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Clinical trials with drugs in Brazil: an analysis of the main characteristics

Ensaios clínicos com medicamentos no Brasil: uma análise das principais características

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ABSTRACT

Introduction: The results of clinical trials (CT) are used by regulatory agencies around the world for the purposes of drug product's registering and marketing. The Brazilian Health Surveillance Agency (Anvisa, in Portuguese) is responsible for the registration of health technologies in Brazil and for creating the rules for the analysis of technical issues in clinical trials. Anvisa has been working to update its regulatory framework regarding clinical trials with drugs in the country, to reduce analysis time and harmonize the normative frame according to international guidelines. **Objective:** To characterize phase III clinical trials, with drug products, conducted in Brazil from the publication of RDC n° 9, *on 20 February* 2015 by Anvisa. **Method:** Exploratory and descriptive study, carried out in three stages: (1) quantitative analysis before and after RDC n° 9/2015; (2) analysis of the population participating in clinical trials that supported medication records; (3) characterization of the clinical trial performed in Brazil. **Results:** There was a 20% reduction in clinical trials conducted in Brazil when compared before and after RDC n° 9/2015 by Anvisa; only 33% of the clinical trials that supported drug product registrations in Brazil were performed with the Brazilian population; synthetic and biological drugs account for 96% of the intervention studied in clinical trials; placebo is still widely used as a comparator (37%); the pharmaceutical industry is mostly the sponsor of the clinical trial (86%). **Conclusions:** In view of this scenario, it is imperative to strengthen pharmacovigilance actions in Brazil, in order to learn about the effectiveness and safety profiles of medicines after exposure of the Brazilian population.

KEYWORDS: Clinical Trial; Legislation; Drug Product; Health Surveillance

RESUMO

Introdução: Os resultados de ensaios clínicos são utilizados pelas agências regulatórias de todo o mundo para fins de registro e comercialização de medicamentos. A Agência Nacional de Vigilância Sanitária (Anvisa) é a responsável pelos registros de tecnologias em saúde no Brasil e regras para análises técnicas de ensaios clínicos. A Anvisa vem atuando para atualizar seu arcabouço regulatório a respeito de ensaios clínicos com medicamentos no país, para reduzir tempo de análise e harmonizar conforme regras internacionais. **Objetivo:** Caracterizar os ensaios clínicos de fase III, com medicamentos, realizados no Brasil a partir da publicação da RDC n° 9, de 20 de fevereiro de 2015, da Anvisa. **Método:** Estudo exploratório e descritivo realizado em três etapas: (1) análise quantitativa pré e pós RDC n° 9/2015; (2) análise da população participante de ensaio clínico que embasou registros de medicamentos; (3) caracterização dos ensaios clínicos realizados no Brasil. **Resultados:** Houve redução em 20% de ensaios clínicos realizados no Brasil quando se compara o período anterior e posterior à publicação da RDC n° 9/2015 da Anvisa; apenas 33% dos ensaios clínicos que embasaram registros de medicamentos no país foram realizados com população brasileira; os medicamentos sintéticos e biológicos somam 96% da intervenção estudada nos ensaios clínicos; placebo ainda é muito utilizado como comparador (37%); a indústria farmacêutica é majoritariamente o patrocinador dos ensaios clínicos (86%). **Conclusões:** Diante deste cenário, é imperativo que se fortaleçam as ações de farmacovigilância no Brasil, a fim de conhecer os perfis de efetividade e segurança dos medicamentos após exposição da população brasileira.

PALAVRAS-CHAVE: Ensaio Clínico; Legislação de Medicamentos; Vigilância Sanitária

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INTRODUCTION

In Brazil, the regulatory framework for the marketing authorization of drugs and other products subject to health surveillance is Federal Law n. 6.360, of September 23, 1976,[1] which deals with medicines, drugs, pharmaceutical and related supplies, cosmetics, sanitizing agents, and other products. This law determines that none of these products, including imported goods, can be manufactured, put for sale or delivered for consumption before receiving the authorization. In addition, especially in the case of drugs, efficacy and safety must be proven through properly designed and approved clinical trials.[1]

Brazil's National Health Surveillance Agency (Anvisa) defines a clinical trial as:

> research conducted with humans with the objective of discovering or confirming the clinical and/or pharmacological effects and/or any other pharmacodynamic effect of the experimental drug and/or identifying any adverse reaction to the experimental drug and/or studying the absorption, distribution, metabolism, and excretion of the experimental drug to check its safety and/or efficacy.[2]

