Does Law 14874, A New Ethical Regulation of Research with Human Beings in Brazil, Violate Human Rights?

A Lei 14.874, uma nova regulamentação ética das pesquisas com seres humanos no Brasil, viola os direitos humanos?

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Abstract

Free, post-study and indefinite access to the best prophylactic, diagnostic and therapeutic method that has been demonstrated to be effective during the study is a fundamental condition for protecting research participants. Since its inception in ethical regulations for research with human beings, Brazil has made this condition a cornerstone of protection for study participants. Through a qualitative analysis of Chapter VI of Law 14874, a new Law that regulates research with human beings in Brazil it was possible to perceive that there was a regression in the protection and recognition of the fundamental rights and dignity of the human beings participating in the research.

Resumo

O acesso gratuito, pós-estudo e por tempo indeterminado ao melhor método profilático, diagnóstico e terapêutico que tenha sido demonstrado eficaz durante estudo é condição fundamental de proteção ao participante da pesquisa. Desde o seu início nas regulações éticas das pesquisas com seres humanos, o Brasil fez dessa condição um pilar de proteção ao participante do estudo. Por meio de análise qualitativa do Capítulo VI da Lei 14.874, uma nova Lei que regulamenta as pesquisas com seres humanos no Brasil, foi possível perceber que houve retrocesso na proteção e no reconhecimento dos direitos fundamentais e da dignidade da pessoa humana participante da pesquisa.

Key words

Bioethics; research ethics; human rights abuses; experimental drugs; health vulnerability.

Bioética; ética em pesquisa; violação de direitos humanos; medicamentos experimentais; vulnerabilidade em saúde.

Fechas

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1. Introduction

The Constitution of the Federative Republic of Brazil, contains in its chapter 1, 5th article, which deals with individual and collective rights and duties, the recognition of the equality of people before the laws, as well as the recognition of the right to life, freedom, equality, security and prosperity as fundamental human rights. It is also said, among other things, that no resident in Brazil will be subjected to inhuman or degrading treatment (Brasil, 1988).

I am referring here to the fact that it ensures the ethical subject participating in the research, access to the benefits that proved to be effective during the research, and which have now come to an end, whether social or individual

Thus, since the right to life is a founding element of human dignity, that is, the one that places greater value on the rights of the person, here not only as a biological element but also as the entire natural subjectivity of the human species, it is necessary to guarantee it. Here we emphasize the need for this guarantee to be ensured in the care of the research participant, an ethical subject, a moral individual who demands his right to human existence, health care, among other things (Moraes, 2023).

It was to guarantee the rights of research participants that on October 10, 1996, through Resolution 196/96, the ethical regulation of research with human beings in Brazil began. Then, on December 12, 2012, 196/96 was replaced by Resolution 466/12. Both were created and maintained by an important social control body, the National Health Council of the Ministry of Health. In common, these Resolutions highlighted the need to maintain a strong system of Research Ethics Committees (CEP) and the National Commission for Ethics and Research (CONEP), there was a national ethical protection network for people who volunteered as research participants, there was concern about their fundamental rights (Silva dos Santos, 2018).

And regarding the fundamental rights of research participants, both Resolutions 196/96 and 466/12, bring with them an important element of care and protection, they aim to ensure that the research participant maintains, post-study, the best result obtained from what was tested, wherever it would be treatment or diagnostic resource. I am referring here to the fact that it ensures the ethical subject participating in the research, access to the benefits that proved to be effective during the research, and which have now come to an end, whether social or individual (Silva dos Santos, 2018).

