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UPDATE

Ethics, law and the regulation of biomedical research in Chile

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Abstract

This article analyzes the relationship between ethics and law in the regulation of biomedical research in Chile. To this end, a comparative study was carried out on the main international ethical regulations (*Declaration of Helsinki* and *Guidelines* of the Council for International Organizations of Medical Sciences), having as a reference the ethical requirements for assessing biomedical research proposed by Emanuel, Wendler and Grady. The tensions and inconsistencies found between the two regulatory areas are evaluated and commented, especially those in which the Chilean legislation presents legal gaps, deficiencies or is more demanding than the international ethical standard. We make some suggestions for improving the Chilean legal regulation of biomedical research, including strengthening the deliberative role of ethics committees and systematizing the legal framework related to research to achieve a more structured and complete legal body.
Keywords: Biomedical research. Ethics committees, research. Ethics.

Resumen

Ética, derecho y regulación de la investigación biomédica en Chile

El presente trabajo analiza la relación entre ética y derecho en la regulación de la investigación biomédica en Chile. Para ello, se lleva a cabo un estudio comparativo entre el marco legal chileno y las principales normativas éticas internacionales (*Declaración de Helsinki y Pautas* del Consejo de Organizaciones Internacionales de las Ciencias Médicas), teniendo como referente los requisitos para evaluar una investigación biomédica propuestos por Emanuel, Wendler y Grady. Se examinan y comentan tensiones e inconsistencias entre estos ámbitos regulatorios, en particular aquellas donde la legislación chilena tiene vacíos, falencias o es más exigente que el estándar ético internacional. Se concluye con sugerencias para mejorar la regulación jurídica chilena, entre las que se incluyen fortalecer el rol deliberativo de los comités ético-científicos y sistematizar el marco relacionado con investigación con el fin de lograr un cuerpo legal más orgánico y completo.
Palabras clave: Investigación biomédica. Comités de ética en investigación. Ética.

Resumo

Ética, direito e regulamentação da pesquisa biomédica no Chile

Este trabalho analisa a relação entre ética e direito na regulamentação da pesquisa biomédica no Chile. Para isso, realizou-se estudo comparativo entre o marco legal chileno e as principais regulamentações éticas internacionais (*Declaração de Helsinki* e *Diretrizes* do Conselho de Organizações Internacionais de Ciências Médicas), tendo como referência os requisitos éticos propostos por Emanuel, Wendler e Grady para avaliar pesquisas biomédicas. São analisadas e comentadas tensões e inconsistências entre essas áreas regulatórias, particularmente aquelas em que a legislação chilena apresenta lacunas, deficiências ou é mais exigente do que o padrão ético internacional. Concluímos com sugestões para aprimorar a regulamentação legal chilena, incluindo o fortalecimento do papel deliberativo dos comitês de ética em pesquisa e a sistematização do arcabouço normativo relacionado à pesquisa, a fim de alcançar legislação mais estruturada e completa.
Palavras-chave: Pesquisa biomédica. Comitês de ética em pesquisa. Ética.

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The review of biomedical research protocols involving human subjects requires a careful analysis of ethical and legal aspects. Although the two normative dimensions regulate research in a parallel way (some aspects are regulated by law and others by ethics), there is no doubt that they are related. A reasonable harmony and some complementarity is usually expected between the two areas, even though this is an ideal not always fully realized.

This review of protocols (and their appendix) is carried out by research ethics committees, also called *Comités Ético-científicos* (CEC), Ethical-Scientific Committees, and requires the analysis of ethical and legal normative aspects, a task with at least three characteristics that indicate its complexity. First, despite their name, CEC are concerned with reviewing not only the ethical but also the legal aspects of research. Law 20.120/2006 [1] states that the investigation must comply *with all the provisions* (art. 10) and requires that every CEC include a law graduate among its members (art. 17c), which is coherent with the international guidelines on this subject [2].