Brazil's legislative framework for clinical research is divided into two main aspects: ethics and technique. In Brazil, information on ethics appeared first, in a context that was highly determined by the global landscape after the second world war. Brazil needed its own ethical rules to prevent its population from being exposed to any recurring harm caused by clinical research. The first time that ethics committees were mentioned in Brazilian legislation was in 1988, when the National Health Council published its Resolution n. 1, in June 13.[3] Resolution n. 196, of October 10, 1996—also of a bioethical nature—revoked the previous document and approved regulatory guidelines and standards for research with human beings. This resolution set out terms and definitions related to clinical research and mentioned the Free and Informed Consent Form (TCLE) for the first time. It provided for the composition, competences, and creation of the National Research Ethics Commission (Conep) and Research Ethics Committees (CEPs), and established research protocols and risk and benefit considerations for clinical trials.[4] In 2012, this Resolution was replaced by Resolution n. 466 of December 12[5] about bioethics, which is currently in force in Brazil.

In this ethical landscape, two fundamental institutions were created: CEPs and Conep. Research institutions may have their own CEP, as long as they follow the rules of Conep. CEPs evaluate research projects and, in some cases, submit the protocols for further analysis by Conep. The main objective of this analysis is to protect research participants, the team, the institution, the society, and the environment.[6]

Conep is a joint review body of an advisory, deliberative, normative, and educational nature.[7] Projects in the following thematic areas require Conep's approval: human genetics, human reproduction, new or unauthorized therapeutic equipment or devices in Brazil, new invasive therapeutic procedures, study with indigenous populations, genetically modified organisms or stem cells or organisms that pose high collective risks, and coordination and/or sponsorship from abroad, except for co-sponsorship by the Brazilian government. If the CEPs deem necessary, they can forward the protocols whose applicant institution is the Ministry of Health or projects that do not have an applicant institution to the Conep (Conep will then appoint a CEP to evaluate the project).[5]

To submit a research project to the CEP/Conep system, applicants have to enter the necessary documents into the Brazil Platform, a computer system that integrates all the participants in the ethical analysis process. This submission via Brazil Platform can be done in parallel with the submission of the clinical trial to Anvisa.

Ever since its inception in 1999, Anvisa has been responsible for the marketing authorization of health technologies in Brazil and also for the rules for the analysis of technical matters in clinical trials. The first Joint Board Resolution (RDC) dealing with this topic was RDC n. 219, of September 20, 2004.[8] It presented the requirements for the design of clinical research dossiers used to obtain the special communication (CE), which is the document needed to import products for the purpose of clinical research.

RDC n. 39, of June 5, 2008[9] revoked RDC n. 219/2004. This regulation set out the rules for approval of clinical research in Brazil and provided information on the documents that had to be submitted to the Agency, the rules for preparing clinical research dossiers, and how to obtain a CE.

This Resolution was revoked by the current standard of clinical research with drugs in Brazil made by Anvisa: RDC n. 9, of February 20, 2015.[2]

RDC n. 9/2015[2] updated the regulatory framework for clinical trials with drugs in the country. Its objective was to reduce the time of analysis of applications and to have a more similar approach to that of other regulatory agencies, so as to encourage more clinical trials in Brazil.[10] This legislation is aimed at clinical trials with drugs that will have all or part of their clinical development in Brazil for the purposes of marketing authorization. In addition, clinical trials with drugs that have marketing authorization in Brazil must follow all the provisions of this Resolution when providing complementary information on: new therapeutic indication, new route of administration, new concentration, new pharmaceutical form, expanded use, new dosing, new associations or any other post-approval change that requires clinical data, including marketing authorization renewal.

