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Comparative Study of Clinical Trials Regulatory Oversight in Burkina Faso and Senegal

Youssou Ndao

Laboratory of Galenic and Legislation, Faculty of Medicine, Pharmacy and Odontology, University Cheikh Anta DIOP, Dakar, Senegal
Email: youssoundao@gmail.com

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Abstract

Introduction: Clinical trials issue is both legal and ethical. Pharmaceutical firms in developed countries are relocating more and more their tests in African continent, where lack of legislation weakens the fact to standardize clinical trials. Our objective was to make a retrospective comparative study on regulatory oversight of clinical trials in Burkina Faso and Senegal, from February 22th, to 1st of June 2016. **Methodology:** Data collection was performed by a literature review and interviews. Data analysis was done by comparing monitoring systems using indicators such as existence of a legal framework, mode of assessment and licensing, monitoring of clinical trials. **Results:** Clinical trials are regulated in Burkina Faso and Senegal. During the study, 34 authorizations were issued, and three sites were visited and one inspection made. The processing time of an application file is estimated at 110 days. As for Senegal, scientific evaluation by experts is not systematic. The processing time of a file is estimated at 40 days, and no inspection or site visit has been recorded. **Conclusion:** Burkina Faso regulatory oversight of clinical trials is implemented in accordance with GCP. Senegal hasn't developed specific texts for clinical trials, and NEHR issues an ethical and scientific opinion. NRA has adopted ICH-GCP, without any mandate for assessing protocol. However, Burkina Faso's current system combined with that of Senegal, could contribute to developing an effective model of regulatory oversight of clinical trials in West African Economic and Monetary Union, for public health benefit.

Keywords

Regulation, Oversight, Clinical trials, Ethics, Scientific, Authorization, Senegal, Burkina Faso

1. Introduction

Clinical trials studies are carried out in human medical therapy to assess safety

and efficacy of a diagnostic method or treatment. Clinical trials raise a range of both legal and ethical issues (Diarra, 2007). To guarantee rights and protection of the people who participate to it, and to establish data reliability by ensuring ethical, scientific and technical quality, it is necessary to put in place documents and procedures regarding their organization and conduct. Indeed, Clinical trials are a formalized and rigorous procedure, essential for the validation and marketing of a new drug (Chippaux, 2002). Most clinical trials are carried out in industrialized countries to serve their own market, and the methodology is based on a great deal of experience.

In Africa, medical and pharmaceutical regulations are obsolete or unsuitable (Sardan, 2004). Risks of breach of ethics are high and the cost of clinical trials is five times lower than in developed countries. Also, the absence of legislation can weaken any attempt to standardize clinical trials, and there is still a great risk of seeing procedures simplified less rigorous, because there is less monitoring (Chippaux, 2004). In addition, private funding has a finalized objective, which would limit research prospects and could lead to exerting pressure on investigators, for a favorable presentation of results, or at least concealment of those which would be unfavorable (Parizeau, 2000). Nevertheless, development of clinical trials favors the emergence of standards allowing the production of texts adapted to concrete practices (Fagot-Largeault, 2002). In West Africa, Burkina Faso, through Muraz center[1], has experience in conducting clinical trials. In Senegal, the regulatory authority issues import authorizations for experimental drugs, but do not assess any clinical trial protocol (Diagne, 2019). In Mali, clinical trials oversight is very limited, due to a lack of infrastructure and expertise, to fully implement the regulation. This represents a risk for the safety of the subjects and the reliability of the scientific results (Diadie Maiga, 2012). Therefore, clinical trials oversight in Africa needs to be context-specific, as regulations are quite recent. Our work consists of comparing regulatory oversight of clinical trials in Burkina Faso and Senegal from 2013 to 2015, to propose harmonized regulatory framework. The first part will analyze the situation, before devoting the second part to a comparison of the regulatory oversight of clinical trials in both countries.

2. Study Framework

These are respectively Burkina Faso and Senegal, given the existence of research centers and platforms dedicated to clinical trials.

2.1. Burkina Faso

Burkina Faso (BF) is a country with an area of 274,000 km^2 which has no outlet to the sea. It borders Mali to the northwest, Niger to the east, Benin, Togo, Ghana and Ivory Coast to the south. The political capital is Ouagadougou. The population of the country is close to approximately 17 million inhabitants with

[1]https://www.centre-muraz.bf/essais-cliniques (consulted on 28-02-23).

about sixty ethnic groups. BF has a tropical climate with two seasons: a dry season from November to June and a rainy season from June to October[2,3]. Burkina Faso is divided into 13 regions and 45 provinces. It houses MURAZ Center located in the commercial area of Bobo-Dioulasso, which extends over more than 20,000 m^2. This center is a clinical trial platform created in 2015.

