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CLINICAL TRIALS HANDBOOK Americas



BRAZIL

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Brazil

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Introduction

In Brazil, the regulators of clinical trials with legislative attributions are the National Health Council, the Ministry of Health, and the National Health Surveillance Agency (**ANVISA**). The main regulations on clinical trials are: Ordinance No. 2,048 from 3 September 2009, published by the Ministry of Health; Resolution RDC No. 9 from 20 February 2015 and No. 10 from 20 February 2015, both published by ANVISA; and Resolution No. 251 from 23 September 1997 and No. 466 from 12 December 2012, both issued by the National Health Council.

Clinical trials are subject to approval from the Committee for Ethics in Research (**CEP**) and, in certain cases, from the National Committee for Ethics in Research (**CONEP**) and ANVISA.

The institution through which research involving human beings is carried out must have approval from the CEP, an interdisciplinary and independent collegiate body created to defend the interests of the research participants and to contribute to the development of research within ethical standards.

CONEP is an independent collegiate body under the National Health Council. Its main function is the examination of the ethical aspects of clinical trials through the evaluation and follow-up of protocols in thematic areas such as genetics, human reproduction, and storage of biological material or human genetic data abroad. CONEP is also responsible for registering CEPs and for enforcing the duties established by Ordinance No. 2,048 from 3 September 2009 and the rules issued by the National Health Council.

ANVISA is the public entity related to the Ministry of Health that acts for the prevention and reduction of health risks arising from the manufacturing and distribution of goods and services. Within its remit are the approval of clinical trials and the control of importation of products involved in the trial.

Regulatory framework

In Brazil, a clinical trial must be submitted to a CEP for analysis of its ethical aspects. In some cases, the clinical trial must be submitted to CONEP. The research protocol document must be submitted to CONEP or the CEP, and must describe the trial's purpose, organization and substantiation. It must also include information on the research participants, and the qualification of the researchers and all responsible parties. Among the documents to be presented with the research protocol is the Informed Consent Form.

After the protocol is submitted to the CEP/CONEP, an opinion will be issued in one of the following categories:

- **Approved:** The research may commence.
- **With pending action:** The presented protocol must be corrected and requires specific review, modification or relevant information.
- **Not approved**
- **File:** The investigator did not respond to the pending items indicated by the authorities for the approval of the clinical study or the appeal against the decision that denied the study.
- **Suspended:** The approved clinical trial must be interrupted for safety reasons.

- **Withdrawn:** CONEP or the CEP accepts the request made by the responsible investigator justifying the withdrawal of the protocol before its ethical evaluation. In this case, the protocol is considered closed.

If approval is denied, it is possible to appeal to the CEP and/or CONEP within 30 days, but only when a new fact is presented for justifying the review.

In addition to the CEP's or CONEP's approval, ANVISA's approval must also be obtained whenever applicable. The approval process is governed by Resolution RDC No. 9/2015 for clinical trials involving drugs, or by Resolution RDC No. 10/2015 for medical devices.

There is a special procedure to obtain authorization for performing clinical trials with drugs intended for rare diseases,¹ which is Resolution RDC No. 205/2017. Such resolution expedites the approval procedures related to the clinical trial and to the product registration, allowing ANVISA to give its consent to the conduct of the clinical trial independently from CEP's consent.

Although there are different rules for drugs and for medical devices, there are some common requirements for requesting approval of a clinical trial.

The sponsor, the investigator-sponsor or the contract research organization (**CRO**) must submit to ANVISA a dossier containing all necessary documents for the evaluation of the stages of the clinical development. When the clinical trial involves drugs, the dossier will be named "Dossier for Clinical Development of a Drug" (**DDCM**). When the clinical trial involves medical devices, the dossier will be named "Dossier for Clinical Investigation of Medical Devices" (**DICD**).

ANVISA will have 90 days to evaluate the DDCM and DICD.

In both cases, after analyzing the DDCM and DICD, ANVISA will issue a Special Communication, which is an authorizing document used when the importation or exportation of investigational products is required. In some situations, ANVISA may also issue the Specific Special Communication, which is required for the importation or exportation of products in specific situations (e.g., in the case of clinical trials subjected to the notification regime).

The documents needed for the approval of the clinical trial vary depending on whether the investigational product is a drug or a medical device. For instance, evidence of the clinical trial's registration in the WHO International Clinical Trials Registration Platform database or in other databases recognized by the International Committee of Medical Journals Editors is required.

The sponsor has the obligation to monitor all adverse events, including those considered not severe. Data must be properly collected, evaluated and reported to ANVISA in a specific electronic form.