Having more studies conducted in Brazil would provide data on the efficacy and safety of specific drugs in this particular

population.[3] Although Anvisa has adopted this measure, its standards that regulate the marketing authorization of drugs allow the submission of clinical studies carried out in other countries, according to specific rules.[11,12,13,14,15] However, the external validity of a clinical trial—which is its ability to generalize data to the general population—may be affected by the characteristics of the population under study, like pharmacogenomic differences, different underlying diseases, pharmacoepidemiological profile, and even eating habits.[16]

An example of these pharmacogenomic differences is the fact that paracetamol has greater hepatotoxicity among African-Americans. Also, Caucasians face less liver toxicity when using isoniazid, but higher toxicity when taking warfarin and higher risks of hypoglycemia with glibenclamide. Western Jews, in turn, may have long lasting muscle paralysis with suxamethonium.[17] Moreover, the clinical efficacy of antihypertensive drugs and the initial response to oral anticoagulants were lower among black populations.[18,19]

Responses to drugs can also be affected by extrinsic factors, like climate, pollution, culture, medical practices, and use of different drugs in different countries. According to guideline E5 - Ethnic Factors In The Acceptability of Foreign Clinical Data, of the International Conference on Harmonization (ICH), an organization that deals with the harmonization of regulatory practices among signatory countries, intrinsic factors have to be assessed among different populations because that will determine whether or not we can derive any generalization from clinical studies, whereas extrinsic factors affect the design and conduct of clinical research.[20] Another relevant guideline, also issued by ICH, to which Brazil is a signatory, is E17 - General Principles For Planning and Design of Multi-Regional Clinical Trials. This document provides the basic instructions that have to be followed in multi-regional clinical trials, that is, trials conducted in various countries.[21]

Another relevant point, in this context, is the current migration of clinical trials from developed countries to low- and middle-income countries, or those with emerging economies. Drain et al.[22] published a study in 2018 showing the 20 countries that had the highest growth rates in the number of clinical trials conducted locally between 2006 and 2012. Brazil is not in this ranking, but other Latin American countries, like Colombia, Venezuela and Panama, are. This lack of substantial growth in Brazil when compared to other Latin American countries should be discussed and the reasons for that have to be identified.

In this sense, amending the framework of Brazilian health legislation to encourage more clinical trials with our population can help inform decision-making processes involved in the marketing authorization of products and support the design of a suitable risk management plan. This plan lists the main risks and critical points of the research and presents suggestions for their mitigation.

All of these normative, ethical, and technical updates reflect the Brazilian effort to increase the country's participation in the world landscape of clinical trials. The publication of RDC n. 9/2015[2] was an important legal landmark that pervades this entire study, whose objective was to characterize phase 3 clinical trials conducted in Brazil based on the publication of the said standard, evaluating the country's progress from a global perspective.

METHOD

This is an exploratory and descriptive study carried out in three stages. In the first, in order to identify changes in the number of clinical trials with drugs conducted in Brazil since the publication of RDC n. 9/2015,[2] we performed a quantitative analysis comparing two moments: before and after the enactment of the current standard that deals with clinical research with drugs in Brazil. In order to determine the evaluation period, we estimated the number of days between the enactment of the standard (March 3, 2015) and the closing date of this study (November 25, 2019), that is, 1,728 days. To make sure we assessed the same number of days before and after the enactment of the resolution, we also considered the period between June 9, 2010 and March 2, 2015. In addition to the evaluation period, the following filters were used in the search: *Interventional Studies | Brazil | Phase 3*.

In the second stage, we analyzed all the marketing authorizations granted by Anvisa that also had a Public Opinion on Drug Assessment (PPAM). We considered the period from the establishment of the database in 2015 until the date of completion of the first phase of this study (November 25, 2019), in order to verify whether or not the approvals were supported by studies done with the Brazilian population. We chose to analyze the PPAM in this study because these documents have detailed information about the marketing authorization of the drug, which, in turn, enabled us to learn whether or not the authorization was based on international studies, for example. In addition, the PPAM implementation date was contemporary with that of RDC n. 09/2015,[2] the target of this study.

In the third and last stage, we analyzed all the characteristics of the clinical trials that were carried out after the enactment of RDC n. 9/2015[2] and registered in the Clinicaltrials.gov international database and in the Brazilian database of clinical trials (ReBEC).

The Clinicaltrials.gov database was chosen for this analysis because it is one of the largest repositories of clinical studies and has very comprehensive research fields. Although it is not the most comprehensive database of clinical trials (compared to the International Clinical Trials Registry Platform - ICTRP), it is a fairly complete and easy to search database.[23]