2.2. Republic of Senegal

Senegal occupies the westernmost end of African continent. and covers an area of 196,712 km^2. It is bordered to the west by the Atlantic Ocean, to the north by Mauritania, to the east by Mali, to the south by Guinea and Guinea Bissau. Its political capital is Dakar. Senegal has approximately 13.5 million inhabitants (2013 estimate) of which nearly 42.1% are under 15 years old. The tropical climate is characterized by drought in the north and abundant rains in the south of the country, particularly in Casamance.

Senegal, made up of 14 administrative regions and 45 departments, is home to the Research Institute for Development (IRD), which has been developing research, training and innovation activities in partnership with Senegalese institutions for over fifty years.

The first studies carried out by the IRD in the Niakhar area concerned the collection of demographic data. This area which extended over eight villages at the beginning was later enlarged to cover 30 villages with a larger population in 1983. The site of Niakhar, a pioneer in the investigation of epidemics, has since the beginning shared its information with the Ministry of Health of Senegal to declare occurrence of cases and prevent epidemics in particular of cholera, yellow fever, measles, influenza, meningitis. It was then chosen as a clinical trial platform (Diallo & Sokhna, 2018).

3. Methodology

This is a retrospective and cross-sectional study that took place respectively from February 22th to March 31th, 2016 for Burkina Faso, and from 1st of May to 1st of June, 2016 for Senegal. Data collection was carried out by a review of the literature, legislative and regulatory texts in the field, but also interviews with certain professionals. The data analysis was done by comparing the surveillance systems using indicators, in particular the existence of a legal framework, the mode of evaluation and granting of authorizations, the follow-up of the trials clinics. Our objective was to compare regulatory oversight systems of clinical trials in Burkina Faso and Senegal from February 22th, 2016 to1st of June, 2016.

4. Results and Discussion

After applying the aforementioned indicators used by WHO in the context of the regulatory oversight of clinical trials, we obtained the following results:

[2]http://www.consulatburkinaparis.org/accueil/ (consulted on April 20, 2016 at 10 p.m.).
[3]https://fr.wikipedia.org/wiki/Burkina_Faso (consulted on April 22, 2015 at 7 p.m.).

4.1. Legislative and Regulatory Framework

Burkina Faso	Senegal
Law No. 23/94/ADP of May 19, 1994 on Public Health Code	Law 54-418 of April 15, 1954 on Book V pharmacy Law n˚ 2009-17 of March 09, 2009: Code of ethics for health research (CEHR)
Decree No. 2002-536/PRES/PM/MS/MESSRS of November 21, 2002 on Ethics Committee for Health Research (ECHR); Decree No. 2010-243/PRES/PM/MS of May 20, 2010 regulating clinical trials; Decree No. 2012-1033/PRES/PM/MS of December 28, 2012 on National Vigilance System for Health Products for Human Use.	Decree n˚ 2009-729 of August 3, 2009: Creation, organization and functioning of National Ethics Committee for Health Research (NECHR)
Joint Order No. 2004-147/MS/MESSRS of May 11, 2004 on the organization and operation of the ethics committee for health research in Burkina Faso (ECHR). Order No. 2010-292/MS/CAB of October 1, 2010 on the condition for granting authorizations for clinical trials; Order No. 2010-293/MS/CAB of October 7, 2010 on composition and operation of Technical Committee for examination of clinical trial authorization applications (TCEC).	Order No. 2009–5036/MSP/DPL of April 22, 2009 on the organization of the national pharmacovigilance system. Order No. 2011-014299/MSPHP/DPL of December 15, 2011 on the adoption of good clinical practices (GCP ICH) for the conduct of clinical trials; Order No. 2013-409 of January 22, 2013 adopting the researcher's guide and the brochure for (NECHR) members for the evaluation and monitoring of research protocols.
Decision no. 2013-980/MS/CAB of August 16, 2013 appointing the members of the technical committee for examining applications for authorization of clinical trials (TCEC).	The members of the (NECHR), before their official entry into office, take an oath before the Court of Appeal of Dakar, sitting in solemn audience.

