

BERC LUSO
BUILDING ETHICS AND REGULATORY CAPACITY IN PORTUGUESE-SPEAKING AFRICAN COUNTRIES



Comparative Legal Study: International Best Practices and Legislative Challenges

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1. Why research is important

Research aims to provide new information, knowledge and understanding — scientific knowledge that can be extended to everyone and that can serve as the basis for improving health and understanding human diseases. It can be conducted in a wide range of fields, including the social sciences, clinical trials and biomedical sciences in general.

Research is very important and can bring valuable benefits to humans and should, therefore, be encouraged. In the field of biomedical research, the benefits to human health and well-being are undeniably valuable. Firstly, by improving the quality of life and well-being of individuals and of the general population, there are visible gains on health care, on its efficiency and quality, on the way it is administered, on a larger number of people being benefited, as well as on more efficient economic outcomes.

Additionally, research findings contribute not only to saving lives, to curing diseases or treating them more efficiently and to better and earlier diagnoses, but also to improved knowledge of the diseases themselves, increasing the quality of life and the life expectancy of individuals. Sometimes, research may not be immediately beneficial or may not directly help participants themselves, but even in such cases, there might be medium-term benefits for younger or future generations.

The interests of researchers also have to be taken into account as they are often relevant and legitimate. Moreover, they need to produce results to obtain funding for their research and professional activity, to advance their careers and to find support and encouragement for their work. But good research is crucial to advance knowledge, to attain better results and to produce good science.

The knowledge generated by good science has an intrinsic value for the benefit it brings to society. Research that cannot be applicable to its recipients — human beings, that is biased and fallacious, that repeats previous studies, that is based on wrong assumptions and that violates the dignity and integrity of the human being cannot be validated and cannot be allowed.

It is equally true that the benefits brought about by research may carry potential risks that may arise during or as a result of such research. Additionally, research is not free of cost — quite the opposite. For these reasons, we need to be cautious in the way funding is raised, managed and used.

The undeniable benefits to humans brought about by research must always be accompanied by an ethical assessment of the conditions under which such research was conducted, since any potential benefit to humankind has, above all, to protect the interests of human beings. This principle, which has been in place since the initial documents, such as the Nuremberg Code or the Declaration of Helsinki, is now consolidated into a binding Convention (for the signatory countries) — the Convention on Human Rights and Biomedicine,[1] whose Article 2 establishes the primacy of the human being: *The interests and welfare of the human being shall prevail over the sole interest of society or science.*

This principle, as we will later see, has been adopted as an inspiring source in legislation on biomedical research. To attain this goal, we must find effective protection mechanisms, starting with the translation of best practices into law. The law needs to set out the principles that should guide research and the pragmatic and effective means of approving, validating and enforcing the application of these principles and standards. This will, in turn, attain a twofold goal: the protection of the rights and interests of human beings that participate in research projects and the promotion of the development of science, medicine and health in general.

As we live in a globalized world of shared knowledge, shared benefits and international investment, it is counterproductive and unacceptable for each country to adopt measures or norms that do not comply with a whole range of universally accepted common principles. It is equally unreasonable if nothing is done, leaving it up to each researcher to determine how to conduct research involving humans. Therefore, it is crucial to establish rules that are not only accepted by the national and international scientific communities but also by all countries, so that they can be scientifically validated and nationally and internationally recognized as appropriate and, therefore, likely to be accepted by everyone.

[1] The CONVENTION FOR THE PROTECTION OF HUMAN RIGHTS AND DIGNITY OF THE HUMAN BEING WITH REGARD TO THE APPLICATION OF BIOLOGY AND MEDICINE (Council of Europe) was adopted on April 4, 1997, and entered into force internationally on December 1, 1999. The purpose of this Convention, as set out in Article 1, is to "protect the dignity and identity of all human beings and guarantee everyone, without discrimination, respect for their integrity and other rights and fundamental freedoms with regard to the application of biology and medicine." See https://www.coe.int/en/web/conventions/full-list/-/conventions/rms/090000168007cf98. Portugal ratified this Convention on January 3, 2001 (Assembly of the Republic Resolution No. 1/2001, dated January 3). The official Portuguese translation is available at: https://dre.pt/application/conteudo/235128

The results of research that has not complied with internationally sanctioned scientific, ethical and legal criteria cannot be implemented, used and consequently adopted by other researchers as valid. And if it has any commercial value, it still cannot be produced, applied and sometimes sold for lack of recognition.

This does not mean that there is no room for the adoption of measures that are adapted to local circumstances, wherever they are justified given certain national particularities and sensitivities. However, the adoption of such measures can never conflict with previously established basic principles. Based on consensually adopted international documents, which have been generally approved and accepted by citizens and states, we can define a set of basic principles that any ethical clinical research needs to follow:

1. The social and scientific value of research, given that research resources are finite and costly and need to be used responsibly.

2. The scientific validity of research, which must be rigorous and scrupulous.

3. The correct selection of test subjects, as they have to be recruited based on the goals of the study (and not on any privilege or economic advantage) and their exclusion can only happen for technical or scientific reasons (not because of their gender, sex or social class).

4. A favorable risk-benefit ratio, as there must be a balance between the risks (that need to be minimal) and the benefits (that need to be maximized) with a fair distribution of benefits.

5. An independent review of the research protocol by external and multidisciplinary experts that have binding authority over the research project in question.