The studies found in both databases were considered only once for this study. For this purpose, the following filters were applied: *Recruiting*, *Active*, *not recruiting*, *Completed*, *Enrolling by invitation*, *Suspended*, *Terminated*, *Withdrawn Studies | Interventional Studies | Brazil | Phase* 3 *Start date from* 3/3/2015 *to* 11/25/2019. With the aforementioned filters, only studies with an arm in Brazil, phase III, within the defined

period, and with the described parameters, were found on the platform. The following filters were not applied: *recruitment not started*, because it was not possible to know whether the recruitment would be authorized, and *undefined status*, because studies without a defined status could have misleading data. Only phase III studies were included, as they are usually the final phase of mandatory clinical analysis before marketing authorization.[11,12,13,14,15] Since the objective is to make an assessment of the status of the records associated with clinical trials, the focus was on this phase. The main characteristics of these studies were considered, including intervention, comparator, intervention type (synthetic, biological, specific, herbal medicine, among others), sponsor and type of sponsor (pharmaceutical company, philanthropy, university research, and development agencies). To classify the sponsors, we did a search on the website of the institution cited as sponsor.

The calculation basis for this analysis was the use of numerical proportions. The sample was considered as 100%, and the sum for each analysis was calculated in relation to the total.

Since the study uses publicly accessible data without identifying the participants, the project did not need to be submitted to the Human Research Ethics Committee.

RESULTS AND DISCUSSION

RDC n. 9/2015,[5] the regulatory framework that is the object of this study, has reduced some of the bureaucracy in the analysis of clinical research, with measures like a shorter protocol analysis time (90 days), with a few exceptions; simultaneous analysis with ethical regulatory bodies; and a streamlined document format to be submitted to Anvisa, the Clinical Drug Development Dossier (DDCM), which is similar to the formats used by other countries.

In the first stage of the study, we observed that the total of phase III clinical trials conducted in Brazil in the pre-RDC period was 653 clinical trials. After the enactment of the RDC, there were 525, a 20% decrease, which suggests that just the mere publication of the standard was not enough to attract research to the country. The clinical development of a drug is divided into four phases, mainly. In phase I, the drug is tested on healthy volunteers to assess its safety. Phase II is a pilot study of efficacy and safety with the target population of the treatment. Phase III is a study with a much larger number of participants and is considered the gold standard for interventional studies. Phase IV is the analysis of the drug after approval, in real life.[24]

Brazil has strengths and weaknesses for conducting clinical trials locally. The main strength is easy recruitment, whereas the main weakness is the long time it takes for studies to receive regulatory approval. This bureaucracy hinders further studies in the country and eventually encourages marketing authorization strategies without clinical research in Brazil.[25] Thus, despite the change in its legislative framework, Brazil still struggles to play a more prominent role in global clinical research. This difficulty reveals that the new legislation has not yet had the expected impact.

There are several reasons for choosing to carry out clinical trials in developing countries instead of developed countries. Some stand out, like populations with lower income and education levels that are more likely to consent with participation in these trials; poor local healthcare, which makes the population more eager for other treatments; the possibility of collecting larger samples for the study; and the opportunity to open a new market for the pharmaceutical company.[26] However, the results suggest that there are still other obstacles for Brazil to become one of the sponsors' locations of choice for clinical trials.

The absence of Brazilian guidelines on Good Clinical Practice, for example, was a gap in Brazilian legislation until 2008, when Anvisa incorporated the Document of the Americas on Good Clinical Practice.[9] In November 2019, the Agency had the ICH Harmonized Guide - Addendum integrated to ICH e6 (r1): Good Clinical Practice Guide E6 (r2)[27] translated into Portuguese. That is an international standard of ethics and scientific quality for designing, conducting, recording, and reporting trials involving the participation of human beings. According to the publication, compliance with this standard offers public assurance that the rights, safety, and well-being of trial participants are protected—in line with the principles from the Declaration of Helsinki—and that the clinical trial data have credibility.

Shenoy[28] analyzed the global rules for multicentric studies and his findings reinforced the importance of minimum worldwide quality requirements for a clinical study to be conducted. These minimum requirements included analysis of intrinsic and extrinsic differences, analysis of differences in basic therapies, harmonization of good clinical practices, randomization considering population variability, among others. The definition of these quality criteria can enable more harmonious multicentric clinical research, making the whole process more predictable and less costly. Consequently, this could attract more studies to Brazil. On the other hand, it tends to harmonize the process between countries, encouraging clinical studies carried out in different nations to serve as a basis for the marketing authorization of drugs in other countries, since carrying out studies in all countries of commercial interest is unfeasible both in terms of cost and time.[29]