In Burkina Faso, even if the 1994 law is obsolete and does not set out principles related to clinical trials, specific texts have been adopted. Decree creating an ethics committee for health research, and decree regulating clinical trials[4,5]. It's the same for Senegal, where law 54-48 of April 15th, 1954 on Book V pharmacy (Code of pharmacy), does not include specific provisions for clinical trials. This legal vacuum was filled by adoption of a law in 2009 on Code of ethics for health

[4]Burkina Faso: Decree No. 2000-010/PRES/PM/MS of January 26, 2000 on the powers, composition, organization and operation of the national drug commission.

[5]**Burkina Faso:** Decree No. 2002-464/PRES/PM/MS of October 28, 2002 creating the General Directorate of Pharmacy, Medicines and Laboratories.

research (CEHR), followed by a decree on creation, organization and functioning of the National Ethics Committee for Health Research (NECHR)[6,7]. However, this law takes into account biomedical research (article 20), and other social science and health research. Unlike Burkina, Senegal has adopted good clinical practices.

In Burkina, pharmaceutical inspection and monitoring of adverse events have been taken into account, respectively, by decree relating to the functioning of the DGPML[8], and by decree establishing a national system of vigilance for health products for human use[9]. Senegal has a national pharmacovigilance system set up by decree[10]. However, this order describes organization and operation of the system, but does not take into account all vigilance. Also, it has not been made more operational by a decision to appoint members who must sit in national commission and technical committee.

In Burkina, procedures relating to signing of confidentiality clauses and declarations of interest for members of ECHR and TCEC have been developed. The inconveniences relating to the deposit of the costs of submitting files to the management were resolved by the adoption in 2012 of a decree authorizing collection of fees relating to certain services at Directorate General for Pharmacy, Medicines and Laboratories (DGPML)[11].

4.2. Institutional Frame

Burkina Faso	Senegal
Directorate General for Pharmacy, Medicines and Laboratories (DGPML)	General Directorate of Pharmacy, Medicine (GDPM)
Ethics Committee for Health Research (ECHR)	Department of Health Planning and Research (DHPR)
Clinical Trial Authorization Application Review Technical Committee (TCEC)	National Ethics Committee for Health Research (ECHR)

In Burkina, institutional anchoring DGPML as general management is interesting given the sensitivity of clinical trial authorizations. Furthermore, establish-

[6]Republic of Senegal: Law No. 2009-17 of 03/09/2009 on the Code of Ethics for Health Research (CNRS).

[7]**Republic of Senegal:** Decree No. 2009-729 of August 3, 2009 on the creation, organization and operation of the National Ethics Committee for Health Research (CNERS).

[8]**Burkina Faso:** Decree No. 2002-464/PRES/PM/MS of October 28, 2002 creating the General Directorate of Pharmacy, Medicines and Laboratories.

[9]**Republic of Senegal:** Decree No. 2009-729 of August 3, 2009 on the creation, organization and operation of the National Ethics Committee for Health Research (CNERS). Burkina Faso: Decree No. 2012–1033/PRES/PM/MS of December 28, 2012 on the creation, allocation, and organization of the national vigilance system for health products for human use.

[10]Republic of Senegal: Order No. 2009–5036/MSP/DPL of April 22, 2009 on the organization of the national pharmacovigilance system.

[11]Burkina Faso: Decree No. 2012-432/PRES/PM/MEF/MS of 24 May 2012 authorizing the collection of revenue relating to certain services of the General Directorate of Pharmacy, Medicines and Laboratories (DGPML).

ment of DGPML and ECHR, two (2) structures, is in accordance with good clinical practice which recommends an establishment review committee (ERC) and/or Independent Ethics Committee (IEC) (WHO, 2016) (Guidelines (ICH1 E6), 2016)[12,13].

The independent ECHR gives an ethical opinion, and the DGPML ensures the regulatory follow-up. In addition, the DGPML has a technical committee called CTEC[14,15], allowing it to fully play its technical role in complete transparency. Thus, clinical trial authorization application files are examined independently, as mentioned in the GCPs.

As for Senegal, the NECHR is the main player in clinical trials and research, the other structures, in particular GDPM, National control laboratory authority NCL and poison center, are involved as members. However, absence of a decree on the attributions, on GDPM organization and functioning, and its institutional anchoring, do not allow it to assume its technical and scientific role, in the process of evaluation and granting of authorizations for clinical trials.