6. The guarantee of informed consent.

7. Respect for test subjects.[2]

Therefore, a research project must have both scientific and social value for it to be ethically acceptable and thus permitted. First published in 1982[3] by the CIOMS (Council for International Organizations of Medical Sciences) in collaboration with the

[2] See António Vaz Carneiro, *Investigação Clínica em seres humanos – principais questões éticas*, em "Investigação Biomédica, Reflexões éticas, ed. Conselho Nacional de Ética para as Ciências da Vida, Gradiva, 2008, pp. 22 and 27-29.

[3] The latest version dates from 2016. Available at https://cioms.ch/wp-content/uploads/2017/01/WEB-CIOMS-EthicalGuidelines.pdf

WHO, the International Ethical Guidelines for Health-related Research Involving Humans provides a good summary:[4]

The ethical justification for undertaking health-related research involving humans is its scientific and social value: the prospect of generating the knowledge and the means necessary to protect and promote people's health. Patients, health professionals, researchers, policy-makers, public health officials, pharmaceutical companies and others rely on the results of research for activities and decisions that impact individual and public health, welfare, and the use of limited resources. Therefore, researchers, sponsors, research ethics committees, and health authorities, must ensure that proposed studies are scientifically sound, build on an adequate prior knowledge base, and are likely to generate valuable information.

Although scientific and social value are the fundamental justification for undertaking research, researchers, sponsors, research ethics committees and health authorities have a moral obligation to ensure that all research is carried out in ways that uphold human rights, and respect, protect, and are fair to study participants and the communities in which the research is conducted. Scientific and social value cannot legitimate subjecting study participants or host communities to mistreatment, or injustice.

2. The need for proper regulation

The need to establish legal norms to regulate research involving human beings is not a contemporary concern and dates back precisely to an extreme time — the post-World War II era, when the Nuremberg Code and its ten research principles were introduced in 1947. Subsequently, the World Medical Association led an initiative to create more foundational research norms that resulted in the so-called Declaration of Helsinki (1964), which is periodically reviewed. What would become a universal norm was made very clear:

The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol. This protocol should be submitted for consideration, comment, guidance, and where appropriate, approval to

[4] Guideline 1.

a specially appointed ethical review committee, which must be independent of the investigator, the sponsor or any other kind of undue influence.

These aspects would be reinforced by the International Ethical Guidelines for Health-related Research Involving Humans (CIOMS) and by the various international documents, conventions and declarations that have outlined and established a set of rules that govern research and cover both clinical trials and other biomedical research. Inspired by these international documents, the various countries would adopt and integrate these guidelines into their national legislation and standardize ethical standards in research, always aiming to find a good balance between the requirements of research and the protection of people.

This normative effort is not static but rather dynamic, and it tends to follow the evolution of science and research with all its particularities, requiring constant reassessments and updates. Today, the legislator's view needs to be broader and include, for example, not only the participation of patients but also of those who are healthy, regardless if they are adults or children, as well as other categories of people considered vulnerable. Besides having strict criteria for the selection of the participants of any research project, we also need to clearly define the financial aspects, the risks and the adverse effects, just to name a few of the items.

Such questions go beyond the traditional doctor-patient relationship and deal not only with medical issues but also with social, economic and institutional matters. This range of questions necessarily requires a diversity of sensitivities that go far beyond medical and biomedical skills and that involve the collaboration of other fields of knowledge. Additionally, "researchers themselves cannot be the sole arbiters of the moral lawfulness of the experiments they plan to conduct."[5] Research can and should contribute to the knowledge of human beings and to the improvement of their health and living conditions. However, the purpose of research cannot in itself justify practices that may at times either undermine human dignity or favor certain interests of society or of some groups.

We should note that all relevant international documents, from the oldest to the most recent ones, contain a common basic principle: it is paramount to protect the

[5] Walter Osswald, "Comissões de Ética: uma reflexão sobre a sua justificação", *in Comissões de Ética: das bases teóricas à actividade quotidiana,* coord. Maria do Céu Patrão Neves, Gráfica de Coimbra, 2002, p. 125.

dignity, rights, welfare and safety of the participants in any given research project. And if research aims to produce reliable results, they can only be valid and accepted if the assumptions of the basic principle are met. To this end, we need to ensure that these principles are followed and simultaneously support robust and quality scientific research.

One of the fundamental pillars for the consolidation of health policies, namely health research, is precisely the need to promote skills that strengthen health research systems. On the one hand, we need to set research priorities and, on the other hand, to develop a conducive environment for research by creating norms and standards that regulate best practices. Finally, we must ensure that high-quality evidence is transformed into accessible health technologies and evidence-based policies.[6]

While it is true that there are a number of ethical and legal principles common to all scientific research involving humans, it is also true that these areas raise specific questions that call for specific answers. Additionally, in developing countries, there are some very significant ethical issues that require us to look even more closely whenever we talk about the respect for human dignity and the protection of human beings in the context of research. Let us think, for example, about the limits and meaning of informed consent (especially about the freedom to consent, to refuse and to abandon a research project); the possible consequences of the socioeconomic and health vulnerability of certain populations; the possible exploitation of the most disadvantaged during research; the competence and ability of ethics committees and local and national health authorities to ethically evaluate a given research project; the real objectives of research in developing countries and populations; the available treatment patterns before, during and after research; the correct use of placebos.[7]

In short, we can condense the different international reference texts[8] that deal with biomedical research into the following basic principles:

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[6] See WHO, Health topics, research, at https://www.who.int./topics/research/en/

[7] See Miguel Oliveira da Silva, "Populações em Desenvolvimento", in *Investigação Clínica em seres humanos – principais questões éticas,* em "Investigação Biomédica, Reflexões éticas, ed. Conselho Nacional de Ética para as Ciências da Vida, Gradiva, 2008, p. 117.