Secondly, CEC often consult documents that set international standards, such as the *Declaration of Helsinki* [3] and the *International ethical guidelines for research involving human subjects*, of the Council for International Organizations of Medical Sciences (Cioms) [4]. In addition to providing ethical guidelines, these documents are legally relevant as soft law, and can be incorporated into national legal systems as general principles of law [5].

These documents refer to principles of a rational and pre-juridical nature that serve as a basis for any legal system and are applicable to cases of legal gaps or insufficiencies. Moreover, the Chilean legal framework explicitly states that CEC must have as a reference the *Declaration of Helsinki* and the Cioms Guidelines and apply national legislation in a way that is coherent with these international standards [6].

Thirdly, according to Law 20.120/2006 [1], investigation protocols can only be carried out if they have a favorable review and report of a CEC, which can also reject a protocol or stop a research, meaning that its resolutions have binding administrative implications similar to those of legal norms. Thus, the duty to comply with an ethical standard is a fully enforceable obligation independent of the will of the researcher.

It is interesting to compare it with the case of the Ethics Assistance Committees, since article 16 of Law 20.584/2012 [7] establishes that an appeal court may *revoke* recommendations. These considerations allow us to assess the importance of articulating the normative levels of ethics and law when reviewing biomedical research protocols.

From a general perspective, these regulatory planes have a common basis in the dignity of the human being, a notion that, although not free of ambiguity, has certainly influenced bioethics. In the regulation of biomedical research, the respect for the dignity of individuals is reflected on the need for their voluntary, free and informed participation, which is institutionalized in the informed consent required by the *Nüremberg Code* [8] and later by the *Declaration of Helsinki* [3]. It is also present in the principle of respect for people of the *Belmont Report* [9].

From a historical point of view, the regulation of research and the human rights system developed in parallel with the intention of ensuring the protection of individuals against abuse and exploitation, largely motivated by the atrocities committed during the Second World War [10]. However, the ethical concept of human dignity takes precedence over its implementation in legal rules, since this philosophical concept is often invoked as the foundation of the international human rights system [11-13].

This idea is explicitly stated in the *Declaration of Helsinki*: *no national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this Declaration* (paragraph 10) [3]. In other words, ethical regulations provide a minimum standard in circumstances where the law does not exist, is insufficient or simply does not ensure respect for human dignity.

Based on the above, in this article we analyze the relations between ethics and law in the regulation of biomedical research in Chile, discussing possible inconsistencies and tensions between the Chilean legal framework and the main international ethical guidelines. For this purpose, we use the seven criteria for ethical evaluation indicated by Emanuel, Wendler and Grady [14]: social value and scientific validity – which we discuss together for expository purposes –, fair subject selection, favorable risk-benefit ratio, independent review, informed consent and respect for enrolled subjects.

These criteria are used as a guide to review research projects, and are widely accepted by CEC in Latin America. As we shall see, they not only establish requirements for the ethical approval of a

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project, but also show tensions between the ethical and legal planes.

Regarding the Chilean legal framework for scientific research, we refer Law 20.120/2006 [1] (which regulates scientific research with human beings), and other laws related to the topic: Law 19.628/1999 [15] (about the protection of privacy), Law 20.584/2012 [7] (about the rights and duties of patients) and Law 20.850/2015 [16] (about financing for high-cost diseases), as well as their respective regulations and the health code [17].

Regarding international instruments, we focus on documents that set ethical standards of greater prestige and influence in our environment: the *Declaration of Helsinki* (hereinafter *Helsinki*) [3], published by the World Medical Association in 1964, with subsequent updates until 2013; and the *Cioms guidelines* (hereinafter *Cioms*) [4], whose latest version dates from 2016, developed in collaboration with the World Health Organization and aimed at assisting the creation of regulatory policies especially in developing countries.

These instruments have some controversy, particularly the *Helsinki* [18]. However, their influence is undeniable and may successfully articulate widely recognized ethical principles.

Finally, we complement our analysis with documents issued by the Ministerial Commission on Ethics in Health Research (CMEIS), a public body currently responsible for establishing a homogeneous interpretation of the legal framework research regulations in Chile, and also some articles of the specialized literature about the topics discussed.

