will. And in this way, the process of institutionalization can be managed proactively by the leaders of the organization, capable of defining and defending its values (Bensedrine and Demil 2005).

The institutional context in this research makes it possible to understand two spheres of influence that will serve as a backdrop for the discussion of the results: the conditions of the organizational field and the social position of the actors in the fi

Regarding the first sphere of influence, neo-institutionalists argue that organizations operate within an environment which is constituted not only by the formal institutions producing regulatory frameworks, but also by actors, groups of actors and organizations which participate, as a whole, to the construction of the normative and cognitive framework to which the organization tries to conform in order to be socially legitimized (Scott 2008). This institutional context or organizational field is a key concept in institutional analysis.

The structure of a field, indicates Scott, would influence and be influenced by the cognitions of the actors (Ibid). By structuring organizational fields, DiMaggio and Powell mean a process made up of four elements: an increase in interactions between organizations in a given field; the emergence of inter-organizational structures of domination and models of coalition; an increase in the intensity of the exchange of information between organizations in the field; the development of a "field consciousness" and the awareness of field members about a common belonging (DiMaggio and Powell 1991). In a way, these four aspects can be considered as indicators of the constitution of the field. We will refer to it if necessary to assess the degree of achievement of the structuring of the regulatory field.

As for the social position of actors in the organizational field, its interest is to consider to what extent groups of actors can have a capacity for action to influence organizational behavior. Studies have shown that the most dominant players in a field are likely to use their position to influence the process. In this regard, Giddens (1979) and Sewell (1992) stress the importance of including material and human resources as well as power asymmetries in any conception of social structure, since these two elements determine the degree to which the interests of the actors present are realized.

Methodology

The main sources of data used in this qualitative study are individual semi-directed interviews, supplemented by a documentary analysis. The project has been approved by the Research Ethics Committee of the Faculty of Medicine of the University of Montreal and the National Ethics Committee for Health and Life Sciences of Mali (CNESS).

Participants

Interviews were conducted with key stakeholders involved in trial regulation clinics. Thirty-five in number, they come from the following bodies or groups:

- 1) the Ministry of Health, the Department of Pharmacy and Medicine (DPM) and the Health Inspectorate;
- 2) the three CEs;
- 3) investigators within research institutes, namely the Department of Epidemiology of Parasitic Affections/Malaria Research and Training Center (DEAP/MRTC) and the Vaccine Development Center (CVD); 4) representatives of NGOs, international institutions (WHO), administrators and hospital practitioners.

Data Collection and Analysis

Data collection took place in Mali from August to November 2008. All interviews were transcribed verbatim. The analysis phase consisted of examining the interviews and documents following the classic approach described by Miles and Huberman, i.e. in four stages (Smith 1995): 1)

- immersion and familiarization with the corpus data aimed at carrying out an exploratory coding from the first of questioning and interpretation;
- 2) systematic inventory and identification of themes emerging from the analyzed corpus and conceptual labeling of these themes to build an analysis grid;
- 3) application of the grid to update the relationships between the different themes (hierarchy, common universe of meanings) illustrated by extracts of raw data, then development of clusters (thematic categories) from the connections between the different themes *and* under themes;
- 4) summary of abstractions in factors influencing trial regulation clinics.

QDA Miner software was used for data analysis.

Context: Mali

The drug market in Mali was until recently dominated by the distribution of products from the Western pharmaceutical industry. Today, despite the absence of national statistics, this proportion can be estimated at around 50 percent. The other half concerns products that mainly come from China and India. However, with reference to public clinical trial registries (www.clinicaltrials.gov), more than two-thirds of the trials conducted in Mali are sponsored by the United States *National Institutes of Health* (NIH). The remaining third is made up

trials sponsored by Western universities, the *Centers for Disease Control and Prevention* (CDC), the Western pharmaceutical industry or NGOs.

Since 2005, the government has been committed to developing a regulatory framework for clinical trials through increased participation in a number of capacity building activities organized mainly by the WHO.

