# Evaluation of clinical trials in Brazil: history and current events

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**Abstract**

Clinical trials must be approved and monitored by ethical and regulatory authorities to ensure that the ethical conduct and technical aspects of the research are in compliance with required standards. The in-depth understanding of this process is crucial for studies to be delineated and conducted in accordance with applicable standards, being an essential part of national technical and scientific training. The evaluation of the studies in Brazil is performed by the research ethics committees, by the National Research Ethics Commission and by the Brazilian regulatory agency, the Agência Nacional de Vigilância Sanitária (National Health Surveillance Agency). Researchers and sponsors claim that the time taken for approval and initiation of clinical trials limits further studies. However, Brazilian standards are constantly improving, demonstrating the interest and ability to improve procedures, without losing quality in ethical evaluation.

**Keywords:** Ethics, research. Human experimentation. Clinical trial. Ethics committees research. Brazilian Health Surveillance Agency.

**Resumo**

**Avaliação de ensaios clínicos no Brasil: histórico e atualidades**

Ensaios clínicos devem ser aprovados e acompanhados por autoridades éticas e regulatórias para garantir que a conduta ética e os aspectos técnicos das pesquisas estejam em conformidade com os padrões exigidos. O conhecimento desse processo é primordial para que estudos sejam delineados e conduzidos de acordo com os padrões aplicáveis, sendo parte essencial para a capacitação técnica e científica nacional. No Brasil, a avaliação dos estudos é realizada pelos comitês de ética em pesquisa, pela Comissão Nacional de Ética em Pesquisa e pela Agência Nacional de Vigilância Sanitária. Pesquisadores e patrocinadores alegam que o tempo para aprovação e início de ensaios clínicos limita novos estudos. No entanto, as normas brasileiras estão em contínuo aperfeiçoamento, o que demonstra interesse e capacidade em aprimorar os trâmites, sem perder a qualidade na avaliação ética.

**Palavras-chave:** Ética em pesquisa. Experimentação humana. Ensaio clínico. Comitês de ética em pesquisa. Agência Nacional de Vigilância Sanitária.

**Resumen**

**Evaluación de ensayos clínicos en Brasil: historia y actualidad**

Los ensayos clínicos deben ser aprobados y acompañados por autoridades reguladoras y éticas con el fin de garantizar que la conducta ética y los aspectos técnicos de las investigaciones cumplan con los estándares exigidos. El conocimiento de este proceso es fundamental para que los estudios sean delineados y conducidos de acuerdo con los estándares aplicables, siendo una parte esencial para la capacitación técnica y científica nacional. En Brasil, la evaluación de los estudios es realizada por los Comités de Ética en Investigación, la Comisión Nacional de Ética en Investigación y por la agencia reguladora nacional, la Agencia Nacional de Vigilancia Sanitaria. Los investigadores y patrocinadores sostienen que el tiempo para la aprobación y el inicio de ensayos clínicos es un factor limitante para nuevos estudios. No obstante, las normas brasileñas están en continuo perfeccionamiento, lo que demuestra el interés y la capacidad para mejorar los trámites, sin perder calidad en la evaluación ética.

**Palabras clave:** Ética en investigación. Experimentación humana. Ensayo clínico. Comités de ética en investigación. Agencia Nacional de Vigilancia Sanitaria.

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Declaram não haver conflito de interesse.

Conducting human trials contributes to the understanding and capacity of disease treatment and is essential for the progress of clinical practice. Clinical research seeks to answer questions and generate knowledge that can benefit future patients and, based on evidence-based medicine and its hierarchy of evidence levels, can help improve medical care. Medical practice aims to provide the best care for a patient or a group [1,2].

Clinical trials depend on the infrastructure of participating research centres, professional qualification, offer of volunteers and regulatory requirements [3,4]. Pharmaceutical industries have adopted internationalisation strategies, in which clinical trials are generally carried out simultaneously in several research centres in several countries. Many ethical issues surrounding the internationalisation of clinical trials should be taken into account, mainly because of the vulnerability of the population in developing countries.