We hope this study can guide and motivate legislators to formulate initiatives to improve the Chilean regulatory framework for biomedical research, and that it will serve as a guide for researchers, sponsors and reviewers of study protocols, as well as an overview of international ethical regulations, facilitating access to them. This may contribute to the harmonization of regulations and the necessary integration of research ethics systems in order to respond adequately to health problems in America [19].

Ethical analysis of the regulation of biomedical research in Chile

Criteria of social value and scientific validity

The social value of a research refers to the need to ensure that its results produce relevant results for the population, regarding improving their health or well-being in general. The scientific value is the capacity of a study to generate reliable and valid information, which allows reaching the established objectives. It implies a methodological design that is scientifically valid and viable. Both values are the minimum ethical requirements for all biomedical research, since the results are expected to provide innovative and implementable knowledge in clinical practice.

The *Helsinki* [3] (art. 21 and 22) states that all research involving humans must have scientific support and methodology clearly described in the protocol, which must be continuously evaluated by the researcher (art. 6). The need to justify the social value of the research (art. 14) and the fact that it is carried out by a qualified research team is also raised (art. 12) [3].

The *Cioms guidelines* [4] also point out the importance of scientific value, emphasizing the need to not waste the resources used for the study, as well as the fact that social value cannot be used to justify researchers that violate the dignity of subjects (Guideline 1). This value, according to the *Guidelines* [4], should respond to the health needs or priorities of the communities or populations where the research is conducted (Guideline 2). An important aspect is that the results are shared with the scientific community, so that the potential benefits may have an effective and durable impact.

This is explicitly stated in *Helsinki* [3] (art. 36) and *Cioms* [4] Guideline 24, which state that negative or inconclusive results should also be published. The need to pay attention to the local context where research is conducted does not figure prominently in the principles of Emanuel and collaborators [20]; however, the authors incorporated them in subsequent publications, both in the criterion of social value and in an additional criterion of "collaborative partnership." In contrast, it is important to note that the Chilean legal framework does not include this requirement.

The collaborative partnership approach is also reflected on sections of *Cioms*, Guideline 2, which states that the bodies responsible for ensuring the criteria of social value and scientific validity should include the relevant researchers, sponsors, ethics committees and health authorities. In addition, it indicates that the responsibility for determining the social value of a research should consider the opinions of the community involved.

Regarding the Chilean legal framework, we find references to the social value of biomedical

research in Law 20.120/2006 [1] and article 8 of Decree 114, which defines it as *any research that involves physical or psychological intervention or interaction with human beings, with the aim of improving prevention, diagnosis, treatment, management and rehabilitation of people's health or increasing the biological knowledge of human beings* [21]. In addition, Technical Standard 151 [6], about accreditation standards of the CEC, includes the scientific validity and social utility of the research among the criteria for reviewing a protocol, as well as the technical competence of those who will conduct it.

In general, the legal framework is coherent with the ethical standards regarding scientific validity and social value present in the *Helsinki* [3] and *Cioms guidelines* [4]. However, these criteria, so relevant from an ethical perspective, have only an indirect mention in the regulatory field (not legal) in the Chilean legal framework.

Fair subject selection

The fair selection criterion states that the incorporation of participants in an research must be objective and impartial. People from a determined group can only be incorporated if the characteristics are related to the scientific questions of the study, and not because of conditions of vulnerability or facility in accepting (for instance, in countries with scarce resources, where it is more profitable to do the research).

This criterion is present in the *Helsinki* [3] (art. 13, 19 and 20) and *Cioms* [4] (Guidelines 2, 3 and 15), where it is stated that research with vulnerable populations can be justified since it responds to the health needs and priorities of the group, cannot be carried out in a non-vulnerable group, and the group must benefit from the knowledge, practices or interventions derived from the study. *Cioms guidelines* emphasize that benefits and responsibilities must be shared equitably when selecting groups to participate in the research, especially when recruiting vulnerable individuals or groups.