The groups of actors directly involved in clinical trials in Mali can be summarized as the instances below. First of all, there are three main research centers whose activities include carrying out clinical trials and which are linked to foreign research institutions, notably the NIH. Malian national regulations do not specify who has the more general mandate of authorizing clinical trials. However, in fact, two types of authorities regulate clinical trials, namely the ethics committees (EC) and the Directorate of Pharmacy and Medicines (DPM).

1) ECs are responsible for ethical review of research protocols and sometimes field monitoring. Three CEs coexist, namely a national committee and two other committees based respectively at the Faculty of Medicine and the National Institute for Public Health Research (INRSP). There is no hierarchy between these committees, nor any functional link. All are authorized to review research protocols of any kind. EC members are generally full-time professionals working on other duties. All participate in it on a voluntary basis.

2) The DPM, as the competent authority in charge of the pharmaceutical sector, is responsible for examining applications for authorization to import investigational medicinal products. In addition, the supervisory authority of the DPM, the Ministry of Health, is increasingly involved in the issuance of regulatory approval.

In this text, to refer to both the DPM, the Ministry of Health and the CEs, we will use the generic term “public authorities”.

Results

By referring to the data, we can categorize the factors according to the five dimensions of the theoretical framework, namely: an increase in interactions between organizations in a given field; the emergence of inter-organizational structures of domination and models of coalition; an increase in the intensity of the exchange of information between organizations in the field; the development of a “field consciousness” and the awareness of field members about a common belonging; and finally the social position of the actors in the organizational field.

The results will be presented according to the five components. The factors have interdependencies between them, which makes it particularly difficult to examine the factors influencing the regulation. However, it is interesting to consider as a starting point for developing a reflection on the regulation of clinical trials.

Table 1. Obstacles and facilitators to the regulation of clinical trials in Mali

Category		
	Obstacles	Favorable factors
Interactions between organizations	Lack of coordination of regulatory services	Existence of 3 EC
Structures inter organisationnelles of domination and coalition models	Absence d'incitatifs	
	Weak capacity for scientific assessment and inspection	Good capacity for ethical evaluation
	Insufficient legal regulatory framework	Short ethics approval times at CE/ FMPOS
	Administrative burden in the public sector Low socioeconomic level of the population	
Intensity of information exchange between organizations	Limited access to information in English	Technical support by WHO and international collaboration (EMA, FDA, Health Canada)
Field awareness	Low priority level for clinical trials	Awareness of health authorities of the need for regulation EC craze
social position of the actors	Low decision-making autonomy and financial dependence on control services Low authority Influence of research groups on other players Competence of investigators Low availability of financial and material resources	
CE: Ethics Committee. FMPOS: Faculty of medicine, pharmacy and dentistry. EMA: Agency European Medicines.		

Increased interactions between organizations

The people interviewed mention influences related to the lack of interaction between the organizations, considered to make the system inoperative. It's about including the lack of collaboration and coordination between public authorities, the transparency of approval processes and the control of conflicts of interest. This has resulted in an irregularity in the regulatory decision-making mechanisms. The researchers consider in this regard that the development of standards and procedures could help to clarify the requirements and standardize the submission of applications for approval.

Appearance of inter-organizational structures of domination and coalition models

The data drawn from the interviews reveals five types of factors that slow down the appearance of structures of domination and models of coalition for a good regulation of clinical trials in Mali. The factors in this category boil down to the regulatory framework, the incentive framework, the capacities for scientific and regulatory evaluation and the institutional framework.

Regulatory framework

For all players, the absence of a regulatory framework appears to be one of the greatest obstacles. This should define the framework of clinical trials as well as the attributions of the different structures and the requirements for sponsors and investigators. Faced with the regulatory barrier, the public authorities seem little committed or take few initiatives to supervise trials. A respondent adds in this regard: *They have so many things to do that*

they rather want to devote themselves to things that are already in the law that created them than to go and work on things on which they are not challenged, (participant 16 , member of an international institution).

