Case Report

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Strengthening Biomedical Ethics - Lessons from a Cabo Verde Clinical Trial Case

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ABSTRACT

The uncertainties caused by the COVID-19 pandemic have stimulated biomedical research worldwide to support evidence-based public health policies aimed at reducing the impact of COVID-19 on populations. the resulting urgency of decision-making in a pandemic context faced by Research Ethics Committees created new challenges leading to new reflections on the basic principles of ethics. Starting from a specific case of the implementation of a clinical trial in a pandemic context, this article analyses the emerging ethical and regulatory challenges for the development of clinical trials in Cabo Verde and the path towards strengthening clinical research and biomedical research ethical decision-making in the country. Research in health is important for the social development of a country. It can push forward non-existent but necessary regulatory frameworks in the countries. Legal and ethical gaps related to biomedical research can be overcome to make clinical research possible, as was the case in Cabo Verde and, thus, contribute to the overall development of well-regulated science.

Keywords: Clinical Research; Research Ethics Committees; Clinical Trials; Africa; Cabo Verde

Abbreviations: CNCA: National Commission for Coordination and Monitoring; PALOP: Portuguese-speaking African Countries; EDCTP: European & Developing Countries Clinical Trials Partnership

Introduction

Research for health is a central component of improving health and equity [1] and to guarantee Universal Health Coverage [2,3]. Research for health, rather than health research, acknowledges that the fields of relevance to improve health, achieve equity and attain Universal Health Coverage bridge across a broad spectrum of determinants well reflected in the Sustainable Development Goals. Good research for health requires credible and sustainable research systems. Credible and sustainable research systems are only possible if several criteria are met, including steering by ethical and legal principles and values, guaranteed and upheld, in each country and/or institution, by Research Ethics Committees [4]. Research Ethics Committees have the formal "authority to approve, reject or stop studies or require modifications to research protocols [2]". In research for health the scope of work of the Research Ethics Committees is expanding and progressively more challenging as research becomes broader and "multifaceted, cutting across a wide range of disciplines, teleologies, epistemologies and methodologies" [3]. Due to their current role, the Research Ethics Committees must include diverse expertise that enables an adequate reviewing process of the research proposals, particularly because the ethical decision issued will determine the permission or not for conducting biomedical and other health related research [4]. This is particularly relevant for the conduct of clinical research, particularly the most frequent design of interventional research - clinical trials [5].

Clinical trials are a necessary step to scientifically develop the countries, in addition to increase the capacity and the quality of health care and services, and support the economy [6]. In 2022, the global clinical trials market size was estimated at USD 4.7 billion and expected to grow around 6% until 2030 [7]. The number of registered clinical trials increased exponentially in recent years. In Africa, for instance, in March 2023, 1,418 trial were registered as complete and 1,373 as active, only in the Clinical Trial Transparency in Africa platform [8]. Good, ethically compliant clinical research cannot be separated from a solid regulatory framework and ethical guidelines. Otherwise, the respect for research participants and ethical principles such as autonomy, beneficence, primum non nocere and justice might be imperilled. In this short report we describe the attempt to conduct a clinical trial in Cabo Verde, its non-approval by the National Committee for Ethics in Research in Health on the basis of the absence of a legal framework for clinical trials, and how this contributed to rally different ministries and stakeholders to strengthen the national research system with the required legal regulatory framework. The research project was a multicenter clinical trial for three countries. Being a clinical trial, ethical procedures had to be respected, so much so that it was approved by the National Ethics Committees of the other two countries (Mozambique and Guinea Bissau).

The Case

With an estimated population of 598,682 in 2023 [9], Cabo Verde is in the Afrotropical realm of Macaronesia, a small island developing state (https://www.un.org/ohrlls/content/about-small-island-developing-states) which has been very successful in its health policy, achieving the best health status indicators of the Sub-Saharan African countries. In Cabo Verde, research for health is a divided responsibility among several ministries and a considerable number of public and private institutions (including those in higher education). It is the case of the National Institute of Public Health, created in 2014 with the mission of "generating, disseminating and developing scientific knowledge about health and its determinants" [10]. Despite this, the country is classified as one of those with lowest investment in research in the world, and, among the Portuguese-speaking African Countries (PALOP), one of those with the lowest scientific production in the health area [10]. Funding for research for health is received from multiple sources and there is a need for more coordination. To address these and other needs, Cabo Verde is creating a Science Foundation that will be functioning as from 2023 [11]. This Foundation will coordinate research funding in the country, including research for health. Such a process will take time but it is actively supported both by the science and higher education sectors and the Ministry of health [12].