The Chilean legislation makes no direct reference to research with vulnerable populations, except for Technical Standard 151, which includes *special protection for vulnerable groups* [6] among the list of criteria considered for the review of protocols. On the other hand, Law 20.584/2012 [7] (art. 28) prohibits studies involving people with "mental or intellectual disabilities" who are unable to give their informed consent. It seems to be the opposite in *Cioms* [4] Guideline 3, according to which it is unfair to exclude from the research vulnerable groups that would benefit from discoveries concerning the diagnosis, prevention and treatment of diseases that affect them, unless there are disproportionate risks or scientific reasons for this exclusion. In addition, the *Cioms* [4] Guideline 16 considers special circumstances for authorizing studies on these individuals.

In short, compared to the Chilean legal framework, *Helsinki* [3] and *Cioms guidelines* [4] are more detailed and specific about the necessary precautions for a research with vulnerable populations, a multidimensional concept particularly discussed in the *Cioms guidelines*. The legal framework is also stricter concerning the recruitment of subjects with mental or intellectual disabilities in scientific research.

Favorable risk-benefit ratio

The risk-benefit ratio in clinical research establishes three ethical demands: minimizing the risks to investigated subjects, maximizing the benefits to subjects or society, and ensuring that the risks are less than or at least proportionate to the benefits.

Helsinki [3] (art. 16 and 17) fully sets out these requirements, adding that investigations must be preceded by careful assessment and that researchers must continually monitor, evaluate and document risks to minimize them. The declaration also provides that if the researcher discovers that the risks exceed the benefits, the discontinuation or modification of the study must be evaluated (art. 18) [3].

Cioms [4] Guideline 4 addresses with more details the risk-benefit evaluation, distinguishing two levels of analysis. The first level corcerns the subject, who must be assured that the intervention corresponds to the best available and effective therapy (or equivalent), which limits the use of placebos in control groups for cases when the expected social and scientific value of the research is favorably weighted. The possibility of recruiting subjects who cannot express consent is always considered when the risks are minimal.

The second level of analysis, which is more comprehensive, requires an appropriate relationship between risks and benefits to participants and the scientific and social value of the study. Finally, we point out that the *Cioms guidelines* postulates that benefits and risks should be evaluated with the community where the research will be conducted.

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Law 20.120/2006 [1] does not expressly include rules regarding the requirement of an adequate balance between risk and benefit, although it emphatically prohibits scientific research with excessive risks, those involving destruction, death or serious and lasting bodily injury to the individual (art. 10). On the other hand, the aforementioned Standard 151 incorporates, as a fundamental aspect to be evaluated in the revision of protocols by CEC, the *not unfavorable risk-benefit ratio and the minimization of risks* [6].

Independent review

The investigation must be evaluated by reviewers who are not affiliated with it and who have authority to approve, reject or suspend it. In this way, conflicts of interest are prevented or reduced. In this sense, an independent review and evaluation of the protocols provides a guarantee to society that the research comply the ethical standards.

Helsinki [3] agrees with this criterion and even goes into more detail on this subject. For example, art. 14 proposes that a physician should not recruit his own patients for a research conducted by himself, although he considers it acceptable if participation in the study does not adversely affects the health of the patients, with prior approval by an ethics committee. In addition, art. 22 states that information about funding, incentives and declaration of conflicts of interest must be included in the research protocol.

The declaration [3] also emphasizes the necessary independence of the ethics committee that reviews the research protocol (art. 23). Finally, it relates the transparency of the study with a complete informed consent, detailing all affiliations, funding, authors, directors, ethical obligations, information about publication of reports and conflicts of interest (art. 26 and 36) [3].

Cioms [4] (Guideline 8) argues that an independent ethical review is fundamental for building trust in the community. It also includes Guideline 25, which warns about conflicts with entities participating in the research and points out the need to implement policies and procedures to detect, reduce and eliminate or manage these conflicts [4]. Specifically, it states that study protocols should include a declaration of interests that may affect the study, and ethics committees should request a declaration of interests from their members and take appropriate mitigation measures in case of conflict.