The result is poor responsiveness to researchers' requests, informal communication of decisions and lack of monitoring of projects in the field.

Incentive framework

The absence of incentives for public authorities emerged among the obstacles cited by the speakers. For example, when talking about regulatory authorities and CEs, the informants express themselves in the following

terms: We must put them in the right socio-economic conditions, sheltered from everything so that they can work well, (participant 12, investigator).

One of the consequences is the low availability of members who tend, with the exception of retired people recruited in the EC, to relegate regulatory activities to the background.

Scientific and regulatory assessment capabilities

The limited capacity of public authorities in the scientific evaluation of clinical trial files and in the inspection of sites was also highlighted as an obstacle to regulation. It concerns a cruel lack of qualified personnel:

The major obstacle is the insufficiency, if not the absence, of competent personnel (participant 3, member of ANR).

It is especially with regard to the scientific expertise required that the obstacles have been mentioned. Moreover, the absence of scientific evaluation has implications

ethical because " what is not scientific is not ethical " had launched Jean Bernard (Lévy 2006). This is particularly important for the ECs in Mali which, in the absence of any other protocol review body, tacitly have the dual obligation of ethical and scientific evaluation to determine whether the risks of the trials are clearly outweighed by the expected benefits. This is not the case in industrialized countries, where prior consultation with a scientific council is often carried out.

Moreover, even if the perception of a lack of skills specific to clinical trials is constant with regard to the ANR, opinions converge to say that the CEs have a significant capital of expertise for the evaluation of the strictly ethical concerns of the protocols. Likewise, the experience in pharmaceutical regulation acquired by the ANR, although limited by its staff, can be used to supervise clinical trials. This experience could be used to determine the optimal regulatory mechanisms for the regulation of trials in Mali.

However, the insufficient capacity of the structures is partly explained by the low priority given to the control of clinical trials, manifested by a lesser representativeness of the skills that would be available locally:

*When you write to certain departments asking them to **appoint their representative, you get the impression that they get rid of some. As we don't know the importance of the thing, we are looking for someone of a lower level, we say you represent us on this committee, we have the impression that it is a riddance,** (participant 15, member of EC).*

Institutional frame

The institutional framework was regularly cited as having an influence on regulation. Some interviewees reported that the existence of particular control structures has an influence on regulation. From this point of view, the absence of a scientific commission has been cited as an obstacle to the appropriate regulation of clinical trials. Likewise, the absence of a service responsible for regulating clinical trials leaves the barrier due to the lack of coordination between the numerous regulatory services remaining.

The existence of the three ECs is recognized as an opportunity, although this number is considered insufficient by certain actors who highlight the absence of ECs in the regions of the country. Similarly, the creation of the DPM in 2000 is mentioned as a contributing factor. It is important to specify that the DPM is solely administrative. It does not yet have the capacity to assess clinical trial records; its activity mainly concerns the evaluation of applications for the importation of experimental medicinal products.

Administrative and socioeconomic context

Contextual factors likely to influence the testing environment were cited by stakeholders. They relate to the administrative and socio-economic contexts. There

administrative heaviness specific to the Malian public sector represented in itself a brake on the adoption of new regulatory texts:

The obstacle that I see is the administrative burden. In Mali, even when decision-makers are convinced that something is good, there is a slowness, this is especially known in Mali (participant 19, EC member).

It appears to take a very long time to get a legal text through. According to the actors, the implementation of a legislative text is always a long process with a lot of discussions and back and forths which extend over several years. This intrinsic obstacle to the context seemed difficult to overcome.

Likewise, the speakers point out that the socio-economic level of the majority of the population, characterized by a high poverty rate and low schooling, could affect their participation:

People often come with very large means to lure populations . We bring you millet, rice, soap, we make them sign anything (participant 26, CE member).

In a context of low availability of health infrastructure and limited accessibility, the unfavorable socio-economic conditions of the population can compromise the autonomy of the participants.