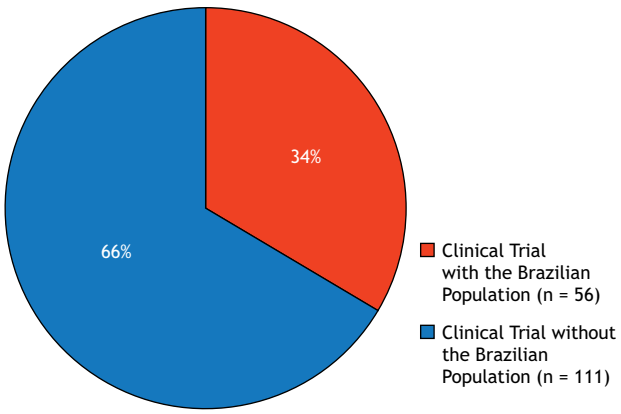
With that in mind, the second stage of this study analyzed the drug marketing authorizations in Brazil in the period after RDC n. 9/2015[2], published via PPAM. Of the 295 authorizations found in the search period, 115 were for generic drugs, 86 for biologicals, 74 for new, six for similar, 13 for specific, and one for a herbal medicine. It is important to mention that drugs classified as generic and similar (n = 121) are exempt from clinical research for marketing authorization, since their safety and efficacy have been proven by bioequivalence studies.[15] In addition, specific medicines and herbal medicines can also be proven safe and effective by other means, like traditional use or scientific

literature.[12,13] This study found that three drugs in the class of specific medicines and one herbal medicine were authorized without clinical research. For three biological products, that information was not available.

Afterward, we evaluated the populations that warranted the marketing authorization of 167 remaining drugs, and only 56 (34%) of them had been approved in Brazil based on clinical research done with Brazilians (Figure 1). For two drugs, that information was not available.

This result may be related to Brazil's low attractiveness to clinical trials, as seen in the first stage, since most of the drugs that were granted marketing authorization in Brazil had their clinical studies carried out abroad. If Brazil were an attractive country for clinical trials, one would expect that most of the drugs authorized in the country would be based on studies with the Brazilian population to decrease the chances of rejection on the grounds of pharmacogenomic problems. Alvarenga and Martins[30] found that emerging countries were the main destination of clinical trials. Adobor[31] reinforced this finding, stating that emerging countries, with their also emerging markets, are considered a reference for hosting new clinical trials. Additionally, that study observed that there is no particular preference for some countries over others, and that Brazil could be included in multicenter studies due to its ease of recruitment.

A study done by Brazil's National Bank for Economic and Social Development (BNDES) presented further information on the main challenges and benefits of clinical trials in Brazil. It addressed the topic of drug marketing authorization with international clinical trials in other countries and in Brazil. In the country, this is common practice and there is no specific recommendation that studies be carried out in a portion of the Brazilian population, as recommended in other countries,[25] which may explain the findings of this stage of the present study.



Source: Prepared by the authors based on the data collected via Public Opinion on Drug Assessment (PPAM), 2020.

Figure 1. Comparison of drug marketing authorizations in Brazil regarding clinical trials in Brazil (n = 167).

A market research report published by the Association of the Pharmaceutical Research Industry (Interfarma), entitled The Importance of Clinical Research for Brazil,[31] stated that Brazil ranks 24th in the global ranking of clinical research, with only 2.1% of the trials. According to the authors, these data show that Brazil dropped seven places in ten years. They also stated that if Brazil's potential were better harnessed, the country could leap to 10th place, attracting an estimated investment of BRL 2 billion, with overall effects on the economy of about BRL 5 billion. This drop in the global ranking is a result of the government's low investment in technology and understaffed regulatory bodies. Moreover, the lack of harmonization of ethical requirements remains an obstacle.[32]

Conducting clinical studies in countries other than those where the applicant intends to receive marketing authorization is a topic that sparks extensive discussion. Gorski[33] stated that many patients are harmed every day because they do not have access to new, effective, and safe drugs that are already available in other countries. One reason for this is that regulatory agencies that are presented with clinical studies conducted in other countries tend to be more rigorous and sometimes even demand new local studies. However, the arbitrary rejection of these studies is criticized, since it could lead to drug shortage, although it could also be a great opportunity to enhance the communication between several regulatory agencies in the world.