This consideration of ensuring the research participant, at the end of the study, access to the best tested has also been included in other Resolutions, such as the number 251, which deals with the ethical regulation of research involving human beings and new drugs, medicines, vaccines and diagnostic tests (Brasil, 1997). In a clearer and more direct way, another Resolution of the National Health Council, number 404, which was revoked by Resolution 466, explained that:

> a) Regarding access to healthcare: At the end of the study, all participating patients must have access to the best proven prophylactic, diagnostic and therapeutic methods identified by the study. (Brasil, 2008)

Ensuring post-study access to the tested medicine or device is a matter of valuing human dignity, especially in poor or developing countries (Cook et al., 2015). Failing to offer what has brought the greatest benefit and which has been shown, in the study, to be better than the control or even placebo is an ethical issue. Imagine what it would be like to fail to offer effective AIDS medication to a group of research participants simply because the study was terminated (Wendland, 2008), or to fail to have better glucose control of research participants with diabetes (Lawton et al., 2019), also, withdraw or stop offering care to a neuro-implanted device to those who voluntarily participated in this study (Lázaro-Muñoz et al., 2022). These are situations that raise a wide range of questions and that must be taken into consideration when limiting post-study access to the benefits that were evidenced during the research. Well, Law 14874 contains in its Chapter VI, Continuity of Post-Clinical Trial Treatment, eight articles that greatly limit access to the post-study medication or device (Brasil, 2024).

Imagine what it would be like to fail to offer effective AIDS medication to a group of research participants simply because the study was terminated, or to fail to have better glucose control of research participants with diabetes

This leads us to question why, after so many years of protecting the fundamental rights of research participants, from 1996 to the present year, through two Resolutions on the ethical protection of research participants, Brazil goes so far back on this concept? Motivated by this doubt, with this study we aim to analyze the elements that make Law 14874, specifically Chapter VI, a setback in the protection and recognition of fundamental rights and thus the dignity of the human person participating in the research.

2. Methodology

This study is in accordance with Resolution No. 674 of the National Health Council, in its chapter 26, items II and III, regarding the exemption from the need to go through the Research Ethics Committee as it deals with public domain information.

This is a qualitative study, through content analysis, where Law 14784 was initially observed only as a manifesto and then we extended the look to its more latent content. We were particularly interested in chapter VI, the one that deals with the continuity of post-clinical trial treatment. Despite being a qualitative study, we carried out a quantitative, inferential analysis of causal elements, thus seeking a greater understanding of the analyzed content. As a guiding element for this study, we adopted what is recommended in Resolution 466 of the National Health Council when it says that post-study access aims to:

> d) ensure that all participants at the end of the study, by the sponsor, have free and indefinite access to the best prophylactic, diagnostic and therapeutic methods that have proven to be effective:
>
> d.1) access will also be guaranteed in the interval between the end of individual participation and the end of the study, in which case this guarantee may be given

> through an extension study, according to a duly justified analysis by the participant's attending physician. (Brasil, 2012)

The text referring to the evaluated chapter was opportunely analyzed in an exploratory phase by researchers in a different way, where each researcher carried out their exploration individually. From these explorations, a unit of registration (the dominant idea within the text) and context (understanding or meaning of the unit of registration) were extracted and created, to then create thematic axes, categorize (groups of elements that represented the recording unit) and analyzed in an inferential and also interpretative way, following Bardin's content analysis methodology.

3. Results

We were particularly interested in Chapter VI, which deals with the continuity of post-clinical trial treatment, as we understand that there are elements that require a more detailed look at human rights and the dignity of the person

Ordinary Law 14874 of the Legislative Branch is expressed as the Law that "Provides for research with human beings and establishes the National System of Ethics in Research with Human Beings." It is structured in 65 articles and was published in the Official Gazette of the Union on May 28, 2024, to come into force 90 days after its official publication.

We were particularly interested in Chapter VI, which deals with the continuity of post-clinical trial treatment, as we understand that there are elements that require a more detailed look at human rights and the dignity of the person. Here the results of the inferential and interpretative analysis carried out regarding the chapters that we believe to be of greatest vulnerability for the research participant will be presented, as we see:

> Art. 30. Before the start of the clinical trial, the sponsor and the researcher will submit a post-study access plan to the CEP, with presentation and justification of the need or not to provide the experimental medicine free of charge after the end of the clinical trial to participants who receive it need.