Increase in the intensity of the exchange of information between organizations in the field

The results show that access to information influences the capacity of public authorities to make the regulation of clinical trials effective in Mali. This is due to the fact that several international documents, such as the ICH standards relating to Good Clinical Practices (GCP), Good Laboratory Practices (GLP) are often non-existent in French, the official language of Mali. Also, training and various international meetings are often given in English. In addition, the files supporting requests for approval of tests consist, for the most part, of documents exclusively in English.

In addition to access to information, members of non-governmental institutions consider that technical support and international collaboration benefit the regulation of trials in Mali:

There is a desire displayed at the highest levels of the WHO to support countries and strengthen their pharmaceutical regulatory authorities (participant 16, member of an international institution).

Since 2005, Mali, like 18 other African countries, has benefited from sustained support from the WHO in the regulation of clinical trials (Maïga et al. 2009). This factor, however, seemed underestimated, if not ignored by the public authorities who do not pay attention to it. However, as part of this initiative, Mali participated in numerous strengthening activities, including the annual meetings of the African Vaccine Regulatory Forum (AVAREF), joint reviews and inspections.

trials, a course on clinical trial regulations, and a meningococcal A conjugate vaccine prequalification meeting at WHO Geneva.

Inter-country consultations and collaboration, including support from WHO, can contribute to the adoption of good regulatory practices. For example, the European Commission, through Article 58 of Regulation 726/2004, provides a mechanism by which the European Medicines Agency (EMA) can give a scientific opinion within the framework of its cooperation with the WHO, for the evaluation of certain medicinal products for human beings, in particular those intended exclusively for markets outside the European community. Also, other organizations, such as the FDA and Health Canada are resolutely committed to working with the WHO to help AVAREF member countries address regulatory issues and strengthen their capacities in this area. Finally, to compensate for the notorious shortage of documents in French, we can count on some important documents, including the Policy Statement of the Tri-Councils of Canada, accessible online: <http://www.ger.ethique.gc.ca/eng/policy-policy/initiatives/tcps2-epc2/Default/>.

In short, the strengthening of synergies between the public authorities and the WHO on the one hand, and with the regulatory authorities of the partner countries on the other hand, can offer options for improving regulation.

Development of a “field consciousness” and the awareness of the members of the field about a common belonging

The awareness and political will of public authorities as well as the professional conscience of researchers emerged as factors falling into this category.

Indeed, on the one hand, the various groups of actors believe that government intervention could improve the regulation of clinical trials in Mali if the health authorities showed real political will. The opinions show an awareness of the highest health authorities of the need to regulate trials. The creation of two ECs (CNESS and INRSP EC, respectively in 2002 and 2006) is mentioned by way of illustration. Also, the enthusiasm of EC members, widely recognized, was considered to facilitate the establishment of a mechanism to regulate clinical trials. However, the data shows that the Ministry of Health does not see clinical trials as a priority, thus limiting its full involvement: *Ethics are not really seen as a priority.*

Sometimes

we are summoned, we are asked for this or that, we even do seminars but we do not really see it as a priority and the regulatory texts that we have sent are still not followed up (participant 19, member of EC) .

On the other hand, a few rare people cited the lack of professional conscience of researchers or promoters, as being an obstacle to the regulation of trials in Mali:

The laboratories which are

practically the basis of all these clinical trials, I think that we have need to moralize them a little, (participant 3, member of ANR).

Without this professional awareness, regulatory authorities may lack relevant information, such as safety information such as unexpected serious adverse reactions that must be reported by the sponsor. or the principal investigator. However, the analysis of such data is crucial to the appropriate regulation of clinical trials, which could be a decision to continue a trial, modify it or interrupt it.

Social position of actors in the organizational field

Factors linked to the social position of the actors or likely to affect it have been cited. They relate to the autonomy or independence of control structures, the authority of public authorities, the ancestry of research groups and financial resources.