The tendency for the participation of several countries in the same study is influenced by the need to reduce costs, either by the possibility of using an infrastructure and skilled labor of relatively lower cost (especially when compared to the values practiced in European and North American countries) or by the ease and speed to recruit volunteers for the studies. This issue may be influenced by the vulnerability of populations and epidemiology of the conditions to be treated.

Outsourcing strategies have also been adopted through *organizações representativas de pesquisa clínica* - ORPC (clinical research organisations), contracted to develop or manage parts of research projects or their totality [5]. As a consequence, a very competitive international market has been formed, particularly in developing countries such as Brazil, thus characterising the globalisation of clinical trials [4].

Clinical trial protocols must be approved, prior to their initiation, by ethics and regulatory review bodies, where applicable. Ethical conduct is the guiding principle for conducting all research projects and is ensured through evaluation and prior approval of protocols and ongoing monitoring of its achievement by ethical authorities, in line with researchers' actions in following the research protocol and all applicable national and international regulations and standards.

Ethics authorities are responsible for examining the ethical aspects of research involving human subjects and should safeguard the rights, safety and well-being of research participants [6,7]. The technical character of research's projects is evaluated by regulatory authorities, which includes the evaluation of physical and safety characteristics of the drugs under study and the authorisation to import medicines.

Although the evaluation of ethical issues is attributed to the *Comissão Nacional de Ética em Pesquisa* and *Comitê de Ética em Pesquisa* (National Commission for Research Ethics and the Ethics Research Committee - CONEP/CEP System), technical and scientific issues can not be dissociated from the ethical aspects of scientific research. It is worth remembering that, although it is the prerogative of ethics and regulatory organisations to monitor the execution of these projects, the researcher and the institution where the research will be carried out (personified in the person of its legal representative), are ,by virtue of regulations, the ones responsible for ensuring that such research follows ethical principles and technical levels of excellence. Although these entities are not the primary proponents of the project, the study will only take place in the research centre in question by agreement about its design by the researcher and the institution. Thus, they become co-responsible for the genesis of the project.

The Brazilian ethical and regulatory environment is in line with changes in the world panorama and with local needs as well, keeping up to date with ethical standards and technologies. In this context, the recent debate on the regulation of clinical research in the country is highlighted by the *Projeto de Lei do Senado 200* (Senate Bill 200 -PLS 200) and the recent inclusion of the *Agência Nacional de Vigilância Sanitária* - Anvisa (National Sanitary Surveillance Agency) in the list of members of the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH). This inclusion denotes the international recognition of the technical capacity of the agency and of the country as well. In addition, Brazil has researchers with a high level of competence in clinical research, many considered opinion leaders [4].

The regulatory process of clinical research is an important step in conducting clinical trials. Understanding the process for conducting clinical trials in the country, including its regulatory aspects, helps to train researchers and the national development of new drugs , being one of the ways to break down barriers between basic research and clinical research [8]. Even so, it is important that sponsors understand the process of approval of clinical trials in Brazil, once the country is inserted in the context of globalisation of these trials and that

the regulatory process is a step that can interfere in the selection of countries and research centres.

In the course of this work, we will present the evolution of the regulation of clinical research in Brazil, its historical milestones and latest updates. It was verified a need to publish papers on the subject in the country, mainly contemplating the changes that have occurred since 2012. The purpose of the article is to contribute to the understanding of the process of approval of studies in the country and the reflection on the recent proposals and updated regulations.

The research on these studies was carried out using PubMed, Medline and SciELO databases, with the following descriptors: ethics in research, clinical trial, human experimentation, research ethics committees and *Agência Nacional de Vigilância Sanitária* (National Health Surveillance Agency) in Portuguese, Spanish and English.

The criteria for the selection of articles were: publications between 2010 and 2016 and the identification of articles dealing with the regulation of clinical research in Brazil, its history and forms of evaluation.We also searched for articles referring to the *projeto de lei do senado - PL 200 (*Senate bill PL 200) - subsequently referred to the Chamber of Deputies , with denomination PL 7.082/2017, published until December 2017.