The investigator must inform the sponsor about any severe adverse event within 24 hours of acknowledging the event.

The sponsor must ensure that all relevant information about fatal or life-threatening events are documented and reported to ANVISA within seven calendar days from the date of knowledge of the case.

All other adverse events must be reported to ANVISA within 15 calendar days from the date of knowledge by the sponsor.

Additionally, it will be necessary to submit to ANVISA annual follow-up reports, as well as a final report after the clinical trials' activities are concluded.

For drugs, the sponsor must also submit to ANVISA annually updated reports regarding the safety of the development of the investigational drug.

¹ "Rare disease" is defined as a disease with incidence of up to 65 cases every 100,000 inhabitants.

At any time, ANVISA may inspect clinical trial centers, the sponsor, the CRO, laboratories and other involved institutions in evaluating compliance with the Good Clinical Practices. Depending on the result of the inspection, ANVISA may determine: (i) the temporary suspension of the research; (ii) the definitive cancellation of the research in a specific center; (iii) the definitive cancellation of the research in all centers; or (iv) the annulment of the data received from centers and clinical trials that are not in compliance with the Good Clinical Practices.

Sponsor and contract research organizations

The sponsor is a natural person or legal entity that supports the clinical trial through financing, infrastructure, human resources or institutional resource. The sponsor is also responsible for initiating, managing and controlling the clinical trial.

The sponsor is not required to have head offices or branches in Brazil. Foreign entities will need to engage a CRO that is legally established in Brazil, enrolled in ANVISA, and compliant with all sanitation legislation on the conduct of clinical trials. The CRO will be responsible for performing all obligations of the sponsor in case the sponsor is a foreign company. If the sponsor is a Brazilian company or a foreign company with a local representative, then the obligations may be partially transferred to the CRO and will have to be expressly described in the agreement executed by these parties.

The transfer of obligations by the sponsor to the CRO does not exempt the sponsor from its responsibilities of ensuring the quality and integrity of clinical trial data. The local CRO has a right of recourse against the sponsor and may be indemnified for the amounts paid resulting from any liability.

Investigator

The investigator is the professional responsible for conducting a clinical trial. If the clinical trial is conducted by a group of people, the investigator is the leader of the group and shall be called "main investigator."

The investigator is responsible for: (i) conducting the clinical trial according to the protocol agreed upon with the sponsor, the Good Clinical Practices, and the regulatory and ethical requirements; (ii) personally supervising the clinical trial; (iii) allowing the occurrence of monitoring, audits and inspections; (iv) ensuring medical assistance for the research participants relating to adverse events from the clinical trial; (v) promptly informing the research participants when the clinical trial finishes prematurely or is suspended for any reason; (vi) ensuring proper therapy and assistance for the participants; and (vii) using the investigational products solely in the context of the clinical trial and storing such products according to the sponsor's specifications.

Further, the investigator has the following additional responsibilities:

- Presenting the protocol properly instructed to the CEP or to CONEP, and awaiting decision on ethical approval before initiating the clinical trial
- Preparing the informed consent form
- Developing the project as outlined
- Preparing and presenting partial and final reports
- Presenting data requested by the CEP or CONEP at any moment
- Maintaining clinical trial data in a physical or digital file under its custody and responsibility for a five-year period after the end of the trial

- Forwarding the results of the clinical trial for publishing, with proper credit to the researchers and technical personnel that are part of the project
- Properly justifying before the CEP or CONEP the interruption of the project or the non-publishing of the results

Financing the clinical trial and supply of products to the research participants

The sponsor finances the clinical trial. According to Brazilian legislation, research participants do not pay for the drugs and/or medical devices used in the research process, nor do they receive remuneration for participating in the trials (except for Phase I or bioequivalence clinical trials). Products under investigation shall be provided free of charge by the sponsor.

Brazilian legislation provides that the investigator, the sponsor and the institution are fully liable for any damages, predicted or not, caused to research subjects. The applicable rules do not limit responsibility and/or indemnification. Even if the clinical trial agreement (CTA) has clauses limiting liability, the judiciary may still impose indemnification for all damages caused.

Brazilian legislation states that the research must guarantee that the benefits of the project, such as access to the proceedings, products or research agents, are available to the research participants. It may be concluded that study drugs and/or clinical trials must be provided to the research participants even after termination of the clinical trial. However, regulatory rules do not specify the conditions for that.

Additionally, pursuant to the legal provision above, it could be understood that the sponsor must provide and pay for the necessary medical proceedings in the conduct of the research. This position was recently confirmed by Brazilian judiciary, strengthening the obligation of the sponsor to finance the medical proceedings involved in the research. In other words, it is understood that the participant must receive the benefits of the results achieved by the research that he or she was part of, and they should not be used only as means for achieving the sponsor's objectives.