Autonomy or independence of control structures

Whether it is financial dependence on research projects or the Ministry of Health, or even supervisory services (as is the case between Faculty of Medicine and its EC), all these factors were cited as obstacles to the functioning of regulatory services and to autonomy in their decision-making:

The fact that the project finances the operation of the CE can soften certain decisions too, that's clear, it's human, (participant 21, member of CE).

The informants note that the establishments do not have resources and this increases their dependence. Thus, for example, the CE/FMPOS is closely linked to the faculty administration whose secretariat it uses for its own functioning. This results in problems with notification of committee opinions and archiving of clinical trial files due to lack of storage space. Likewise, the operating costs of the CE/FMPOS are taken from research projects, which makes a member of the CE say that:

If you take someone's money you have to take their mood into account, (participant 17, CE member).

This clearly reflects the reasonable fear of conflict of interest due to the lack of independence. This could also harm the ability of members to make a fair and objective evaluation or to be perceived as such. In addition, the lack of autonomy has sometimes resulted in operational problems, including the inability for the EC to contact all of its members to convene meetings.

Public authority

Some interviewees felt that there was often a lack of government authority.

We don't really have the power to say okay, we'll stop. It is only the opinion that we give, the power is limited, (participant 15, member of the CE).

**This lack of authority applies in the same way to the ANR:
*As an investigator I do not feel obliged to respect or submit to an injunction from the director of the DPM. He gives me permission to import the products. I don't think he has a way to check what I do with it and he also doesn't have a way to influence how I use it (participant 9, investigator) .***

The absence of authority from public authorities can affect the regulation of clinical trials. For example, statements from several investigators mention certain trials that they started before obtaining regulatory approvals. It was also reported by EC members that trials were carried out although ethical approval was refused. These situations are simply demoralizing for EC members. Finally, stakeholders recognize that if we succeed in making the power of regulatory authorities effective, this would optimize evaluations, make it possible to carry out control activities and to know precisely how protocols are executed on the ground.

Ancestry of research groups

The ancestry of research groups has a significant influence on regulation insofar as public authorities often use these players as outside experts to evaluate research projects.

The ascendancy comes not only from the fact that researchers are solicited as the only available experts, but more generally because of an unequal balance of power:

We are at the mercy of researchers. Whatever anyone says, there is the food aspect, they are looking for protocols by all means because they have 4x4s, they have 2 to 3 million per protocol, and that is the problem, (participant 26, member of C

The competence of investigators working in clinical research institutions in Mali has often been recognized by all stakeholder groups as a factor that improves the quality of trials. In the absence, in Mali, of a formal assessment of skills in this area, it is difficult to conclude on the issue. For example, we do not have precise information on the nature of the skills acquired, we do not know if these relate to the scientific principles applicable to clinical trials or more to international regulations such as good clinical practices or even to the ethics of research.

Financial resources

Informants noted a low availability of material and financial resources specific to the regulation of clinical trials. Lack of resources tends to weaken trial regulation efforts. It seems difficult for the public authorities to carry out regulatory control missions:

The structures have very limited means. For control missions in the field they cannot travel, they do not have the financial or logistical means to see on the ground what exactly is happening (participant 15, EC member).

The absence of public resources contributes to increasing dependence on research structures. It does not only reflect an absolute lack of resources, but above all the absence of a regulatory framework allowing resources to be allocated to the control of clinical trials.

There are two explanations for this situation. On the one hand, the authority has not received a clear mandate to intervene in clinical trials, this is the case with the ANR and to a lesser extent with the CEs. However, it must justify the use of resources in accordance with its mandate. On the other hand, the authority does not have a legal status allowing it to benefit from its own resources, this is the case for all ECs. These have no legal personality and exist only through their subordination to research institutions with the exception of the CNESS which is attached to the Ministry of Health. The corollary of this attachment is to subject this structure to the system of a subsidy from the ministry, the granting of which is still uncertain

To conclude the results section, it appears that the factors influencing the regulation of clinical trials can be synthesized into five groups distributed between two spheres of influence. They consist essentially of obstacles that prevent the full exercise of regulation by the public authorities.