In 2009, the European Medicines Agency (EMA) published some thoughts on the extrapolation of international clinical data to the European population. The document reported that international studies can be accepted in the marketing authorization application, however, a case-by-case analysis is necessary to assess whether or not the study addresses intrinsic and extrinsic characteristics that match those of Europeans.[34] In an attempt to improve the analysis of studies carried out in other countries, the US Food and Drug Administration (FDA) opened offices in other countries and increased international inspections.[35] The high variability between populations makes regulatory agencies insecure. Other regulatory agencies, like those from South Korea, India, and Taiwan, request that the drug has been tested on at least part of their populations before it is authorized in their countries.[25]

Brazil is very particular case because its population is considered tri-hybrid, that is, descendants of Africans, Europeans, and Amerindians. In this sense, selecting a portion of a certain ethnicity may not be genetically representative of the population as a whole, which makes additional mechanisms for monitoring the use of the drug in the country necessary.[36] Studies are being carried out to apply genomic analysis programs and statistics to assess the heterogeneity of the Brazilian population and its possible implications for decisions that affect regulatory control.[37]

Furthermore, there is a difference between genetics and ethnicity. Genetics is related to people's physical characteristics, like skin color, metabolic pathways, facial aspects, among others,

whereas ethnicity refers more to cultural aspects, like religion, education, and eating habits. In clinical research, genetics influences pharmacogenomic aspects of drug response, while ethnicity influences whether or not to participate in the study. In view of this, there is a clear need to include populations from several countries in studies aimed at receiving marketing authorization in the world.[38]

To identify the main characteristics of clinical trials carried out in Brazil after the enactment of RDC n. 9/2015,[2] these studies were fully screened (step 3). Between the enactment of that RDC and the closing date of this research, we found 525 studies conducted in Brazil, of which 33 were excluded: three because they were duplicated, 29 because they had no drug intervention and one because it was a phase 2 study. Thus, the characteristics of 492 studies were analyzed.

Regarding the classes of drugs used in these clinical trials, we noticed that the most studied classes were synthetic (n = 269; 55%) and biological (n = 203; 41%) drugs, accounting for 479 studies of the 492 we analyzed (97%) (Figure 2).

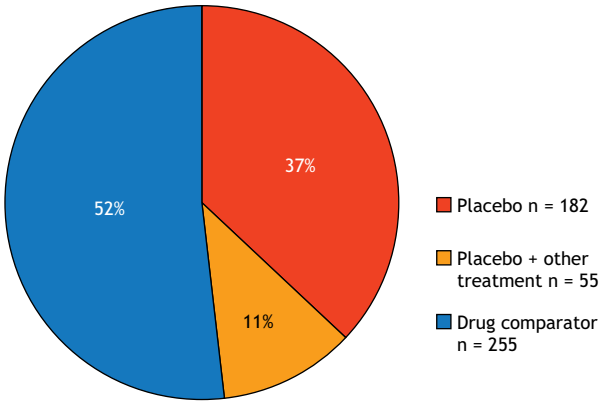
The results shown in Figure 2 were expected, considering that Anvisa requires proof of efficacy and safety, irreplaceably, for drugs in the categories of synthetics (new/innovative) and biologicals. The areas in which there is more investment in clinical research worldwide are oncology and central nervous system, which have a large amount of biological and synthetic drugs, respectively, in addition to genetic therapies that are on the rise.[32]

Another characteristic we analyzed in the clinical studies carried out in Brazil was the comparator chosen for the design: whether the studied therapies were compared with placebo or with another drug indicated for the same disease. We noticed that there is still a widespread use of placebo as the only comparator (n = 182; 37%) (Figure 3). This should be treated with caution, with focus on the justification for the exclusive use of placebo.

Finally, there must be extreme rigor in the ethical analysis for approval of clinical trial designs that use placebo as the comparator, in order to protect the rights, safety, and well-being of research participants. In Brazil, this analysis is the responsibility of the CEP/Conep system, based on Resolution n. 466/2012 of the National Health Council (CNS).[39]

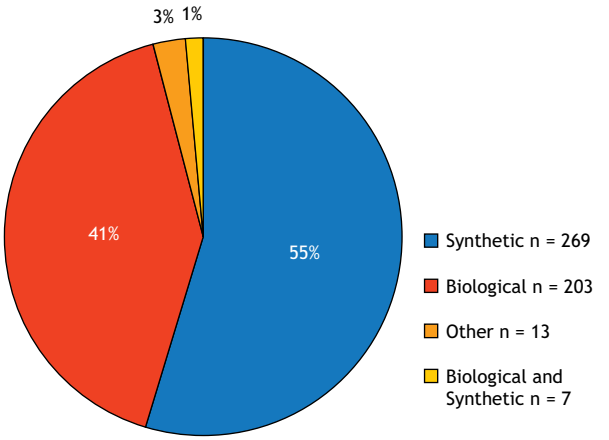
The type of funding of the clinical trials is also important and should be analyzed, since studies can be funded by the pharmaceutical companies that manufacture the drugs or by research and development institutions, in a non-profit manner. In the Brazilian context, we identified that the vast majority of studies are sponsored by pharmaceutical companies (n = 431; 88%) (Figure 4).