[8] We consulted the Declaration of Helsinki (WHO – World Health Organization) in its various versions, the last of which dates from October 2013; the Convention on Human Rights and Biomedicine (Council of Europe, 1997); the Additional Protocol to the Convention on Human Rights and Biomedicine (Council of Europe, 2005); the Universal Declaration on Bioethics and Human Rights (UNESCO, 2005).

1. **Primacy of the human being** (the interests and welfare of research participants must prevail over the sole interest of society or science).

2. **Lack of alternatives** (research can only be conducted if there are no alternatives of comparable effectiveness).

3. **Proportionality between benefits and risks** (research should neither involve risks nor harm humans disproportionately to its potential benefits).

4. **Scientific quality** (any research must be scientifically justified, must take into account generally accepted scientific quality criteria and must be conducted in accordance with applicable professional standards and obligations).

5. **Approval by an independent ethics committee** (the acceptability of any project must be examined by an independent ethics committee).

6. **Log of research projects and publication and dissemination of results** (each project must be logged in an accessible database and researchers must disclose all research results, including negative ones).

Therefore, as a way of protecting the dignity of participating human beings and their interests and well-being, researchers always need to adhere to the following minimum standards:

1. **Informed consent** (participants in a research project must give their voluntary, express, specific and informed consent to participate).

2. **Special protection of vulnerable people that cannot consent** (we must take into consideration situations in which participants are unable to consent to participate in a research project due to their age, physical condition or vulnerability).

3. **Adequate information prior to consent** (information must be provided in an appropriate and understandable manner before participants consent);

4. **Minimal risks and burden** (there must be a solid assessment of the risks and benefits of the research project to ensure that it involves a minimal risk and burden for the participant).

5. **Confidentiality** (the information collected during and for the research project must be treated as confidential).

3. The role and legitimacy of research ethics committees and their relevance in assessing research projects

In life sciences, ethics committees[9] are different from the regulatory ethics entities of a given profession since they are neither field-specific, nor self-regulatory, nor exclusively include members of a single profession. They have been created through a comprehensive process that institutionalized bioethics and can take different forms[10] depending on their jurisdiction. At the national level, there are ethics councils, health ethics committees, hospital ethics committees and clinical research ethics committees. Internationally, there are entities such as the Committee on Bioethics or the Steering Committee on Bioethics (CDBI) of the Council of Europe, the European Commission's Group on Ethics in Science and New Technologies,[11] the UNESCO International Bioethics Committee (IBC), the UNESCO Intergovernmental Committee on Bioethics (IGBC) and the UNESCO World Commission on the Ethics of Scientific Knowledge and Technology (COMEST),[12] among others.

Moreover, these international institutions recommend (often in a binding fashion) the establishment of research ethics committees, setting out their guidelines and the principles that should govern them. This is the case of UNESCO and of its Universal Declaration on Bioethics and Human Rights,[13] which includes a chapter titled "Application of the principles," whose Article 19 on "Ethics committees" states:

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[9] For simplicity's sake, we have adopted here the designation "ethics committees" to designate bodies with the same role that may also be called ethics commissions or ethics councils.

[10] See Maria do Céu Patrão Neves, *Investigação Clínica em seres humanos – principais questões éticas,* em "Investigação Biomédica, Reflexões éticas, ed. Conselho Nacional de Ética para as Ciências da Vida, Gradiva, 2008, p. 390

[11] See https://ec.europa.eu/info/research-and-innovation/strategy/support-policy-making/scientific-support-eu-policies/european-group-ethics-science-and-new-technologies-ege_en

[12] See https://en.unesco.org/partnerships/partnering/bioethics and http://www.unesco.org/new/en/social-and-human-sciences/themes/bioethics/

[13] Universal Declaration on Bioethics and Human Rights, adopted by acclamation by the General Conference of UNESCO in October 2005. It has become a worldwide reference document and addresses the ethical issues raised by medicine, life sciences and associated technologies applied to human beings, taking into account their social, legal and environmental dimensions. It lists the basic worldwide principles and binds member states to respect and apply these fundamental principles. See https://unesdoc.unesco.org/ark:/48223/pf0000146180

Independent, multidisciplinary and pluralist ethics committees should be established, promoted and supported at the appropriate level in order to:

(a) assess the relevant ethical, legal, scientific and social issues related to research projects involving human beings;

(b) provide advice on ethical problems in clinical settings;

(c) assess scientific and technological developments, formulate recommendations and contribute to the preparation of guidelines on issues within the scope of this Declaration;

(d) foster debate, education and public awareness of, and engagement in, bioethics.

Similarly, in the same year (2005), the Council of Europe approved virtually the same requirement in the Additional Protocol to the Convention on Human Rights and Biomedicine, concerning Biomedical Research, which calls for the submission of research projects to independent ethics committees:[14]

Article 9 – Independent examination by an ethics committee

1 Every research project shall be submitted for independent examination of its ethical acceptability to an ethics committee. Such projects shall be submitted to independent examination in each State in which any research activity is to take place.

2 The purpose of the multidisciplinary examination of the ethical acceptability of the research project shall be to protect the dignity, rights, safety and well-being of research participants. The assessment of the ethical acceptability shall draw on an appropriate range of expertise and experience adequately reflecting professional and lay views.