Discussion and conclusion

The objective of this study was to identify the obstacles as well as the factors favoring the regulation of clinical trials in Mali.

As described previously, we identified two spheres of influence: the conditions of the organizational field and the position of the actors in the field. We discuss the factors influencing regulation in relation to these two elements.

Organizational Field Requirements

It immediately appears that the process of establishing the field of regulation of clinical trials has not been completed in Mali.

The first indicator of the structuring of the field refers to the nature of the interactions between organizations. In this respect, the data indicates that the actors maintain very little interconnection. They have no relationships of interdependence, nor effective interactions. The only interaction between the public authorities (EC and ANR) took place during reinforcement activities organized by the WHO. At these regional platforms, these organizations do not seek to accentuate cooperative complementarities. Very few opportunities for direct interaction exist between the different groups of actors to construct the field and collectively produce shared meanings. However, according to Meyer et al., who qualify such gatherings as *field-configuring events* (Meyer et al. 2005), these are moments allowing disparate entities to coordinate their actions, build an agenda and mutually influence the configuration of the field (Anand 2008).

The second indicator of structuring of the field is due to the emergence of inter-organizational structures which organize and regulate relations between actors. In the context of clinical trials, no coordination body is formally designated in order to encourage the cooperation necessary for the proper functioning of the system. In theory, the Department of Pharmacy and Medicine is intended to coordinate the activities of the pharmaceutical sector. However, it has not been able, far from it, to get involved in the control of clinical trials up to expectations. The effective coordination between public authorities which it has been able to promote has been extremely limited. A supposed coordination body, it did not have the necessary power to direct and regulate the system, allowing the organizational logic of each public body to predominate.

Thirdly, the study shows that between organizations in the field the exchange of information is weak, poorly developed and unstructured, which reinforces the hypothesis according to which the field of regulation of trials is still emerging in Mali.

Finally, the structuring of a field involves its members' awareness of interdependence and a feeling of participation in a shared field of activity. In this regard, if the data attest to a greater collective awareness of the need for regulation of clinical trials in Mali, concrete achievements, such as the dissemination of information guides or guidelines for researchers, remain limited.

In short, if we examine the degree of interactions, coordination structure, mutual information and awareness in the constitution of interdependencies, we can argue that the structuring of the field of regulation of clinical trials in Mali appears incomplete. It does not seem impossible to us that this situation explains, at least partially, the predominance of obstacles to the regulation of clinical trials in

Position of actors in the organizational field

The literature suggests that the evaluation of regulatory policies must take into consideration three important groups of actors or potential participants in the regulatory process: 1) regulators or regulatory bodies; 2) regulated groups; and 3) the general public (Berry 1982). In this study, these groups correspond respectively to the following entities: 1) national regulatory authorities and ethics committees; 2) researchers; and 3) the general population and human subjects. Our research observations show that the general public does not intervene in the conduct of regulatory processes in Mali. More generally, it is considered that the public does not show a great interest, nor does it represent an important stake in regulatory decisions.

The concept of institutional entrepreneur allows us to focus on the respective positions of the two groups of interested actors and their potential to influence institutional contexts (Lawrence et al. 2009). This concept describes individuals and organizations who can become agents who innovate, act strategically and contribute to institutional change.

In this respect and with reference to international regulations, the ANR is called upon to play an increased role in regulating the functioning of the field of clinical trials.

(World Health Organization 1995). It is expected to play the leading role in the regulation of clinical trials, like an institutional entrepreneur in a given field. This justifies the support given by WHO since 2005 to strengthen the NRAs of 19 African countries, including Mali. Despite this support, the capacity of public authorities to appropriate the regulation of clinical trials in Mali and to integrate it into their institutional strategies has proved to be very limited.