However, the National Health Council recently approved Resolution CNS No. 563/2017, which regulates the subject's right to post-study access to clinical research protocols intended for patients diagnosed with ultra-rare diseases. According to this regulation, the sponsor must undertake responsibility and guarantee to every subject at the end of the study free access to the best prophylactic, diagnostic and therapeutic methods shown to be effective over five years after its registration before ANVISA. The period will be counted from the issuance of the product registration, or in the case of drugs from the definition of the price before the National Medicines Pricing Commission (CMED). Lastly, Ordinance No. 2,048/2009 requires the investigator to publish the research results with proper credit to the associate researchers and the technical personnel involved in the project.

Intellectual property (IP) and data

The general rule under Law 9279/96 ("IP Law") is that the invention shall be owned by the person (natural person) who developed it.

Conversely, Article 88 of the IP Law provides that the employer will exclusively own the invention resulting from the labor agreement or from an agreement in general that is executed in Brazil, the scope of which is the research or inventive activity. This is also the case when the invention results from the nature of the services for which the employee (or investigator, or anyone who participated in the development of the invention or contributed to the result) was hired.

Article 91 of the IP Law determines that the property of the invention shall be shared equally by the employer and the employee (or investigator) when resulting from the personal contribution of the employee (or the investigator, or anyone who participated in the development of the invention or contributed to the result) and from resources, data, means, materials, installations or equipment of the employer, except where there is a contractual provision to the contrary.

Pursuant to Article 92, the contractor company is generally considered to have employer status for ownership purposes.

Therefore, to avoid any discussion or dispute over the ownership of the inventions or results from a clinical trial, it is advisable to define expressly in the CTA who will own the inventions or results. The agreement should also include clauses regarding the assignment of the inventions, and should share the commercial results to the employee (investigator, or anyone who participated in the development of the invention or contributed to the result), to the contracting company (i.e., the sponsor) or to the rightful owner.

It is important to stress that the general rule pursuant to the Copyright Law ("**Law No. 9610/98**") is that the author (natural person) will own the copyright to the intellectual work he or she has developed. This law does not have provisions about intellectual work ordered or contracted by third parties. If any copyright to the invention or the results of the clinical trial exists for the investigator or whoever developed them, we reiterate our recommendation to specify in the CTA the rightful owner and the assignment of applicable rights.

If the clinical trial involves the participation of public entities, it is advisable to define expressly in the CTA the share of each party in the invention or test results, in order to comply with the applicable rules for technological inventions involving public and private entities.

Even if the Copyright Law confers ownership of the intellectual work or invention to the author, it is important to highlight that Law 10,973/2004 ("**Innovation Law**") allows the sharing of the independent investigator's invention with public or private entities, provided they establish in an agreement the division of economic gains deriving from the industrial exploration of the protected invention. Thus, agreements may be created stating the division of ownership rights over the invention, or stating ownership of the rights in the name of one person, but with division of the financial gains deriving from the industrial exploration of the protected invention.

Investigator-initiated trials are allowed by Brazilian legislation and occur when the investigator does not have the financial support of a specific sponsor, or when it receives study drugs as a donation but the donor does not wish to be characterized as a sponsor for the study. In such cases, the investigator also assumes the responsibilities of the sponsor and is called "investigator-sponsor."

Pharmaceutical companies may support investigator-initiated trials or independent studies, either through the donation of study drugs or through financial resources. In the event of donation of drugs that are not registered in Brazil, the donor will share the sponsor's responsibilities. In the case of donation of registered drugs, the donor will be considered as a sponsor only if study results are transferred to the donor or are of its property.

Finally, it is important to note that Brazilian laws provide special protection against unauthorized use of the results of clinical trials and other undisclosed data submitted to the health authorities as a condition of product approval.

Such protection, often referred to as Data Package Exclusivity, is conferred by Article 39.3 of the WTO TRIPS Agreement, internalized in the Brazilian legislation through Decree 1,355/1994, Article 195 (XIV) of the IP Law and Law 10,603/2002. The latter specifically protects the results of tests or other undisclosed data submitted to the competent authorities as a condition for the approval of pharmaceutical products for veterinary use, fertilizers, pesticides and related products.

There is no legal term of protection for the results of clinical studies and other data relating to the approval of pharmaceutical products for human use. As a result, there is intense jurisprudential debate about the respective term and enforcement of such protection. Decisions confer protection for a 10-year term using, by analogy, the term provided in Law 10,603/2002.



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