In 2007, the first and so far only Research Ethics Committee (National Committee for Ethics in Research in Health – Comité Nacional de Ética em Pesquisa para Saúde - CNEPS), was officially constituted by the Decree-Law 26/2007 of July 30 in which it is stated that research involving human participants was being held without ethical approval [13]. The CNEPS is "an autonomous and independent, multisector and multidisciplinary entity that ensures the safeguarding of the dignity, rights, safety and well-being of all potential participants in health research" whose activity extends from the private to the public sector [13]. It is formed by representatives from the Ministry of Health, the national Committee on Human Rights, the Medical and Lawyers Councils, the Non-Governmental Organism platform, a religious institution and the University of Cabo Verde. Later, in 2019, the Independent Health Regulatory Authority (Entidade Reguladora Independente da Saúde - ERIS) was created (Decree-Law nº 03/2019 of 10 of January) supplementing part of the attributions of the CNEPS, mainly in terms of promoting the scientific research in pharmaceuticals and other medical products and in the regulation and supervision of the application of pharmaceuticals to humans [14]. Both CNEPS and ERIS were beneficiaries of two projects on regulation and ethical training in African Portuguese Speaking Countries funded by The European & Developing Countries Clinical Trials Partnership (EDCTP): Strengthening Bioethics Committees in Lusophone African Region – LusoAfro-BioEthics (https://www.lusoafro-bioethics.org/) coordinated by University of Cabo Verde (Uni-CV) and Biomedical Ethics

and Regulatory Capacity Building Partnership for Portuguese-Speaking African Countries - BERC-Luso coordinated by ERIS (https://www.berc-luso.com/EN/) which ran from 2016 to 2022.

The first aimed at strengthening the capacity for clinical research within health ethics, targeting institutional and personnel capacities in Lusophone African Countries, by sharing good practices on Standard Operation Procedures, Protocol Review and international regulatory ethical and legal norms and standards and to promote the establishment of University of Cabo Verde Institutional Review Board (https://www.lusoafro-bioethics.org/). The BERC-Luso aimed to establish and develop well-grounded, sound, robust and long lasting ethics and regulatory capacities at the five Portuguese Speaking African Partner Countries with special emphasis on clinical trials (https://www.berc-luso.com/EN/, [15]). Concomitantly in 2020, in the initial phase of the COVID-19 pandemic, a multicentre clinical trial entitled "The BCG vaccine to reduce unplanned absenteeism due to illness of health professionals during the COVID-19 pandemic, a multicentre trial, randomized controlled trial (BCG-COVID-RCT)" (trial registered at clinicaltrials.gov: https://www.clinicaltrials.gov/study/NCT04641858) was submitted to CNEPS. The main objective of the clinical trial was to test whether BCG vaccination can reduce unplanned absenteeism due to illness among health professionals in hospitals in Cabo Verde, Guinea-Bissau and Mozambique, during the COVID-19 pandemic. The secondary objectives were to test whether BCG can reduce the number of COVID-19 cases and hospital admissions, and to improve clinical research capacity in these countries, especially in Cabo Verde, where a clinical trial had never been conducted.

At the very beginning of the COVID-19 pandemic, where no specific therapeutical option was yet available for the SARS-CoV-2 infection, the use of BCG vaccine to reduce the incidence and/or severity of COVID-19, or as a prophylactic treatment, based on several studies that had been produced evidence of non-specific effects of this one century old vaccine, in particular in low-income settings, provided the scientific rationale for the study [16,17]. Besides, the BCG vaccine not only was being administered to new-borns as part of the national immunization plan in the three trial countries but had, in the end of the 1990s and beginning of the 2000s, been administered as a booster dose to health and care professionals entering the profession [18]. Based on these arguments, the team of Cabo Verdean researchers considered that the project had criteria for its implementation for the benefit of science, the country and of the health and care professionals. The BCG-COVID-RCT Clinical Trial research protocols were submitted to the Research Ethics Committee of the three participating countries and received approval in Guinea-Bissau and Mozambique. In Cape Verde, carrying out scientific research that is carried out on human beings, namely clinical trials and others, must always have authorization from the CNEPS, which is the first step, before creating the effective conditions for carrying it out. As this authorization was not obtained, it was not possible to proceed with any of the subsequent steps such as validating the consent form, acquiring the contract from the national insurers for the risks, etc.