Public authorities mobilize few mechanisms to influence institutional rules or to create new ones. There appears in their opinion a tendency to justify their capacity for action as being highly dependent on institutions. However, current institutions are more often described in terms of constraints. For example, starting from the observation that regulatory authorities constantly refer to the absence of legislative texts to explain the absence of collective action frameworks, we can see the constitutive and cognitive character of institutions, even their essential role in channeling their actions. In their opinion, their action remains subordinate to the rules, resources and restraints emanating from institutional frameworks. Rather than looking to current institutions for means of action, these authorities tend to see them as an environment that constrains their ability to bring about change. In fact, they build around them an environment that constrains their ability to bring about change. The corollary is that the agency capacity of the Malian public authorities has turned out to be very limited. They do not seem to act as an institutional entrepreneur capable of influencing regulation. Ultimately, regulation is constrained by the impossibility of regulatory authorities to build the means and to give themselves the ability to enforce them.

When an organizational structure is dynamic and acts as an institutional entrepreneur, it tends to have a strong and definitive influence on the structuring of the field. The example of another developing country inspires us to illustrate this hypothesis. Indeed, informed by the WHO that a clinical trial refused in 2006 in South Africa was subsequently inadvertently accepted in Malawi, a member of the ANR of this country (Pharmacy, Medicines, and Poisons Board) resolutely *committed* to changing the framework of regulations of his country. Since then, he has succeeded in having a law adopted by parliament in 2008 and developed more than ten regulatory documents including guidelines, procedures and various forms (World Health Organization 2010).

Conversely, when an organizational structure is inert and unresponsive to the need for change, the evolution of the field can come to an impasse (O'Brien and Slack 2003). The relative inertia of the public authorities in Mali is partly explained by the social condition of the actors who find themselves in unequal positions. Numerous studies from the neo-institutional current demonstrate the existence of an association between the social position of actors and their capacity for agency (Lawrence et al. 2009). Here, on the one hand, there is a developing country with few resources and a relatively weak state apparatus, and on the other hand, research groups that are on the whole well endowed, better trained and have strong links with foreign countries. The forces are unequal and the behavior of the main players seems to be influenced by the interplay of this balance of power.

To conclude, it should be recalled that this empirical study offers a detailed analysis of the factors influencing the regulation of clinical trials in Mali. The article constitutes a first step in the study of the influences on the regulation of trials

clinics in developing countries. Other research on this theme seems necessary in order to account for the influences in a context where the degree of structuring of the organizational field is higher.

Two spheres of influence are identified. They are certainly not the source of all the obstacles to regulation. However, the results show how much they contributed. 1) Despite the authorities' awareness of the need to regulate clinical trials, several indications suggest that the field of regulation is still emerging and in the process of being structured, and that this weak structuring may have contributed to negatively influencing regulation. 2) Our analysis highlighted how the position of the actors involved in the construction of the field can explain the persistence of obstacles and the limits of the current regulation of trials in Mali.

The data from this study argues for a need to improve and restructure the clinical trial environment. They show that the regulation of clinical trials does not automatically result from strengthening the capacities of public authorities alone. It is not a simple technical exercise either, but a search for rationality constantly influenced by contextual forces. It is a very complex activity insofar as it connects several actors whose actions converge very little. It must reconcile social and private objectives. Moreover, most of the basic problems stem from a need to restructure the organizational field and strengthen the position of the public authorities. A theory of the regulation of clinical trials in developing countries must seek to specify the institutional context in which each of the groups of actors can exert an influence. It also implies that it can be established who controls and who must control the environment. To be able to change things, the study shows that governments could use mechanisms at their disposal to strengthen control over many aspects of the behavior of the institutional environment of regulation, including its members and the relationships between stakeholders. This leads us to suggest: 1) an increase in the scope of interactions between the different organizations in the field of clinical trials to allow the emergence of a well-defined structure of power or coordination within the health authorities; 2) the strengthening and use of human and institutional capacities in the field of clinical trials. The management and responsiveness of public authorities vis-à-vis these new problems depend to a large extent on the strengthening and maintenance of the capacities of their civil servants.

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