4.3. Assessment of Application Files

Burkina Faso	Senegal
DGPML: two (2) copies	NCHR : Twenty (20) copies
Systematic assessment by experts	Transmission of files to NCHR members Assessment by experts as needed
TCEC meeting held	Holding of members meeting
Processing time = 90 days	Processing time = 40 days
34 authorizations issued	Information unavailable

In Burkina Faso, ethics assessment entrusted to ethical scientific review board (ESRB). Technical and scientific evaluation is systematically entrusted to a committee of experts and to TCEC. The SOL of the DGPML provides the secretariat. The file for ethical decision is different from the file for authorization of clinical trial and it is necessary to have ethical approval before submitting request for authorization of clinical trial. The functioning of these two (2) structures is in accordance with the spirit of good clinical practice (WHO, 2016) (Guidelines (ICH1 E6), 2016)[16,17]. The process allows the ESRB and drug regula-

[12]Harmonized guidelines on good clinical practice (GCP) in AVAREF member countries, August 2009.

[13]Health Canada: Guidance for Clinical Trial Sponsors: Clinical Trial Applications, Our File Number: 13-108409-403.

[14]Burkina Faso: Order No. 2010-293/MS/CAB of October 7, 2010 on the creation, powers, composition and functioning of the technical committee for the examination of applications for authorization of clinical trials (CTEC).

[15]Burkina Faso: Decision No. 2013-980/MS/CAB of August 16, 2013 appointing the members of the technical committee for examining applications for authorization of clinical trials (CTEC).

[16]Harmonized guidelines on good clinical practice (GCP) in AVAREF member countries, August 2009.

[17]Health Canada: Guidance for Clinical Trial Sponsors: Clinical Trial Applications, Our File Number: 13-108409-403.

tory authority to work well together.

Experts must sign a declaration of interest and confidentiality clause document before studying each file. They make observations on various points of the file in the form of a technical summary, and propose an opinion to the TCEC (acceptable without reservation, acceptable with reservation, rejection), which notifies each promoter/sponsor, after each session.

In addition, the CTEC will propose an opinion to the minister in charge of health, who has a maximum period of 90 days for the notification of the granting decision. This processing time is similar to that of the National Medicines Safety Agency (ANSM), which is 60 days. However, the ESRB should issue an ethics certificate instead of an approval letter, but above all register the trials in the clinical trials register.

With regard to Senegal, the CNERS examines the protocols, and issues both an ethical and scientific opinion. Its members take an oath before taking office, and must sign a declaration of interest document and a confidentiality clause before the study of each file. Although this mode of operation of the CNERS is in accordance with the spirit of good clinical practice, this system is not free from criticism.

CNERS members are not appointed by regulatory act as in Burkina Faso. They have too extensive prerogatives, where the DPM in charge of regulation has no mandate to suspend, prohibit the continuation of research, or even terminate it. This situation risks compromising the conduct of trials in the future, with the risk of conflicts of interest or a lack of transparency in the handling of certain files; the CNERS being both judge and party.

4.4. Follow-Up Inspections/Visits

Burkina Faso	Senegal
DGPML, CNVPS, CERS	DPM, CNERS
Out of 34 trials authorized • One (1) single inspection (2%) • Three (3) field visits (8%)	• No inspection • progress report
Monitoring of adverse events • Notification tools and circuit	Monitoring of adverse events • Notification tools and circuit

Control of compliance with regulatory aspects is carried out by the DGPML through the pharmaceutical inspection service by inspecting CE sites. The clinical trial monitoring mechanism ensured by the DRLP, the SIP and the CNVPS is well described with procedures and working tools. However, it is weakly implemented, and there is practically no inspection of clinical trials. Compliance with ethical principles is monitored by the CERS through visits to clinical trial sites.

The SIP, the DRLP and the CERS content themselves with the obligatory progress reports submitted by the promoters, to take stock during the sessions of the CETC and the national vigilance commission. Adverse events are monitored

by the CNVPS with field visits.

This situation at the level of inspection could be explained by the non-inclusion in the State budget of resources dedicated to inspection services. Consequently, the inspection/monitoring of clinical trials in Burkina Faso must be functional, for better control of the conduct of trials and the reliability of data. In Senegal, the monitoring of adverse events is well ensured by the CNERS, which has a team of members well trained in good research practices. As for the inspection of clinical trial sites, this is the soft underbelly of clinical trials. It is carried out as needed at the request of the CNERS, and does not appear in the schedule of inspection activities of the DPM. At this level, the CNERS limits itself to the promoters' progress reports. VS' this explains the absence of supervision of the regulatory aspects, which are not regularly carried out by the DPM. This absence is not without consequence on the quality of the data and the smooth running of clinical trials on the sites. These deficiencies need to be corrected to ensure compliance with GCP requirements.