[14] See https://www.coe.int/en/web/conventions/full-list/-/conventions/rms/090000168008371a or the Portuguese version included in Resolution of the Assembly of the Republic No. 29/2017, dated February 20, available at https://dre.pt/application/conteudo/106476971

3 The ethics committee shall produce an opinion containing reasons for its conclusion.

Article 10 – Independence of the ethics committee

1 Parties to this Protocol shall take measures to assure the independence of the ethics committee. That body shall not be subject to undue external influences.

2 Members of the ethics committee shall declare all circumstances that might lead to a conflict of interest. Should such conflicts arise, those involved shall not participate in that review.

Article 11 – Information for the ethics committee

1 All information which is necessary for the ethical assessment of the research project shall be given in written form to the ethics committee. …

Article 12 – Undue influence
The ethics committee must be satisfied that no undue influence, including that of a financial nature, will be exerted on persons to participate in research. In this respect, particular attention must be given to vulnerable or dependent persons.

The primary role played by any research ethics committee set up for the purpose of reviewing projects involving human beings is the ethical assessment of such projects and the assurance of adequate protection for participants. These committees are by nature multidisciplinary, independent and advisory bodies as is the case with any other ethics committee in the realm of life sciences. However, as far as research ethics committees are concerned, this advisory nature has become, in many cases, binding thanks to a number of legal provisions laid out in the legislation that regulates clinical trials and biomedical research. This binding nature requires an even more responsible and rigorous action on the part of ethics committee, dictating a uniform application of the criteria underlying the assessment. Moreover, researchers can be made to comply with the protective principles of the human being and can equally be monitored and

punished for non-compliance or disobedience. These committees guarantee, therefore, compliance and the uniform application of justice.

These ethics committees for clinical (or biomedical) research consequently play two roles. On the one hand, their function is exclusively ethical, in the sense of safeguarding ethical standards in life sciences, protecting and guaranteeing human dignity and integrity and providing adequate reflection on health-related ethical problems. On the other hand, they play a more technical role dictated by ethical and legal constrains, as they apply pre-established norms usually stipulated in specific research-related legislation, which predetermines the requirements that must govern the assessment carried out by any ethics committee.

By law, these requirements have to be applied uniformly and it is up to the ethics committee to verify if a particular research project, clinical trial protocol or any other study whose approval by an ethics committee is legally required meets the pre-established criteria. This procedure aims to ensure that all submitted projects are analyzed and evaluated by the same standard and that the same criteria and requirements are objectively applied to all of them.

Despite the technical nature of assessing research projects, the fact remains that the members of an ethics committee do not simply fill out a checklist to verify the compliance with each item. Assessing compliance with all the criteria requires each member of an ethics committee to do a real exercise of ethical reflection because, in practice, the simple analysis of a document detailing the consent of participants and the information they were provided or checking the protection of the confidentiality of their data, just to give just two examples, are often overwhelmingly complex tasks. Every project is unique and includes human beings from many backgrounds, often vulnerable, poorly informed (or poorly informed about science) and without any experience as participants in clinical trials or research.

As a result, ethics committees appear to be "absolutely necessary as a process of external regulation of scientific research, which is the only way to guarantee that science remains at the service of humanity. For ethics committees to attain this goal, their internal competence and external independence must be maximized."[15] As with everything else, there is no magic formula, no single model, no perfect example. And

[15] Maria do Céu Patrão Neves, *Op. cit.*, p. 414.

honestly, this is not the point. Rather, ethics committees should base their action on international principles that are recognized by all and that were debated and approved by representative and reputable international entities. These principles should serve as the foundation of national legislation on the subject and for the creation of entities that, though not identical, should be based on a common goal — the protection and defense of human dignity — and share the same assumptions and apply the same principles in practice.

Having the need to set up research ethics committees at the national level as a starting point, we have to define the most appropriate format of these committees, how to appoint their members, their roles and their objectives. The more their format suits the reality of a given country, the more likely their work will be viewed as worthy, respectable, credible, useful and effective. The following passage by Walter Osswald[16] lays out the characteristics that should guide the work of an ethics committee:

"Besides its independence, which is a basic condition for its credibility and usefulness, the main characteristics of a CES[17] seem to lie in its unbiased reflection and in staying within their area of expertise, making an honest effort to build consensus, respecting people (regardless if they are clinical trial subjects, researchers or other stakeholders in the process) and having at least reasonable knowledge of the fundamental principles of bioethics and confidentiality. …

The independence of a CES is crucial; it cannot be influenced, serve interests or obey orders but it must also be immune to much more subtle forms of coercion. If the dignity and self-respect of its members are the best guarantee of maintaining such independence, then the presence of members that are neither contractually bound nor dependent on the institution will obviously constitute an additional assurance of this indispensable independence.

A CES will also have to stay within its area of expertise, not invading that of others, including the scientific, administrative, supportive or disciplinary areas. It should, therefore, neither issue an opinion on the scientific and professional

[16] Walter Osswald, "Comissões de Ética: uma reflexão sobre a sua justificação", *in Comissões de Ética: das bases teóricas à actividade quotidiana,* coord. Maria do Céu Patrão Neves, Gráfica de Coimbra, 2002, pp. 127-128. This passage is quoted with the express permission of the author.

[17] Portuguese acronym for Health Ethics Committee. Despite their more general purpose, the base model of these committees can also be used in the present case for research ethics committees.

qualifications of any member of its own institution nor settle disputes or select candidates, although ... it needs to evaluate the scientific qualifications of researchers proposing an experimental protocol or clinical trial to ensure the proper execution of said protocol or trial. … When discussing any matter … it should engage in free and unbiased reflection … always rational and substantiated, and it may build consensus … Besides being produced in written form and properly reasoned, its reports must be completed in a timely manner."