In addition to articles, norms and regulations related to the theme, both current and obsolete, were also used. None of the identified articles presented the history of the evolution of clinical research in the country, encompassing the recent events that, because they are of a very relevant character, can have a great impact in the conduction and approval of clinical trials in the country. We did not include in this review articles on regulations related to the storage of biological samples, since this subject does not belong to the scope of this work.

## History of regulation of research in Brazil

The *Código de Deontologia Médica* of 1984 (Medical Code of Ethics)[9], in articles 30, 31 and 32, already dealt comprehensively with ethical questions in the conduct of research, considering, for example, as an infraction the use of therapy not yet released in the country, and studies without the appropriate authorisations and without the informed consent of the patient or the person responsible.

However, the regulation of research ethics involving human beings in Brazil began with Resolution 1 of June 13, 1988. This deliberation created committees for ethics analysis in any health institution that conducts research on human beings, being the responsibility of the committees to issue opinions on the ethical aspects of the research[10,11]. However, since it had no relevant practical impact in scientific research, it was revoked by the Resolution of the *Conselho Nacional de Saúde - CNS* ( National Health Council) - Resolution CNS 196[12] of October 10, 1996, which instituted the system composed of the Comitês de Ética em Pesquisa - CEP (Research Ethics Committees) and the *Comissão Nacional de Ética em Pesquisa* (National Commission for Research Ethics - Conep), the CEP/Conep System.

This resolution approved the "Guidelines and norms regulating research involving human beings", creating and standardising the system of ethics appraisal constituted by regional bodies, the CEP, and a federative entity, Conep, a national body which controls research involving human beings[4,10,11]. Clinical research started to consolidate in Brasil with the publication of the norm, considered one of the main landmarks of clinical research at national level, and the creation of a solid system of ethics appraisal, essential for the development of human research and others that complement it[11-14].

After a validity of more than 15 years, Resolution CNS 196/1996[12] was revoked and replaced by CNS Resolution 466[15], of December 12, 2012 (currently in force), which purpose would be to consolidate the CEP/Conep System through cooperative work between the members of the system, coordinated in a decentralised manner, aiming at the protection of research participants in Brazil.

Thus, institutions that conduct research on human beings must establish a CEP, or use that of another institution, which is responsible for analysing the ethical aspect of the research, issuing a formal analysis, as well as having an educational and consultative role for researchers, institutional community, research participants and the community in general as co-responsible agent for the development of the study[16].

Conep, in addition to being responsible for ethical aspects, issuing formal opinions, and taking charge of the normative aspect, coordinates and supervises the CEPs, being responsible for the accreditation and registration of these committees, according to Resolution CNS 370[17] of March 8, 2007. This process verifies if the CEP meets the minimum operating conditions: 1) the dispatch of reports on approved projects, every six months, to Conep; 2) existence of exclusive and adequate

 http://dx.doi.org/10.1590/1983-80422018263254

physical space, so as to keep the confidentiality of documents; and 3) existence of internal regulations after the first year of operation, among others.

Some ethics committees can still be accredited by the Conep, which has been done by Resolution CNS 506[18] of February 3, 2016. The resolution approves the accreditation process of the CEPs that constitute the system. This norm aims to decentralise the recognition of the institutional CEP, since accredited committees would be able to evaluate high risk protocols, that is, those that fall within the thematic areas of the Resolution CNS 466/2012 (Table 1) [17,18].

The technical and sanitary aspects of clinical trials, as well as the authorisation for possible imports of materials and medicines necessary for the study, are evaluated by the Brazilian drug regulatory agency. Anvisa was created by the Law 9,782 of January 26, 1999. The agency has its own equity and administrative and financial autonomy[19]. Prior to the creation of the agency, the technical regulation of clinical trials was related to import requests of products not approved in the country for research purposes, including medicines, vaccines and diagnostic products, and did not apply to studies carried out with products manufactured in Brazil.

After the creation of the agency, the enactment of the *Resolução da Diretoria Colegiada* – RDC (Collegiate Board of Directors) 219, of September 20, 2004, was promulgated, which started to cover all clinical studies with products that can be registered with Anvisa, including products manufactured in the Country, besides recognising the ORPC and introducing elements of good clinical practice in the light of the policy on health norms. [20] However, this resolution had some limitations which, as a consequence, led to an excessive time demand for the evaluation of a study by Anvisa and the delay in initiating a clinical study in the country.