4.5. Resources

Burkina Faso	Senegal
Human ressources • DGPML • (31) pharmacists • 1 unsworn inspector • CETC (11) • ESRB (9)	Human ressources • DPM (9) pharmacists • 5 inspectors • 1 sworn • CNERS (32)
Financial ressources • Revenue generated	Financial ressources • Revenue generated

In Burkina, the DGPML has only one pharmacist trained in pharmaceutical inspection. The only specialist pharmacist has not taken an oath before the Ouagadougou High Court[18]. Furthermore, not all DGPML pharmacists are trained in good clinical practice inspection. This makes inspections and follow-up reports difficult.

The number of pharmacists who provide the secretariat for the receipt of files is insufficient because the secretariat receives all license applications. The various commissions are made up of multidisciplinary members, which allows an analysis of the files on all aspects. The number of commission members is not excessive: CTEC, eleven (11) members, national vigilance commission and two specialized technical committees of twenty-four (24) members respectively, eleven (11) and nine (9) for the ESRB

A controlled number allows a smooth running of the work session.

Commissions and technical committees are chaired by the DGPML which allows a good understanding of the subject. The members of the various commis-

[18]Burkina Faso: Decision No. 2013-980/MS/CAB of August 16, 2013 appointing the members of the technical committee for examining applications for authorization of clinical trials (CTEC).

sions are appointed by regulation. But not all committees are without difficulties. Not all ESRB members are trained in ethics review.

With regard to financial resources, the support of the members of the various commissions is ensured by the application fees retroceded to the DGPML and by the State budget. This gives continuity to the existence and regular holding of committee sessions. But there are no budget lines for inspections, the conduct of vigilance inquiries and investigations as well as field visits. This encourages non-compliance with clinical practices, some provisions of which are not implemented.

Material resources are insufficient. This would explain the poor implementation of pharmaceutical inspection/follow-up visits. There is also the dilapidated state of the DGPML vehicle fleet.

In Senegal, the CNERS has a total of 32 members trained in research ethics, including a pharmacist inspector representing the DPM, for the supervision of clinical trials. The number is plethoric and does not ensure a smooth running of the work sessions. This situation could be explained by the fact that the CNERS is the main player in clinical trials, and has too extensive prerogatives.

However, not all CNERS members have training in PCBs; the president is not named, and the administration of the committee is ensured by the national coordinator of the CNERS. Furthermore, not all members are regularly convened, and most of the DPM pharmacists trained in both pharmacy inspection and PCBs are not members of the CNERS. This is not without consequences for the smooth running of committee sessions. This is a limit that testifies to a weakness in the operationalization of the decree establishing the CNERS. A decision to appoint members and a clear definition of the roles and responsibilities of CNERS and the DPM in the conduct of clinical trials would ensure better regulatory monitoring of trials,

Financial resources are coming from application fees retroceded to the CNERS, and are managed according to the rules of public accounting. These funds are used to support members of the CNERS, and also to perpetuate the organization of the sessions. On the other hand, the national commission and the pharmacovigilance technical committee do not have the resources to carry out their activities.

The poor logistics of the structures involved (DPERS and DPM) explains the difficulties in covering both follow-up visits and on-site clinical trial inspections.

5. Quality Documents

Burkina Faso	Senegal
EC Authorization Procedures Manual	Researcher's Guide
General inspection procedure	Brochure of CNERS members
Written in 2011	Written in 2009 Adopted in 2013

Burkina has developed a manual of procedures governing the authorization of clinical trials and a general inspection procedure. However, these procedures date from 2011 and need to be revised. For Senegal, there is a researcher's guide and a brochure for CNERS members[19,20] which facilitate good file management, but also ensure good traceability. These two documents, drafted in 2009 and adopted by regulation in 2013, also apply to clinical trials.

6. Conclusion

In Burkina Faso, the provisions put in place come close to the requirements of good clinical practice, but need to be improved. The independent ESRB gives an ethical opinion, and the DGPML issues regulatory authorization. In Senegal, regulatory monitoring is supervised, but the CNERS, which has too extensive prerogatives, delivers both an ethical and scientific opinion to the Minister of Health. As for the DPM responsible for regulation, it has no mandate and does not carry out any inspections.

In Senegal as in Burkina Faso, it is necessary respectively to strengthen the capacities of actors on the inspection of clinical trials and GCPs, and to adopt new texts specific to biomedical research. However, Burkina Faso's current system could serve as a model for regulatory oversight of clinical trials in West Africa, to ensure protection for those who take part.

Conflicts of Interest

The author declares no conflicts of interest regarding the publication of this paper.

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