The caput of this article informs about the need to present a "post-study access plan" to the CEP, as if it was not necessary to bring this information previously included in the research project. It structures an additional document that can be presented in a way disconnected from the aforementioned project, it is not known whether this plan will be presented before or after the ethical analysis, creating doubts that may make it difficult to ensure that the research participant will have the possibility of having access to the medicine; justifying the need or not for free provision of the experimental medicine is not the same as ensuring the research participant free access to the best prophylactic, diagnostic and therapeutic method that has proven effective as stated in Resolution 466; it is not the experimental medicine, and here we emphasize that the word "medication"

identifies the main alternative to be offered post-study throughout this Law, which must be guaranteed, this too, but we cannot fail to list the possibility of offering the non-experimental medicine that served as a comparison and presented itself as the best therapeutic alternative; Furthermore, it is not just about medication, as mentioned, it is necessary to have access to other prophylactic and diagnostic methods that have been the subject of study. Only at the end of this chapter is it observed through art. 37 that this Law applies to medical and therapeutic products and devices; Furthermore, in Law 14874, it is stated that post-study access is linked solely and directly to the sponsor and the researcher, with no reference to the patient's attending physician as provided for in Resolution 466.

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We highlight here the word "medication," which within our inferential analysis is the one that appears most as an object of study and can be extended to the research participant, identifying with this the only studied alternative offered post-study. It is as if other research involving diagnostic means were not a reason for attention by this Law.

Beyond the caput, art. 30 brings three paragraphs in which is stated "post-study supply program" in synonymy with that described in the caput of the aforementioned article "post-study access plan." Analyzing the paragraph individually, we observe in § 1 the statement "under the terms of regulation," although it was not found at any time, throughout the Law, what it means and what the content of these "terms of regulation" are; §2 draws attention to the Law's emphasis on making it clear that post-study access is "for a determined period" in contrast to what is listed in Resolution 466 when it makes it very clear that access is "for an indefinite period;" in §3 what stands out is procrastination and this is clear and clear when it is said that "The post-study supply program must be started only after regulatory approval." It is understood that in addition to the CEP approving the research project, it will also have to approve, when presented, the supply program, that is, the participant who benefited from the medication used in the study will have to wait for regulatory approval to have access to treatment, even though it is stated that such a request must be submitted in a timely manner.

> Art. 31. At the end of the clinical trial, an assessment must be carried out individually on the need to continue the experimental treatment for each participant.

This article specifically addresses the need to evaluate the continuity of experimental treatment of the post-study research participant, without making it clear whether this evaluation is clinical or other factors (e.g., costs, access to medication). The obligation to evaluate is placed here, that is, the existence of the need will still be observed, it does not take into account that this certainty already existed, this excludes those researches where, for example, the results have been apparent since before, studies without masking or blinding of groups. It is contrary to Resolution 466 when it makes it

clear that all participants must be "guaranteed at the end of the study, by the sponsor, free and indefinite access to the best (...) therapeutic methods that have proven to be effective." While Law 14874 "evaluates" Resolution 466 "guarantees."

Then, analyzing the paragraphs of the article above, it is clear that Law 14874 insists on the need to comply with the "terms of regulation," with the sponsor and the research participant being heard, with such assessment being the responsibility of the researcher. This is present in §1, however, despite extending attention to the participant, it removes the doctor who accompanies him, not necessarily the research doctor, Resolution 466 calls him the participant's assistant doctor. We understand the need to have the opinion of the participant's attending physician, let us not forget that this participant is also a patient and is therefore possibly being accompanied by another doctor who is not one of the researchers, and this attending physician may have a different opinion about the need for the best therapeutic proposal, differing from the researcher and the study sponsor; §§3 and 4 deal with the need to provide the "experimental medicine" free of charge whenever it "is considered the best therapy or treatment for the clinical condition of the research participant," contrary to what Resolution 466 says when it states that it must be ensured the best therapeutic method and not just the experimental medicine. If the control treatment is the one that has proven to be most effective, the sponsor, and not the public health service or research participant, must guarantee post-study access to this treatment.