During the validity of RDC 219/2004, in the case of clinical trials with more than one research center, it was necessary to issue an approval document, known as a *comunicado especial* (special communiqué -CE) for each participating centre. In that format, an Anvisa's assessment was made for each specific request from a particular research center participating in the study. In addition, the receipt of the specific dossier from a research center was conditional on ethical approval of the study, and it was mandatory to wait for the ethical approval by the institutional CEP and Conep to initiate Anvisa's assessment of a participating center.

The format of the evaluation required by the RDC 219/2004 allowed aspects of each research center to be more rigorously assessed by the regulatory agency prior to the start of the study at the research center concerned, taking into account peculiarities and characteristics of each site where the study would be carried out. In addition, it avoided technical evaluation without full ethical reflection on the study, what would waste time and agency staff on a study that might not be initiated, given the possibility of the study not getting ethical approvals.

However, the sponsors argued that the segregated assessment, that is, the specific evaluation for each research center, would occasionally result in divergent formal opinions about the same study. Moreover, the requirement to wait for ethical approval by the institutional CEP and CONEP, when applicable, in order to send the dossier to the Anvisa, extended the period to initiate multi centre studies, which were mostly sponsored by pharmaceutical industries.

The RDC Anvisa 219/2004 was repealed by RDC 39 of June 5, 2008, which established that the evaluation by the agency should occur simultaneously for all centres and only one CE should be issued for each study. This resolution had a great impact on the conduct of multi centre studies and allowed the evaluation by Anvisa to be conditional upon receiving the ethical legal opinion only from the CEP of the coordinating center.

A coordinating center is determined for for multi centric studies, and its respective CEP is denominated "coordinating CEP". Thus, Anvisa's analysis could be done concomitantly with Conep's analysis, when applicable. The RDC 36[31] of June 27, 2012 was published complementarily to the RDC Anvisa 39/2008 . In general, this resolution allowed the simplified analysis of studies that had already begun to include patients in another country or been analysed and approved by another regulatory agency, including the United States Food and Drug Administration (FDA), the European Medicines Agency (EMA), the European Union, the Pharmaceuticals and Medical Devices Agency (PMDA) of Japan, or the Health Canada, from Canada.

In addition, the submission of clinical trials to databases of the *Registro Brasileiro de Ensaios Clínicos* (Brazilian Registry of Clinical Trials - ReBEC) was started. Studies that had been registered prior to the validity of the resolution on the primary registries of the International Clinical Trials Registry Platform (ICTRP) of the World Health Organisation (WHO) [21] would also be accepted. ReBEC is publicly owned and managed by the Fundação Oswaldo Cruz - Fiocruz (Oswaldo Cruz Foundation), the

leading Brazilian governmental research organisation operating on a non-profit basis and composing the ICTRP/WHO network as primary registry. For this reason, registration with ReBEC meets the requirements of the International Committee of Medical Journal Editors (ICMJE) [22,23].

More recently, Anvisa published the RDC 9 of 20th February, 2015, revoking resolutions RDC 39/2008 and RDC 36/2012. This resolution has considerably altered Anvisa's analysis of clinical trials in Brazil. Previously, each clinical trial was evaluated separately. With RDC 9/2015, the *Dossiê de Desenvolvimento Clínico do Medicamento - DDCM* (Clinical Drug Development Dossier) has started, in which all the clinical trials carried out in the country for registration of a pharmaceutical drug in Anvisa would be inserted, not being applied to bio equivalence studies and bioavailability.

Since the enactment of this resolution, the agency has sought to implement the new standard by working in a clear and instructive way, through the preparation of manuals and drawing together agency's own sectors involved in clinical trial and drug registration processes. RDC 9/2015 is considered a new regulatory framework for clinical research in Brazil.

As a result, the regulatory deadline had a significant reduction of approximately five months for evaluation, as reported by the agency. Anvisa reinforces that the time of analysis is a relevant factor to attract clinical studies to Brazil and to give more credibility as well as national and international recognition to the Agency. However, it should be noted that this reduction does not compromise the quality of the technical evaluation [24].