In short, after analyzing the different international documents, as well as a number of research ethics committees of the world, we can highlight the essential requirements of an ethics committee:

1. **Independent:** members must be independent both from the institution that appointed them and from the researchers and companies seeking the assessment of a research protocol.

2. **Multidisciplinary:** members must be from various fields of knowledge, not limited to the medical and scientific areas.

3. **Plural:** the expression of diverse ideas and values must be favored.

For this reason, at least the following should be taken into consideration when it comes to biomedical research:

1. Reference to a glossary or, for legal purposes, definition of the meaning of (for example and not exhaustively) clinical trial or any other type of research (and/or clinical study), including the various types of studies; best clinical practices; participant; researcher; promoter and other parties involved in a clinical trial or in any other study; informed consent; adverse effect; places where research may be conducted, among others.

2. The principle of the primacy of the human being.

3. The principles of best clinical practice.

4. Risk and benefit assessment and definition of the assessment entity.

5. Protective measures for the participants in a clinical trial or in any other study, ensuring the minimum conditions for the protection of participants, namely:

5.1. Voluntary and free participation.

5.2. Appropriate information (including the nature and goals of the study, risks, drawbacks and potential benefits, conditions for completion, expected duration, right to withdraw from the study without any harm).

5.3. Informed consent, expressly and freely provided in written form.

5.4. Right to confidentiality, to privacy and to the protection of personal data.

5.5. Responsibility of the promoter and of the researcher for any harm that the study may cause to participants and for the compensation for such harm.

6. Participation of minors, other people unable to consent and vulnerable people.

7. Exceptional circumstances.

8. Names, skills and duties of those in charge of the clinical trial or of other type of research.

9. Requirements for conducting clinical trials and instructions.

10. Requirements for conducting other clinical studies, including medical devices and cosmetic products when applicable.

11. Types and features of financial contracts (between the promoter and the center where the study is conducted).

12. Terms and conditions for the suspension and cancelation of the clinical trial.

13. Procedure for notifying adverse effects.

14. Logging of clinical trials and other studies.

15. Process for disseminating trials and other studies.

16. Supervision and control of best practices and requirements for their implementation.

17. Mandatory and binding ethical assessment by an independent entity.

As we stated in the descriptive part of this study, we should pay special attention to the local characteristics and sensitivities when we draft legislation, taking into account the customs, practices and type of relationship between the parties, among others. All of this must be considered whenever it does not collide with the aforementioned ethical and legal principles.

In this regard, when establishing a National Research Ethics Committee, we should also:

1. Define its jurisdiction in view of the necessary research requirements included in the law to be drafted.
2. In this respect, the committee must decide on:[18]

   2.1. The relevance of a given clinical research project and of its framework.

   2.2. The assessment of predictable benefits and risks.

   2.3. The procedure for obtaining informed consent.

   2.4. The minimum conditions for the protection of participants.

   2.5. The protocol, including the plans to disseminate the study's findings.

   2.6. The qualifications of the lead researcher and the rest of the team members.

   2.7. The material and human conditions necessary to conduct clinical research.

   2.8. The amounts and procedures for paying researchers and compensation,[19] as well as the relevant items of the financial contract to be signed between the promoter and the center where the research will be conducted.

   2.9. The procedures for recruiting participants.

   2.10. The cases of conflict of interest of the promoter or researcher involved in the study.

   2.11. The timeframe and conditions for the clinical follow-up of the participants after the conclusion of the clinical study.

   And if applicable:

   2.12. The researcher's brochure.

   2.13. The quality of the facilities.

   2.14. The provisions stipulating the compensation for property and non-property damage, including death, attributable to the study and how such compensation will be funded.

   2.15. The rationale for carrying out the research in the case of the participation of minors, of adults unable to consent or of other vulnerable individuals.

[18] We follow closely the Portuguese legislation on clinical trials and ethics commissions as we deem it to be adequate.

[19] When we talk about "compensating participants," we are referring to the reimbursement of the expenses that they incurred to participate in a given research project (e.g. transportation costs) and the reimbursement of any losses they suffered with their participation in the project.

The Ethics Committee should equally:

3. Monitor research studies, whenever possible, especially with regard to the minimum requirements for the protection of participants and to other ethical aspects of research.

4. Criteria used to prepare this legal study

With the help of the representative of each country, we surveyed the relevant national legislation in force on biomedical research in general, on studies and clinical trials in particular and also on the general ethical principles applicable to these matters. We also checked the possible application of international guidelines or other recommendations even if they were not binding.

Above all, we wanted to become familiar with the legislation of each country in the areas that this project focuses on and with the existence of adequate guidelines. In their absence, we wanted to understand if the general legislation contemplates some of the underlying ethical principles of research. We have identified the relevant concrete provisions on clinical trials involving medicines and on other biomedical research.

In our survey, we have also paid particular attention to any legislation that determines the existence of ethics committees (or identical entities that have different names). We have checked the minimum requirements when it comes not only to their jurisdiction and operation but also to their ethical assessment of clinical trial protocols and/or other research. As far as it was possible to determine, we have also verified the current operational level of the existing ethical assessment entities, as well as whether they contemplate, in their regulations and practical work, the minimum requirements that must guide any review process. Additionally, we have identified other relevant ethical principles contemplated in the documentation we analyzed, and we have highlighted them in this study.