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> Art. 32. The assessment of the need to continue supplying the experimental medicine post-clinical trial must be carried out in accordance with the following criteria:

Note in this article and its paragraphs the idea of restricting post-study access to research participants, now explicitly assessing the severity of the disease and the threat to the participant's continued life (§1); whether there are other "satisfactory" therapeutic alternatives available (§2); whether the drug being tested would address an unmet medical need (§3); and whether evidence obtained in the study with the experimental medication supports benefits over risks (§4). The article and its paragraphs in question make it clear that the experimental therapy is not enough to be marked, better than the control for the research participant, it is now necessary to consider the severity of the disease, survival, whether the medication being tested cannot be withdrawn Alternatively, there is indeed a need to address a therapeutic gap and whether, again, the benefit is greater than the risk. These are impediments that will be placed when in reality and when choosing the intended sample, inclusion and exclusion criteria have already been addressed and were made taking into account benefits and risks, therapeutic control alternatives and the location where the research participants were located. What you are looking for now is simply, through the best result found in the study, to guarantee access to the experimental treatment or control treatment in accordance with what proved to be best and in accordance with what is recommended in Resolution 466.

Art. 33. The free supply of the experimental medicine within the scope of the post-study supply program may be interrupted, upon submission of justification to the CEP, for consideration, only in any of the following situations:

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Art. 33 deals with the possibility of interrupting the post-study supply of "experimental medication," arguing for this, above all, the "introduction of satisfactory therapeutic alternatives" (section II) and "availability of the experimental medication in the public health network" (section VII). We emphasize the superficiality of what may be satisfactory, whether or not there is therapeutic superiority as must have been found in the study with the medication under test, after all, satisfactory could be the previous medication consumed by the patient and which was discontinued at the time of the research and which did not if it presented or presents results equal to or superior to the drug under test, but which is tolerated by the patient, as well as, satisfactory may also be the medication that is already sold in your region or that exists in the public health network and that now may be recommended by the study without incurring costs in providing this measurement to the study sponsor, transferring these costs to the State. What is sought and included in Resolution 466 is what was best demonstrated in the study and will be provided free of charge to the study participant.

Art. 34. The researcher will be responsible for requesting the sponsor to begin post-clinical trial supply of the experimental medicine to the research participant, according to the criteria defined in this Law.

In this article we have the figure of the sponsor as supplier of the post-study "experimental medicine," even if by request or, most likely, by indication of the researcher, but it is not seen either in the caput of the article or in the paragraphs corresponding to the presence of the research participant's attending physician, given the need to recognize that the researcher will not always be the doctor who will assist the patient's clinical follow-up. Perhaps it is the attending physician who is not a researcher in the study, if any, which can best indicate whether or not there was benefit from the experimental medication or any other therapy used as a control in the study. Here the researcher is the one who will define whether the "experimental medicine" is the best therapeutic choice and whether the risk-benefit is favorable, compared to "other available treatments." It is important to highlight that the comparison is made with available treatments and not with other treatments that were part of the control group.

Art. 35. The researcher, the sponsor and the institution in which the research took place must make transition plans for participants who continue to need care or health measures, after the end of the clinical trial, to appropriate health services,

according to availability, under the terms of this Law, provided that such precautions are not related to reactions arising from the study itself.