## Regulatory flow of the clinical research in Brazil

The process to analyse clinical trials includes the ethical evaluation, which in Brazil is carried out by the CEP and Conep, and the regulatory evaluation carried out by Anvisa. In the country, the entire communication process and dispatch of documents for ethics appraisal is done by an online platform, called *"Plataforma Brasil"*. It is the national and unified database of research records with human beings. The objective is to ensure agility and transparency by allowing the submission of documentation through digital channels and the monitoring of processes via Internet [4].

In each institution where the clinical trial will be conducted, the documentation required for ethical evaluation, called ethics dossier, must be sent by the responsible researcher or by a delegated person to the institution's CEP. If the institution does not have a CEP, it can ask Conep to use the CEP from another institution to do the evaluation. In the case of multi centre studies, the research should initially be approved by the coordinating CEP and, if applicable, by the Conep, and subsequently replicated to the other participating centres and their respective CEP. Each CEP must approve the protocol to evaluate both ethical aspects and the feasibility of the project in the institution (aspects of infrastructure and available resources).

After issuing the formal opinion of approval of the study by the CEP, in some cases, the project still needs to be appraised by the Conep, depending on the thematic area on which it fits. According to the current resolution, any project that falls into one of the areas presented in Table 1 should be sent to the Conep for analysis.

Any sponsor who is interested in doing clinical trials in the national territory with medicines for registration purposes must send the *Dossiê de Desenvolvimento Clínico de Medicamento - DDCM* (Clinical Drug Development Dossier) to Anvisa, accompanied by at least one specific dossier of clinical trial with the study drug. The DDCM is the set of documents with information on the development stages of the pharmaceutical drug being researched, including the development plan and the investigator's brochure, and should be evaluated by Anvisa in 90 calendar days or 180 days for national development cases, of biological products and Phase I or II studies. If there is no manifestation of the agency in this period, clinical development may be initiated, provided that applicable ethical approvals have been obtained [24].

The specific clinical trial dossier is unique for each case and contains specific details of the study such as the research protocol, record of registration in the database, formal opinion of approval of the study by the CEP, and in the case of multi centre studies, by the CEP coordinator. Anvisa's manifestation regarding the authorisation of these tests is given by issuance of a CE, mentioning the trials that may be conducted in the country for each DDCM. If the manifestation does not occur, a document allowing the importation or exportation of the product (s) under investigation, the Import Document of the product (s) under investigation of the Clinical Drug Development Dossier may be issued [24].

 http://dx.doi.org/10.1590/1983-80422018263254

**Table 1.** Areas of Research Projects that should be appraised by the Conep

| Special Thematic Areas |
|---|
| Human Genetics |
| If genetic material or any human biological material has been sent abroad to obtain genetic material, except in cases where here is cooperation with the Brazilian government<br>If there is storage of biological material or human genetic data abroad and in the country, when in a manner agreed with foreign institutions or commercial institutions<br>If there are changes in the genetic structure of human cells for in vivo use<br>If they are researches in the area of the genetics of human reproduction (reprogenetics)<br>If they are research on behavioural genetics<br>If they are researches in which the irreversible dissociation of data of research participants is foreseen |
| Human reproduction |
| Researches that deal with the functioning of the reproductive tract, procreation and factors that affect the reproductive health of humans, being that in those researches will be considered "participants of the research" all that are affected by those researches procedures |
| Assisted reproduction |
| Manipulation of gametes, pre-embryos, embryos and fetuses<br>Fetal medicine, when involving invasive procedures |
| Therapeutic equipment and devices, new or not registered in the country |
| New invasive therapeutic procedures |
| Studies with indigenous populations |
| Research projects involving genetically modified organisms, embryonic stem cells and organisms posing a high collective risk, including organisms related to them, in the fields of: experimentation, design, cultivation, handling, transport, transfer, import, export, storage, release in the environment and discard |
| Protocols for the constitution and functioning of biobanks for research purposes |
| Researches with coordination and / or sponsorship originated outside Brazil, except those co-sponsored by the Brazilian government |
| Projects that, at the discretion of the Research Ethics Committee (CEP) and duly justified, are deemed deserving of analysis by the National Commission for Research Ethics (Conep), will be classified as "At the discretion of the CEP" |