5. Layout of the study

We have prepared legislative tables for each country,[20] which were validated by the respective national representatives, and added our comments to each table. We have also listed the most important steps that, in our view, each country should consider when drafting legislation in this area to fill the gaps, to implement the existing legislation and to apply the international norms and guidelines in force. We have also considered the need to adapt all of this to the different national circumstances without, of course, hampering the meaning and scope of these principles.

6. The study

After a survey and a detailed analysis of the information available, we were able to conclude that, in general terms, all the countries that are part of this project undoubtedly have something in common: a serious interest in supporting health research. Additionally, there is also an unequivocal will to establish ethical entities able to assess clinical trials.

Regarding the legal framework of biomedical research, this study draws a multifaceted picture, ranging from countries without a legal framework (or with draft legislation not yet passed) to countries with a legal framework that already includes rules for conducting clinical trials / research and that stipulates the need for specific regulations and entities to validate and monitor all research. In some cases, the legislation even identifies these validation and monitoring entities, but the law is neither regulated nor implemented.

Due to the lack of regulation, some countries apply international guidelines, largely from the WHO. In other countries, we were able to find draft legislation on biomedical research, but it has not yet been discussed and passed by the corresponding parliamentary bodies. In most cases, we found a number of provisions in separate legislation that incorporate fundamental ethical and legal principles in biomedical research, such as the principles of human dignity and integrity and of the primacy of the human being.

Likewise, when we searched for the existence of ethical assessment entities (health ethics committees, ethical research committees, national ethics councils or equivalent entities with jurisdiction over the field of biomedical research), we found out that some countries do not have research ethics committees or any other ethical

[20] The legislative tables prepared for each country are included as an appendix to this study.

assessment framework (they coincide with countries without specific research regulations). However, there are also countries with functioning ethics committees, but due to the lack of regulation, they do not assess clinical trials / research or they do it informally without a regulatory basis.

All of the aforementioned situations allow us to conclude that, in general, there is an urgent need both to legislate from scratch and to implement existing standards, given the lack of adequate legislation or the absence of regulation. There is also a need to consolidate the entities with specific jurisdiction over the ethical assessment, so that they can carry out this assessment effectively and in an appropriate manner.

Therefore, to properly comply with international best practices, each country ideally needs to pass robust and adequate legislation on biomedical research, which simultaneously contemplates the creation of ethics committees (for health with dual jurisdiction or only for research with their own operating rules and authority) that are independent, multidisciplinary and with binding authority in the field of clinical research.

Consequently, in particular, we recommend:

1. Legislation on clinical research in the countries where there is no such legislation in force and that equally stipulates the creation of research ethics committees.

2. Solid regulation of clinical research (with the identification of assessment and inspection entities) in countries where legislation already exists but where it has not yet been regulated. In the regulation of such laws, the assessment requirements of research protocols must be well defined.

3. Effective and adequate implementation of the legislation and of its regulation, as soon as they enter into force.

We are convinced that it is possible to take the three steps we have outlined, but it is not an easy path, given the complexity of this issue and the need to address the priorities that have already been set in other equally pressing areas. However, we believe it is possible to adapt the legislation to local circumstances without deviating from the ethical and legal principles that should guide clinical research. Once taken, these steps will represent a powerful and necessary contribution to an approach to

research that respects the fundamental ethical principles, protects human beings and promotes scientific knowledge that is effectively aligned with international best practices.

7. Conclusion

Nowadays, no one denies the importance of research when it comes to the benefits it provides to human beings, to the different populations and to a given country in general. Health, quality of life and consequently the economy can benefit enormously from the progress of science, medicine and consequently research. The results of research that did not comply with internationally accepted scientific, ethical and legal criteria cannot be implemented, used and thus adopted by other researchers as valid. And if it has any commercial value, it cannot be produced, applied and often traded given the lack of recognition.

References

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- Standards and Operational Guidance for Ethics Review of Health Related Research with Human Participants, WHO, 2011

Legal instruments cited and recommended

(In chronological order)

- Declaration of Helsinki (WHO – World Health Organization) in its various versions (latest: October 2013)

- Convention on Human Rights and Biomedicine, Council of Europe, 1997, https://dre.pt/application/conteudo/235128 and in the other official languages at https://www.coe.int/en/web/conventions/full-list/-conventions/rms/090000168007cf98
- Additional Protocol to the Convention on Human Rights and Biomedicine, concerning Biomedical Research, Council of Europe, 2005, https://dre.pt/application/conteudo/106476971
- Universal Declaration on Bioethics and Human Rights, UNESCO, 2005, https://unesdoc.unesco.org/ark:/48223/pf0000146180_por
- International Ethical Guidelines for Health-related Research Involving Humans, Council for International Organizations of Medical Sciences (CIOMS) in collaboration with WHO, latest revision in 2016: https://cioms.ch/wp-content/uploads/2017/01/WEB-CIOMS-EthicalGuidelines.pdf
- Regulation (EU) No. 536/2014 of the European Parliament and of the Council of 16 April 2014 on clinical trials on medicinal products for human use https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-1/reg_2014_536/reg_2014_536_en.pdf
- Law No. 21/2014, dated April 16 (clinical research) https://dre.pt/application/conteudo/25344024 and Law No. 73/2015 dated July 27 (1st amendment) https://dre.pt/application/conteudo/69879383
- Decree-Law No. 80/2018, dated October 15 (Health Ethics Committees) https://dre.pt/application/conteudo/116673880

Sources (International Organizations)

World Medical Association (WMA)

Council for International Organizations of Medical Sciences (CIOMS)

European Commission (EC - EU)

Council of Europe (CE)

World Health Organization (WHO)