Concerning the legal framework, the most detailed legal instrument for the ethical aspects of protocol review is the Standard 151 [6], which establishes several measures to ensure the independence of CEC members, including the obligation to declare if they have conflicts of interest and do not participate in the review in case it merits any of them. Meanwhile, the regulation of Law 20.120/2006 [1] requires that investigators who present a protocol to be reviewed by a CEC include a declaration of "potential or apparent" conflicts of interest (art. 18 bis).

In summary, the national legal framework addresses the independent review criterion in less detail compared with international ethical standards, without referring to aspects such as the prevention of conflicts of interest by institutions and research's sponsors.

Informed consent

The respect for the autonomy of subjects requires adequate informed consent for their participation. Consent requirements include that the person has received and understands all information regarding the protocol in which will participate (what it is about, what the objectives are, risks and benefits, treatment alternatives, etc.) and that the person made this decision freely and not forcedly.

Helsinki [3] bases the importance of informed consent (art. 7 and 9) and specifies in several articles that it should be voluntary and without any pressure (art. 25, 27 and 31), with adequate information and preferably written (art. 26). It also indicates the figure of the legal representative in case the subject is incapable of giving consent (art. 28 and 30) and refers to a consent when the participant is incapable (art. 29). Finally, it mentions the need of informed consent in research using material or data that allow the identification of the individuals (art. 32) [3].

The *Cioms guidelines* [4] addresses this topic throughout out the whole document. Like *Helsinki* [3], they recommend the written consent (Guideline 9), but allows modifications and even renunciations in justified cases: when it is not possible or feasible to obtain the information in that way, the risk to participants is minimal, and the research has significant social value. However, these cases must be approved by an ethics committee (Guidelines 4 and 10) [4].

Cioms [4] also refers to obtaining the mentioned criterion regarding collection, storage and use of biological materials and related data (Guideline 11), an aspect that is not yet legislated in Chile. However, a recommendation of the CMEIS [22], regarding the storage of samples in biobanks, establishes the characteristics of an informed consent for such purpose and admits some conditions under which a CEC can approve the use of historical samples from a biobank without the informed consent of the bearers.

Law 20.120/2006 [1] (art. 11) states that all research involving human beings must have the informed consent of the participant or, alternatively, of a legal representative. It also addresses the type of information required from the participant and emphasizes, as do international ethical standards, the possibility of the subject revoking the consent at any time during the study without receiving any penalty.

Unlike the ethical framework mentioned, this law establishes that the consent must be registered in a document signed by the participant, adding the signature of the responsible researcher and of the director of the institution where the research will be carried out, acting as a representative. The regulations authorize the director to delegate this function to another person [1].

In the Chilean regulation, Decree 114 [21] refers to research involving minors, regarding the fact that their refusal to participate or continue in the study must be respected (art. 11), an aspect that is not mentioned in the *Declaration of Helsinki* [3], but addressed by *Cioms* [4].

On the other hand, Law 20.584/2012 [7] prohibits research involving subjects with mental or intellectual disabilities who cannot express their wishes, thus excluding the possibility of a legal representative to authorize the participation of these individuals. In addition to being stricter than the international ethical standards, it may be interpreted as discrimination, contrary to Law 20.422/2010 [23], which establishes rules about equal opportunities and social inclusion of people with disabilities.

While the Chilean legal framework is generally in accordance with international ethical standards, it is stricter since it requires written and signed informed consent. It limits the conduct of some types of research, especially retrospective studies [24]. Although it does not strictly correspond to a research protocol, we consider it appropriate to mention the situation regarding the requirement of informed consent for case reporting, an issue not addressed by the *Cioms guidelines* [4], *Helsinki* [3] or Chilean law. The international recommendations allow an ethics committee to authorize the dispensation of this permission in qualified circumstances [25].

In short, in the legal framework we find a lack of regulation of increasingly relevant issues, such as broad consent that allows the use of biological material for future research or the creation of anonymized databases from clinical files.