*Source: Adapted from Resolution CNS 466/2012*

The sponsor has to forward follow-up reports of clinical trials to the Anvisa, containing information on conducting the research in Brazil, including statistical analysis data, protocol deviations, adverse events and results obtained, among others. The documentation must be filed with the agency annually within a period of up to 60 days after completing each year from the date of beginning of the study in Brazil, which corresponds to the date of inclusion of the first research participant in the country. The entire procedure of this process for Anvisa must be done by the sponsor of the study or by a contracted ORPC[24]. The deadlines determined in the regulations related to the regulatory process for approval of clinical trials are presented in Table 2.

In addition to the deadlines and procedures established by the Brazilian resolutions, it is worth mentioning that, for the study to begin, it is necessary to fulfil several stages of project development and implementation, which requires skilled manpower and financial resources.

Any documentation for analysis in Brazilian ethics and regulatory proceedings must be submitted in Portuguese and, in the case of studies with a country of origin outside Brazil, the time for a quality translation should be taken into account at the time of the planning study in the national territory.

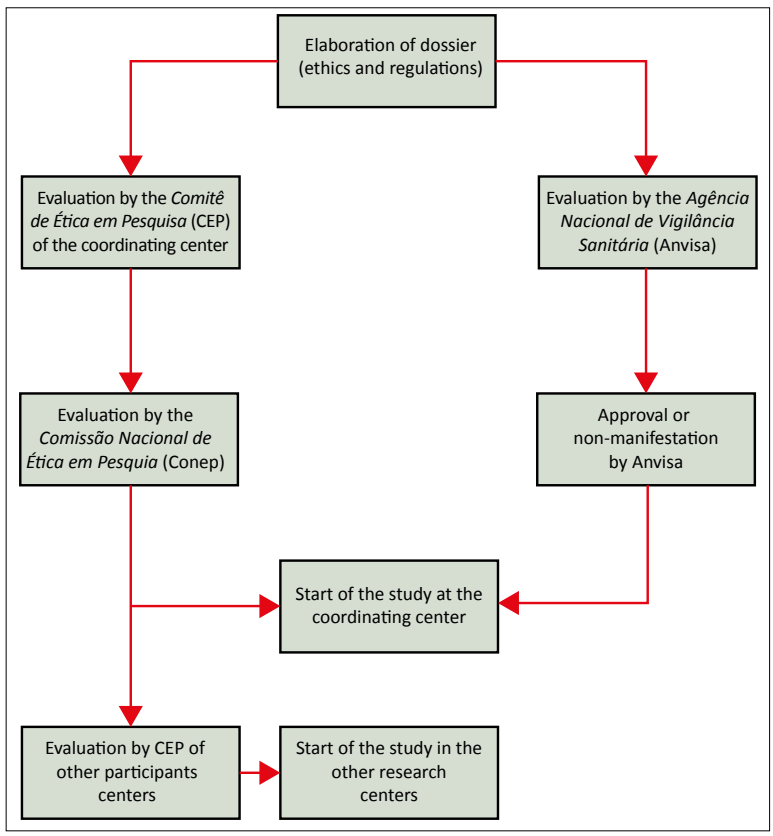
Another important step is the selection of research centres participating in the study. To this end, specific parameters, such as adequate infrastructure, availability of skilled labor, calibrated equipment and analytical laboratory (s) should be evaluated. Finally, the beginning of inclusion of patients in the study is marked by the training visit, called the initiation visit in research centers. On that occasion, the study team members are properly trained by the sponsor or sponsor-researcher and then, after resolving any issues, the center will be able to begin recruitment. Figure 1 shows the flowchart of the clinical trial approval process in Brazil.