United Nations Educational, Scientific and Cultural Organization (UNESCO)

Glossary

CES – Comissão de Ética para a Saúde (Health Ethics Committee)

WHO – World Health Organization

CIOMS – Council for International Organizations of Medical Sciences

UNESCO – United Nations Educational, Scientific and Cultural Organization

Appendix

Legal framework of each country

ANGOLA

Applicable Legislation

Legislation	Name	Specific provision	Clinical trials on medicines	Other research
Law No. 21-B/92, dated August 28	Basic Law of the National Health System	Article 16 (Research) (1)[21] and (2)	Article 21 (Clinical Trials on Medicines)[22], [23]	_
Presidential Decree No. 180/10, dated August 18	General Basic Law of the National Pharmaceutical Policy	Article 16 (Samples of Medicines) (2)[24]	_	_

Independent validation and oversight[25]

Legislation/ Soft Law	Name	Specific provision	Clinical trials on medicines	Other research	Binding

Checklist of essential items already stipulated in existing legislation or in internal regulations:

[21] Law No. 21-B/92, dated August 28, Article 16 (1): "Support health research that is deemed beneficial and encourage collaboration in this field between the services of the Ministry of Health, the Agostinho Neto University and other public or private entities." Article 16 (2): "To be supported, all research activities must always comply with the principle that human life is the ultimate value and that it must be promoted and safeguarded in all circumstances."

[22] Law No. 21-B/92, dated August 28, Article 21: "Clinical trials on medicines are always conducted under medical supervision and responsibility, according to the rules to be defined by the Minister of Health in specific legislation."

[23] The law this provision refers to has yet to be passed.

[24] Presidential Decree No. 180/10, dated August 18, Article 16 (2): "For products intended for clinical trials, researchers must submit: (a) Statements confirming that the studies were previously authorized by the competent authority of the Ministry of Health; (b) Documents with complete and up-to-date scientific information on the pharmacological and toxicological results of any other research already conducted on animals, humans or human cell cultures; (c) Protocol of the proposed study, list of the centers involved and researchers in charge."

[25] Ethics Committee, Commission or Council or equivalent entity.

Primacy of the human being/ Dignity	Scientific approval	Ethical approval	Informed consent	Consent of people who cannot consent	Data confidentiality	Conflict of interests	Weighting risks / benefits	Safety and oversight
√[26]	√[27]	–	–	–	–	–	–	–

CAPE VERDE

Applicable Legislation

Legislation	Name	Specific provision	Clinical trials on medicines	Other research
Law No. 41/IV/2004, dated April 5[28]	Basic Law of the National Health System (LBSNS)	Article 22 (Research)[29]	Yes	Yes
Regulatory Decree No. 23/2014, dated June 10	Articles of Association of the National Institute of Public Health	Article 5 (1): "The functions of the INSP in the field of health research are: … (h) develop clinical research in collaboration with the units providing assistance services."	Yes	Yes[30]
Resolution No. 5/2008, dated February 18	National Health Policy (2007)[31]	VIII.8 Strategies for health research[32]	Yes	Yes

[26] Law No. 21-B/92, dated August 28, Article 16 (2): "To be supported, all research activities must always comply with the principle that human life is the ultimate value and that it must be promoted and safeguarded in all circumstances."

[27] Presidential Decree No. 180/10, dated August 18, Article 16 (2).

[28] This law is under review.

[29] The definition of the rules for conducting clinical trials is referred to specific legislation (Article 22 (3)): *Clinical trials are always conducted under medical supervision and responsibility, according to the rules to be defined in specific legislation.* It is not regulated.

[30] Regulatory Decree No. 43/2014, dated June 10, Article 5 (3) (b): the functions of the INSP include *acting as a central laboratory that coordinates any peripheral centers conducting any biomedical, epidemiological and clinical research and clinical trials on communicable and non-communicable diseases.*

[31] Prepared by the Minister of State and Health with technical assistance from the WHO, it was passed in 2007 and published in 2008.

[32] VIII.8: The strategy points to the need of developing institutional mechanisms to support and promote research in the country, prioritizing the coordination, the compliance with ethical standards and the connection between existing services in order to:

Independent validation and oversight

Legislation	Name	Specific provision	Clinical trials on medicines	Other research	Binding
Resolution No. 5/2008, dated February 18[33]	National Health Research Ethics Commission [34]	VIII.8 (5)	_	_	_
DL 26/2007, dated July 30	National Health Research Ethics Committee (CNEPS)	Entire law	All health research	All health research	Yes
Regulatory Decree No. 43/2014, dated June 10	National Institute of Public Health, as the national coordinating agency for health research in the country	Article 5 (1) (a)	Yes	Yes	_

Checklist of essential items already stipulated in existing legislation or in internal regulations:

1. Encourage healthcare professionals to develop a systematic research attitude as a means of updating their knowledge and improving their individual skills.

2. Promote research on health systems at all levels as an instrument for improving the management of health services and the relations with related sectors.

3. Create conditions for the development and support of biomedical research as a way to boost the skills of researchers, to increase the knowledge about the situations that affect the populations and to adjust the interventions of professionals and of the system to those situations.

4. Cooperate with national higher education institutions and with regional and global research centers to ensure technical and procedural support for any research activities.

5. Provide the country with a health research ethics committee.

[33] Prepared by the Minister of State and Health with technical assistance from the WHO, it was passed in 2007 and published in 2008.

[34] VIII.8 (5) determines the creation of a national health research ethics commission.