Respect for enrolled subjects

This criterion states that participants must be respected during and after the clinical research. In addition to safeguarding privacy and confidentiality, individuals should be informed of any changes in the study that may affect their integrity, while retaining their freedom to discontinue participation. The importance of continuous monitoring of subjects, including the treatment of any adverse reactions, and the need to inform them the results of the research are also considered.

This principle is broad and is one of the founding aspects of research ethics, so it is not surprising that it is addressed in various places by *Helsinki* [3]. Likewise, *Cioms* [4] establishes the importance to protect the rights of the subjects beyond the social value expected from the study (Guideline 1), although Guideline 3 qualifies this point by indicating the risks should be proportional to the social and scientific value of the expected knowledge. This regulatory framework is, in general, compatible with Law 20.120/2006 [1] regarding respect for subjects. However, *Cioms* [4] is more specific in addressing the particular case of pregnant or lactating women, children and adolescents (Guidelines 17, 18 and 19), as well as focusing on research with vulnerable subjects or groups (Guideline 15) [4].

The use of the clinical file deserves special mention. Law 20.584/2012 [7] (art. 13 and 21) restricts this use to those involved in the patient's health care and adds some exceptions, excluding research. Furthermore, it stipulates that the use by third parties require a power of attorney. Law 20.120/2006 [1] (art. 11), however, allows subjects to authorize their participation in studies by written consent, without notarial mediation. According to Circular A15/15 issued by the Ministry of Health [26], it was interpreted as a legitimate form of access to the clinical record, on

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the grounds that Law 20.120/2006 [1] is specific to research and therefore takes precedence over Law 20.584/2012 [7] in this area.

The Chilean legislation is more restrictive than the *Cioms guidelines* [4], since the latter allows the use of personal data without consent when the individual has the opportunity to refuse it (for example, during a previous clinical session), and when the social value of the research is high while the risks are minimal. This last point seems reasonable, since it allows access to clinical records to consolidate data for statistical purposes, a low-risk process when accompanied by anonymization or misidentification.

The same legislation allows the use of statistical data, but is silent about the access required for clinical records for their preparation. CMEIS [27], on the other hand, refers to the use of personal data for epidemiological, statistical, or research purposes in exceptional situations, as well as allows exemption from informed consent when it puts the validity, registration, and consequently the research at risk, or when the request puts the person in the research at risk.

Law 20.850/2015 [16] (art. 111c) requires the provision of post-test treatment, not allowing any possibility of suspension agreements, contrasting with *Cioms* [4] (Guidelines 2 and 6), which allows for some flexibility in stating that post-test treatment could be limited to a pre-established period, with the participation of all involved participants.

Cioms [4] Guideline 14 requires compensation for damages that result from the intervention without specifying the procedure for proving such damages. Law 20.850/2015 [16] (art. 111e) is more specific and restrictive in stating that the possible damages are the result of the intervention, without prescribing a period of accreditation (although it defines the limitation of liability after ten years of the damage).

CMEIS has expressed concern because the articles mentioned above impose difficulties and burdens that restrict the development of biomedical research in the country [22]. At the time of our research, a project was being processed in the Chilean Congress to modify the articles of Law 20.850/2015 mentioned in the two previous paragraphs.

Finally, *Cioms* [4] Guideline 9 highlights the importance of communicating to participants significant changes in the research protocol or new relevant information. *Helsinki* [3] (art. 26), on the other hand, emphasizes respecting people's right to know the results of the study. The Chilean legal framework (Standard 151 [6]) requires a notification to the CEC about changes in the research and the appearance of adverse effects on individuals, as well as the investigator's duty to inform them about the progress of the study.

Final considerations

Establishing ethical standards for research is not a task exclusive to law, but shared with the norms of international ethical guidelines, such as the *Declaration of Helsinki* [3] and the *Cioms guidelines* [4]. In many countries, legislation about biomedical research has followed the publication of these guidelines and the formation of ethics committees. Although these documents do not have the same legal significance as a law, they have a binding character for health professionals who conduct research with human subjects, since they are issued by organizations called upon to regulate the practice of these professions.