**Table 2.** Deadlines established by regulation for regulatory procedures for the approval of research projects involving human beings in Brazil

| Actions | Deadline | Determined by |
|---|---|---|
| Documentary review of the protocol by the Research Ethics Committee (CEP) | 15 days (from the date of submission of the protocol) | Operational Norm 1 of 30 September, 2013) |
| Issuance of a formal opinion by the CEP | 30 days (counted from the documentation acceptance) | |
| Submission of reply to the CEP 's formal opinion | 30 days | |
| Documentary review of the protocol by the National Commission for Research Ethics (Conep) | 15 days (from the date of submission of the protocol) | |
| Conep's formal opinion issued | 60 days (counted from the documentation accepted) | |
| Submission of response to pending formal opinion of the Conep | 30 days | |
| Issuance of the special notice by Anvisa | National development and organic products, and phase I and II in up to 180 days; studies in up to 90 days. If Anvisa does not manifest within this period, clinical development can be initiated | Collegial Board of Directors Resolution 9 of 20 February, 2015 |
| Reports to Anvisa | Annual monitoring reports. Final report within 12 months of the end of the clinical trial | |
| Reports to CEP | Every six months | Resolution CNS 466/2012 |

*Source: Adapted from Resolution CNS 466/12, RDC 9/15 and Operational Standard 1/2013.*

**Figure 1.** Process for approval of clinical trials in Brazil for multi centric studies that fall within the special thematic areas of the *Comissão Nacional de Ética em Pesquisa* - Conep (National Commission for Research Ethics).





Rev. bioét. (Impr.). 2018; 26 (3): 350-9
http://dx.doi.org/10.1590/1983-80422018263254

## Recent changes and perspectives

Both Conep and Anvisa have sought to devise ways and tools to improve the process of project analysis, with respect to the time of analysis and guidance to researchers, sponsors and the ORPC. Communication with research groups is essential, since protocols presented with lack of data and deficient technical questions require more time for analysis [25].

In 2015, the Conep published a handbook of frequent delays in research protocols, providing clear guidance for the completion and preparation of study papers as well as for those related to responses to requirements, correlating them with standards that justify these obligations. On the part of the regulatory agency, technical and manual guides became a new work tool.

Since the publication of RDC 9/2015, Anvisa has released publications with specific technical guidelines for the submission and analysis of clinical trials, such as the *Manual para Submissão de Dossiê de Desenvolvimento Clínico de Medicamento e Dossiê Específico de Ensaios Clínico* (Manual for Submission of Clinical Drug Development Dossier and Specific Dossier for Clinical Trials ) and the guide *Perguntas & Respostas: Principais questionamentos sobre a RDC 9/2015* (Questions & Answers: Key Questions Concerning DRC 9/2015) [26]. In addition, previous meetings with research groups have been held, according to Jarbas Barbosa, the agency's current director [25].

Barbosa has pointed out on occasions that the centralisation of analysis by the CEP / Conep System needs to be reviewed and considers as reference the determination of the deadline for analysis, similar to that determined by the regulatory agency by DRC 9/2015 [25]. One of the Conep's proposals to strengthen decentralisation and shorten study time would be the accreditation of some ethics committees that would take Conep's role. In this model, the studies would be analysed by the authorised CEP and only local aspects would be analysed by each committee participating in the study. These aspects include analysis of local documents, adaptation to the *termo de consentimento livre e esclarecido* (informed consent form -TCLE), according to the need of the region, analysis of the institution's capacity to conduct the study and the competence of the researcher responsible for the trial. Another aspect is that if the CEP believes that more clarifications are necessary, as long as it does not require changes in the project or detailed TCLE, with possibility of non-approval, as regulated by Resolution 506/2016 [17,18,20].

In 2015 was introduced the *projeto de lei 200* (Bill 200) of Senators Ana Amelia, Waldemir Moka and Walter Pinheiro. Previously, in 2003 and 2006, other bills had also been created, but were shelved. If, on the one hand, the current bill has gained momentum from some researchers - many associated with the pharmaceutical industry and sponsors, who claim that bureaucracy shuns research and development of technologies and health knowledge - on the other hand, a significant part of the academic community accuses the proposal of taking commercial interests to the forefront, favouring the pharmaceutical industry [27] to the detriment of the safety of research participants. The Conep also considered the proposal as a retrocession that eliminates the system of ethical analysis and does not take into account the essential ethical dimensions, putting the research participants at risk [28].