The art. 35 raises doubts regarding the "transition" of the research participant to other health services, with the need for continuity of care, as we see: having completed the study, the research participant, who is no longer a research participant, starts to be monitored in the public health service or elsewhere? Who will pay for the therapeutic sequence of this patient, now and again? Paragraph 1 makes it very clear that "The transition" of participants who have received the medication or post-study treatment "to other available means of supply" must also be considered. As for other available means, it could easily be the public health service, it could also be the patient himself or his health insurance. It is important to consider that there may be an interval between the end of the study for the individual participant and the end of the study as a whole. During this interval, the researcher and the sponsor must guarantee continuity of care for this participant, as provided for in Resolution 466.

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Under an inferential view of the articles and paragraphs that make up Chapter VI, one can observe the protagonism of the expression "experimental medication," which is sometimes also recognized as "experimental treatment," disregarding the fact that access is assured not only to "experimental medication," as well as any other therapeutic alternative that has proven effective and that was used as a comparator group in the study.

4. Discussion

There is a consensus among members of ethics committees in Brazil that it is necessary to guarantee to the research participants post-study access to the therapeutic method that proved to be superior during the research. Not only the experimental drug, but also other therapies, which can be considered implanted devices, for example, that have proven to be superior during and at the end of the study (Brasil, 2012).

This need to ensure post-study access to the research participant comes from the context of seeking to offer those who proposed to participate in a research and, as a result, run risks and suffer limitations, which no one else would be willing to do, moreover, they are generally people with serious illnesses, seeking in that research the possibility of having better treatment for their condition, even if they altruistically and voluntarily seek to contribute to the therapeutic advancement of that particular situation. Here, I re-emphasize, no matter how much one tries to avoid other benefits, such as financial ones, for example, and with this there is a loss of participant autonomy, for them the fact of participating in a study that proposes the testing of a new medicine, with the

possibility of better results and which may not be available in your region for a given clinical condition, makes taking part in the study very attractive.

To make better use of what was studied, we will divide the discussion into four main topics: I. From access to the best result; II. Free access; III. Access time limit; IV. From the person responsible for indicating access.

4.1. From access to the best result

It is notable throughout Chapter VI that the access to be guaranteed must be through experimental medication, with the expansion of this concept to medical products and devices, and also "experimental advanced therapy products" (Art. 37). When we analyze Article 30 and its paragraphs, it becomes more evident that medication is the concrete object of research with human beings to be protected by this Law. There is no guarantee of access to the best prophylactic and diagnostic methods as stated in Resolution 466. Furthermore, what is sought to be offered is only the experimental medicine, without considering the possibility of access to that used as a control, after all, the medicine used in the control group may prove to be superior to the medicine under test, as the research participant taking the control medication and getting benefit from it, access to it must be ensured as well as access to the best therapeutic method. In Brazil, there is a demand for guaranteeing post-study access to the best therapeutic proposal found in the study, even if it was the control medication (Brasil, 2012).

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4.2. Free access

In the caput of art. 30, it is said that a post-study access plan will be presented justifying whether or not the experimental medicine will be provided free of charge. Furthermore, art. 35 in its 1st paragraph explains that there may be a transition from free access to medicines or treatment "to other available means of supply." It is important to highlight that, in accordance with what is recommended in Resolution 466, there is no need to restrict free access to the best result, it must be guaranteed free of charge, after all, the research participant provided precious data that would not otherwise have been obtained. The costs of providing an experimental medication that has proven to be superior to others under study can be and are mostly prohibitive for the research participant and for the Public Health Services in their location, especially for countries with lower incomes (Cook et al., 2015). In this case, wanting to transfer the responsibility for offering access to a certain therapy to the State, even if it is part of the public network or available commercially, it is wanting to transfer responsibility and costs for an obligation that should belong solely to the study sponsor. It is about being committed to more than ethical research practices, now we go further, it is a commitment to the resources applied and the way they become part of the local economy; a political and economic

relationship is established in the environment, failure to adapt to this condition can lead to ethical exclusions (Geissler et al., 2008).