Primacy of the human being / Dignity	Scientific approval	Ethical approval	Conflict of interests	Informed consent	Approval of people who cannot consent	Data confidentiality	Weighting risks / benefits	Safety and oversight
✓[35]	-	✓[36]	-	✓[37]	-	-	-	✓[38]

Others:
Voluntary

GUINEA-BISSAU

Applicable Legislation[39]

Legislation	Name of the law	Specific provision	Clinical trials on medicines	Other research
–	National Regulatory Authority for Medicines and Health Products (ARFAME, I.P.)[40]	Article 4 (2) (c) and (d)[41]	√	–

Independent validation and oversight[42]

Legislation	Name	Specific provision	Clinical trials on medicines	Other research	Binding
–	–	–	–	–	–

[35] DL 26/2007, dated July 30, Articles 1 and 6 (a): *safeguard the dignity, rights, safety and well-being of all potential participants; CNEPS Rules of Procedure, Article 2 (a).*

[36] DL 26/2007, dated July 30, Article 6 (b); *CNEPS Rules of Procedure, Article 2 (b).*

[37] DL 26/2007, dated July 30, Article 9 (1) (b); *CNEPS Rules of Procedure, Article 10 (1) (b).*

[38] DL 26/2007, dated July 30, Article (6) (c); *CNEPS Rules of Procedure, Article 2 (d) and Article 12*. Base on the information provided by the source, there is no oversight.

[39] Draft legislation. It is not in force and needs to be passed.

[40] Draft legislation. It is not in force and needs to be passed.

[41] Article 4 (2): "The functions of the ARFAME, I.P. include … (c) Ensuring the regulation and supervision of research, production, distribution, marketing and use of medicines for human use and health products, including medical devices and cosmetic and body care products; (d) Ensuring compliance with the rules applicable to the authorization of clinical trials involving medicines, as well as the monitoring of compliance with best clinical practices while conducting them."

[42] Ethics Committee, Commission or Council or equivalent entity.

Checklist of essential items already stipulated in existing legislation or in internal regulations:[43]

Primacy of the human being/ Dignity	Scientific approval	Ethical approval	Informed consent	Consent of people who cannot consent	Data confidentiality	Conflict of interests	Weighting risks / benefits	Safety and oversight
–	–	–	–	–	–	–	–	–

MOZAMBIQUE

Applicable Legislation

Legislation	Name of the law	Specific provision	Clinical trials on medicines	Other research
Law No. 12/2017, dated September 8	Law on medicines, vaccines and other biological products for human use	Articles 39-44 (clinical trials — to be regulated)[44]	Yes	–
Resolution No. 4/2017, dated May 26	Organic Statute of the Ministry of Health	Article 10 (1) (f)[45]	–	–

Independent validation and oversight[46]

Legislation	Name	Specific provision	Clinical trials on medicines	Other research	Binding
Law No. 12/2017, dated September 8	Law on medicines, vaccines and other biological products for human use	Articles 42 and 43: Inspection of clinical trial establishments to verify compliance with best clinical practices[47] (Article 42 (1)); in case of non-compliance, the tests can be temporarily suspended or permanently canceled	Yes	–	–

[43] Given the lack of laws and regulation and of formal approval of existing entities, we cannot check if they meet the minimum essential requirements that should guide clinical research.

[44] Regulation dependent upon the Council of Ministers.

[45] Article 10 (1): "The functions of the National Pharmacy Directorate include … (f) Propose rules for the activities of production, import, export, distribution, storage, transport, marketing, prescription, dispensing, research and use of medicines, vaccines and other biological products for human use."

[46] Ethics Committee, Commission or Council or equivalent entity.

[47] Not yet regulated.

		(Article 42 (2)); send partial and final reports and report adverse effects to healthcare authorities (Article 43).			
Internal document	National Bioethics Committee for Health	_	Yes	Yes	Yes (for clinical trials only)

Checklist of essential items already stipulated in existing legislation or in internal regulations:[53]

Primacy of the human being	**Scientific approval**	**Ethical approval**	**Conflict of interests**	**Informed consent**	**Approval of people who cannot consent / vulnerable people**	**Data confidentiality**	**Weighting risks / benefits**	**Safety and oversight**
-	**-**	**✓[48]**	**✓[49]**	**✓[50]**	**-**	**✓[51]**	**✓[52]**	**-**

Others:
Project description ✓[54]
Voluntary ✓[55]
Dissemination of findings
Adverse effects: mandatory report to healthcare authorities. (Law No. 12/2017, dated September 8, Article 43)

[48] The authorization must include a binding opinion from the National Bioethics Commission for Health (Law No. 12/2017, dated September 8, Article 39 (2)).

[49] National Health Bioethics Committee Document.

[50] National Health Bioethics Committee Document.

[51] National Health Bioethics Committee Document.

[52] National Health Bioethics Committee Document.

[53] Principles dependent on the regulation of "Clinical Best Practices."

[54] National Health Bioethics Committee Document.

[55] National Health Bioethics Committee Document.

SAO TOME AND PRINCIPE

Applicable legislation

Legislation	Name	Specific provision	Clinical trials on medicines	Other research
–	–	–	–	–

Independent validation and oversight

Legislation	Name	Specific provision	Clinical trials on medicines	Other research	Binding
–	–	–	–	–	–

Checklist of essential items already stipulated in existing legislation or in internal regulations:

Primacy of the human being/ Dignity	Scientific approval	Ethical approval	Informed consent	Consent of people who cannot consent	Data confidentiality	Conflict of interests	Weighting risks / benefits	Safety and oversight
–	–	–	–	–	–	–	–	–

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