Since it was filed in the Senate, the bill has undergone several amendments, with positions against and in favor of the text by important organs, institutions and associations directly related to clinical research. Among the changes in the initial proposal we can highlight the fact that the PL started to cover all clinical researches and not only clinical trials [29,30].

In addition, the text on *comitês de ética independentes* (independent ethics committees - CEI) was withdrawn, as was also excluded the proposal to link the body called S*istema Nacional de Revisão Ética das Pesquisas Clínicas* ("National System for Ethical Review of Clinical Research") to Anvisa, maintaining that body directly linked to the Ministry of Health. The elimination of the CEP / Conep System's is still pending , as it is the possibility of weakening or eliminating the progresses achieved with the system, by the extinction of the Conep and the transfer of its responsibilities to the Ministry of Health [29,30].

The bill was approved by the Federal Senate in 2017. Despite the criticism it received, the text was sent to the Chamber of Deputies for analysis, considering that it had undergone changes. The bill continues its process's steps, now under the denomination PL 7.082 / 2017 [31]. According to data from the *Associação Brasileira de Organizações Representativas de Pesquisa Clínica* (Brazilian Association of Organisations Representing Clinical Research -Abracro), in a report from 2016, the regulatory scenario of clinical research in Brazil showed a significant improvement in relation to

the time of analysis by both Conep and Anvisa. In September 2016, for example, the average time of approval by the Conep, including the pending response time, was on average four and a half months. In 2013, the time under review by Conep in some cases reached 322 days, compared to the average time of 81 days in the second quarter of 2016. As for Anvisa, in 2013 the analysis time spent by the agency on average was 342 days and, after the DRC 9/2015, improved to 177 days [32]. The significant reduction in analysis time is due to the efforts made by the Conep and is expected to be even more relevant with the CEP [30] accreditation process.

## Final considerations

Brazil has a well-established ethical and regulatory environment, aligned with universal norms. It is open to reviews, guidance and clarification of the standards themselves. Brazilian regulatory and ethics bodies are constantly improving, with recent revisions of standards, such as the one brought by Resolution CNS 466/2012 and RDC 9/2015. However, they are being pressured both by researchers and by sponsors to make the process for the evaluation of clinical trials more "efficient" with regard to the time of analysis. It should be considered from the foregoing that there was a significant reduction in the time of analysis, around 25% between 2013 and 2016. According to the Conep, this evaluation period is currently less than one quarter.

The search for greater agility in the process of ethical-regulatory review is salutary and beneficial to improve clinical research in the country, aiming at greater competitiveness of Brazil in relation to other countries. However, one should not lose sight of the need to maintain the protection of study volunteers, and improve the process without giving up essential ethical precepts. The set of mechanisms to protect participants, established over the years, was the fruit of many debates in the scientific community - a plural and balanced construction that included researchers, experts, representatives of "users", among other actors of the process.

All this effort should not be ignored or run down by the craving for "speed", which may in some cases only be convenient for the industry. The consideration of the "agility" versus "protection" binomial of volunteers should be valued at this current time of revision of the norms, to bring up the discussion about the cost / benefit of each proposition. However, it should be borne in mind that certain issues need to be treated with rigorous conditions, so that the integrity of the rights of volunteers is not misrepresented by other interests.

The bodies involved can remain open to changes and demands of researchers and society, as demonstrated in this article, which summarises the processes of change of the RDC and resolutions of the CNS. This continuous movement of discussion and improvement aims to ensure the protection of research participants and the speed of analysis processes. However, it should be emphasised that, despite the proclaimed merit that the creation of a law will be the new framework for clinical research in Brazil, in the way it is presented, the law will weaken existing regulatory mechanisms and withdraw from the hands of ethically and technically competent bodies - CNS and Anvisa - the duties of updating standards and safeguarding good practices in all studies carried out in the country.

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Cíntia Maria Lanzarini Gouy wrote the first version of this article, reviewed by Tiago Porto and Carmen Penido. The revisions continued until we reached the final consensual version.

Recebido: 16. 2.2017
Revisado: 14.12.2017
Aprovado: 7. 5.2018