4.3. Access time limit

Being granted the post-study access to the best therapeutic method, ensuring that this is done free of charge for the research participant and for an indefinite period of time is what is contemplated in Resolution 466, but it is not what is seen in Law 14874. In this case, in §2 of art. 30, it is said that access to the experimental medicine, after the study, will be for a "determined" period of time. It also lists, but in art. 32 that there are conditions, such as "satisfactory" therapeutic availability, which is a review criterion to maintain post-study access, even though it is not clear what "satisfactory" means. What determines the time to be offered is not the prior contract described in the research project or in the Free and Informed Consent Form, what will determine the time for offering the medication in post-study access is the clinical evolution of the research participant, this already it was previously guaranteed by Resolution 466 (Brazil, 2012). Depriving someone who had been benefiting from a certain treatment within a research study, and who now enters a post-study access program to this medication, and will no longer receive it due to the end of the study is unfair, especially when the research is carried out in poor countries (Dainesi & Goldbaum, 2012). Taking away from someone the benefit of the cure or clinical improvement of a serious illness not only asserts maleficence in the organic sense but also in the mental sphere (Lawton et al., 2019). Here it is important, more than before, to consider the need to know the moral limit of these actions. Conditions like the one discussed here can easily characterize violation of human rights as a whole or violation of a person's dignity as a research participant, when their right to health or even life is limited or taken away (Wendland, 2008).

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4.4. From the person responsible for indicating access

Although the researcher has the possibility of accessing clinical information about the research participant, no one has more knowledge about the patient's clinical evolution than the attending physician. Most of the time the attending physician is not the study researcher. Therefore, the participant's attending physician must indicate access to the treatment that proved to be best during the study (Brasil, 2012). In analysis of art. 31, on the occasion of the "evaluation of the need to continue the experimental treatment," §1 states that this evaluation "will be carried out by the researcher, after consulting the sponsor and the participant;" further on, in art. 34, §1, emphasizes that the supply of the experimental medication, post-study, will be guaranteed by the sponsor when the best

therapeutic proposal is considered by the researcher, thereby excluding the research participant's attending physician. When dealing with the health issue of a person or a group of them, where issues of cost with the treatment under study may be more considered than the social or personal benefit for the research participant, letting a decision like this in the hands of only the sponsor is worrying. Most of the time, we are dealing with studies that involve several other research centers in several other countries; there is no deeper social knowledge about the real situation in which these people live. It is very difficult to concentrate such a decision to indicate the treatment that was shown to be best in the study in the hands of researchers and sponsors. The participant's attending physician, the one who was most present and followed up the person's progress and knows the local scenario, should be the one to be heard in prior (Wendland, 2008).

5. Conclusion

Analyzing Law 14874, specifically Chapter VI, it is clear throughout its articles and paragraphs that its main order is to be restricted in terms of free post-study access to the experimental medication, or any other medication that has been used as a control during the study, and which has proven to be superior, limit the time of access to the medication, now access is for a determined period of time, excluding the participant's attending physician from the indication of access, the researcher will be the main actor in this issue. It is easily seen behind the long lines that make up this chapter the intention of making post-study access as difficult as possible. This condition has always been the subject of much discussion in the ethical environment of research with human beings in Brazil. Now, this same country that prided itself on having important regulatory control over research with human beings, has managed to turn Law into an instrument that will make it very difficult to access new drugs and experimental medicines, which in some cases will not even be sold in Brazil. This condition will make the research participant more vulnerable. It is important to recognize that, with the exception of participants in "phase one" studies, all others need some form of health care, are more vulnerable in their personal essence, are patients and not just research participants (Hossne, 2009). Law 14874, by restricting the opportunity to access better treatments, even during research, limits the provision of quality of life to people who are mostly seriously ill, attacks the person's dignity, violates the rights to life, attacks human rights.

It is important to recognize that, with the exception of participants in "phase one" studies, all others need some form of health care, are more vulnerable in their personal essence, are patients and not just research participants

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