In Cabo Verde, although there was initially a deliberation issued on July 30, 2020 that could lead to the perception of a favourable outcome (CNEPS Deliberation nº40/2020) as it stated that it was an opportunity to strengthen and initiate clinical research in the country. There were requests for other documents, suggestions for improving the project, especially the informed consent form, and other considerations exposed in the deliberation, but a final deliberation (deliberation nº 63/2020 dated September 20, 2020) definitively excluded the possibility of conducting the clinical trial in the country. The main reason for the refusal was the legal vacuum for carrying out the clinical trial, more specifically, the absence of a regulatory law for conducting clinical trials in the country. This situation was similar to that in Guinea Bissau where, however, clinical trials have been conducted for several decades, including the present one, using instead international regulations and guidelines to ethically guide decisions. However, this was not the understanding of the CNEPS that saw an opportunity to move forward the national agenda concerning research in health and more specifically clinical trials and further strengthen the biomedical ethical decision latitude in the country. Consequently, the Cabo Verdean researchers made several contacts (face-to-face and in written) with the CNEPS, the ERIS, the Ministry of Health, and the Deputies of the National Assembly to propose an ad doc emergency authorization for conducting the trial, and the elaboration of the regulation for clinical trials and other procedures that could guaranteed the effective implementation and conduct of the trial.

The researchers considered that the implementation of this trial, given that BCG was a long used vaccine, including in Cabo Verde (despite not approved for prevention or prophylaxis of SARS-CoV-2 infection), had a good momentum: it could really push the country to further develop its legislative body concerning health research and, more specifically, the implementation of clinical research. Such was the relevance of this research that, faced with the impossibility to conduct the clinical trials, the researchers adapted the research question to an observational case-control study design of the BCG vaccination rate among health care workers who did or did not get COVID-19, thus fulfilling two of the objectives of the project, which were to study the association between BCG and COVID-19 incidence and to strengthen the capacity for health research in the target countries of the project.

Discussion

The aim of this paper was to analyse the reasons presented by the CNEPS for the non-approval of the BCG-COVID-RCT Clinical Trial in the country, and how they derive and influence the ethical and legal constraints for clinical research in Cabo Verde. We further describe the enabling advances that this case brought to the development of clinical research in the country. The possibility of conducting, for the first time, a clinical trial in Cabo Verde represented an opportunity to

advance clinical research in the country. However, the refusal by the CNEPS of implementing the clinical trial brought to light existent gaps that prevent the implementation of clinical research in the country. These gaps included the lack of a legal framework to frame this type of research activity and study and the absence of institutional and normative conditions at several levels, including the CNEPS, created in 2007. The main reasons for not approving the clinical trial, were mainly related to the inadequate legal and regulatory framework, lack of adequate standards and minimum procedures for ethical review of clinical research, resulting in inexistent governance structures for research. However, given international guidelines for conducting clinical trials, the authors we think that the CNEPS could have based itself on and acted in accordance with international guidelines and see the possibility of Cape Verde carrying out the first clinical trial. However, we believe that the CNEPS preferred not to create precedents and force the creation of the legal diploma.

The specific case in analysis, as well as the contributions and impacts of the LusoAfro-BioEthics and BERC-Luso projects drove and led to a very relevant and enabling advance – the creation in 2021 of the National Commission for Coordination and Monitoring (CNCA) in charge of elaborating and reviewing the normative framework on biomedical research and other medical investigations and the ethics in public health policies. (Cabo Verde, 2021). The National Commission for Coordination and Monitoring includes representatives of the public sector and professional bodies. The publication of the proposed biomedical legislation is expected in 2023. However, and despite the recent efforts in strengthening bioethics framed by the two EDCTP projects LusoAfro-BioEthics and BERC-Luso, the CNEPS needs further support, especially regarding the development of a legal framework to operate and monitor the implementation of clinical research in the country and to act in the safeguard of the clinical research participants (e.g., by creating conditions to insure participants in clinical trials). Additionally, it is paramount to build capacity within the CNEPS to ethically evaluate clinical trial protocols. There is also a need to create a specific law that regulates the 2004 law of implementation of Ethics Review Boards within the Health Organizations foreseen in the basic law of the National Health Service and to implement it. A clearer definition of the role of the ERIS in these matters would also benefit the development of clinical research.

Conclusion

This short report presents a case where a setback in the implementation of a clinical research in a country led to advances in the field. As such, and despite not being possible to conduct a clinical trial (somehow overcome by the implementation of an observational design study), it was an opportunity to focus on the relevance of enabling legal and conceptual frameworks, well defined institutional roles and the capacity to advance research in health in general. Only by conducting research, it is possible to strengthen research and thus, strengthen the provision of more accessible, timely and appropriate health care. Researchers can be drivers for development, even in the face of imminent impossibilities. On the other hand, ethical literacy of researchers, policy makers and stakeholders are necessary. The authors believe that the non-approval of the clinical trial has strongly contributed to the creation of the National Commission for Coordination and Monitoring [19], and that shortly Cabo Verde will have a normative framework that will enable the conduct of ethically-approved clinical trials, thereby strengthening the clinical research capacity of the country.

Competing Interests

None declared.

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