When there are gaps or deficiencies in the current legislation in the field of scientific research, international guidelines acquire regulatory pre-eminence, especially because of the authority of the organizations that issue them, highlighting the representativeness of the World Medical Association (*Helsinki* [3]) and the global presence of the World Health Organization (*Cioms guidelines* [4]).

As for the Chilean legislation, we may identify certain gaps regarding the use of clinical record data for retrospective studies, storage and use of biobank material, research in vulnerable populations or unqualified subjects, conflicts of interest, among others. This situation is worrisome, since these issues deal with actions that may violate fundamental rights. Therefore, it is important the corrections of these regulatory shortcomings by modifying or adding legal standards.

We must also emphasize that not every absence of criteria in the law corresponds to a regulatory gap. First, it may be inconvenient establishing some criteria by law when they relate to situations that depend on contextual factors and variables. For example, the law may establish general considerations on the protection of subjects unable to give consent without the absence of mention of specific groups being considered a regulatory gap [28,29]. Overregulation may prevent the law from fully achieving its purpose – for example, when protecting individuals with

intellectual disabilities denies them any possibility to participate in a research, including those with potential benefit.

Second, the normative definition of technical matters or scientific details should be delegated to bodies that are better positioned from a technical (expert knowledge) and institutional point of view (for instance, an independent, pluralistic committee with the capacity to supervise research in time) [30]. In this regard, we believe that the international *Cioms guidelines* [4] achieve an adequate balance between defining specific research topics and applying flexible criteria that are sensitive to different contexts.

Third, there is the possibility that, for issues not explicitly regulated, there are more general principles (constitutional and legal) not specifically formulated to cover research topics, but which can be applied to these cases.

Another aspect of this review includes cases involving local legal regulations that are more restrictive than international ethical standards. This is particularly clear regarding the obligation of post-test treatment and compensation for damages, adding restrictions to access to clinical records and research on subjects with mental or intellectual disabilities. As we have pointed out, in line with what was expressed by the CMEIS, a legal framework that is more restrictive than international regulations may discourage the development of biomedical research in Chile and affect those who could be benefited by it, a situation that has generated concern in the professional and academic sector [31].

More than promoting legal and guarantee regulation, the international trend is to strengthen the deliberative role of CEC for specific cases, with an analysis of particularities and circumstances, including monitoring or auditing the development of the investigation. Likewise, there is a paradigm shift based on the need to justify the inclusion of vulnerable subjects rather than having to justify their exclusion.

We believe in the importance of promoting a qualified institutionality capable of setting standards for specific situations, in which contextual and dynamic factors make it inconvenient to have a regulation that anticipates and solves them via legal norms. Therefore, it is appropriate to highlight the role of ethics committees for the development of biomedical research and the importance of promoting accreditation processes that allow them to standardize their practices and operate autonomously.

These suggestions are consistent with the initiatives of the Regional Bioethics Programme of the Pan American Health Organization [19] concerning the strengthening of research ethics systems, from an adequate legal framework to the development of capacities for researchers and ethics review committees.

Finally, this review describes the dispersed nature of the legal norms on biomedical research in Chile, since they are limited in different normative bodies, some of which are mainly oriented towards different regulatory objectives, such as health care. This situation is partially responsible for the regulatory gaps and inconsistencies that we find when analyzing the regulatory framework as a whole.

The mission of advising the State authorities on the modification of this framework falls mainly to the National Bioethics Commission, created by Law 20.120/2006 [1] (art. 15). The fact that this Commission has not yet been set up in Chile may explain why the above-mentioned problems have not been solved yet. One way of regulating research may be to concentrate legislative changes in the mentioned law, which deals specifically with the theme. Another, more radical, strategy would be to create a new research law, which would cancel the previous regulations and address research with human beings, in biomedicine or in the social sciences, in an updated and complete way [32].

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Participation of the authors

Bernardo Aguilera, Gonzalo López and Bernardita Portales conceived the article. All authors analyzed the data and contributed to the first draft. Bernardo Aguilera, Gonzalo López and Bernardita Portales participated in the writing and final review of the text.

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