Considering the other characteristics of the studies carried out in Brazil, we observed that the pharmaceutical industry is the main sponsor of studies. Another Brazilian study[40] corroborates these findings. The authors concluded that, in general, clinical trials conducted in Brazil are marked by a strong influence of the



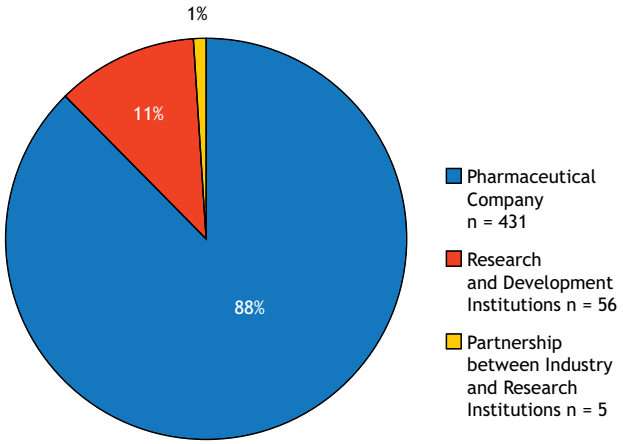
Source: Prepared by the authors based on data from clinicaltrials.com, 2020.

Figure 3. Comparison of clinical trials conducted in Brazil in relation to the chosen comparator (n = 492).



Source: Prepared by the authors based on data from clinicaltrials.com, 2020.

Figure 2. Comparison of clinical trials conducted in Brazil by drug classification (n = 492).



Source: Prepared by the authors based on data from clinicaltrials.com, 2020.

Figure 4. Comparison of clinical trials conducted in Brazil in relation to the sponsor (n = 492).

market, with private funding and projects that are mere extensions of research originating in other countries.

After analyzing the three stages of this study, we found that a significant number of drugs have been authorized in Brazil based on studies in foreign populations, using placebo as the comparator, and sponsored by pharmaceutical companies. This increases the need to prioritize and strengthen pharmacovigilance initiatives in the country to ensure that the monitoring of real-life use of authorized products generates safety and efficacy data in the Brazilian population, with analysis of its intrinsic and extrinsic factors.

This seems to be the best solution because requiring mandatory local clinical studies for the authorization of pharmaceutical products in Brazil would probably make the country even less attractive for this type of activity. The result would be fewer authorized products available, since pharmaceutical companies or organizations sponsoring a clinical trial tend to choose countries with fast recruitment, good infrastructure, lower costs, trained workforce, and a steady ethical-regulatory environment.[25]

Clinical studies remain concentrated in developed countries. This is because these countries have larger numbers of skilled professionals to work in the clinical research area, which requires great intellectual involvement.[41] Therefore, changing the regulatory framework to ease some deadlines and enable harmonization with international entities is necessary but may not be enough. Greater investment is needed in this area with the objective of creating good expertise and qualified professionals, which can eventually lead to the general improvement of this situation in Brazil.

It is important to remember the limitation that this study did not use the ICTRP database, since searches in this database were not feasible. With this, some studies carried out in Brazil may have been disregarded because we only used ClinicalTrials.gov and Rebec.

This study focused on research based on dates only, so no term of Medical Subject Headings (Mesh) or Health Sciences Descriptors (Decs) was used, and all the studies found in the search by date were considered for the analysis.

The clinical trials included in this manuscript were not categorized according to the International Statistical Classification of Diseases and Related Health Problems (ICD). This is because the classification of treatments was performed with a focus on the regulatory framework of the studied drug. Preference was given to this type of classification, considering the regulatory focus of this study.

CONCLUSIONS

This study found that the attempt to make the regulation of clinical trials more attractive in Brazil does not seem to have been sufficient, since there was a reduction in clinical trials after the publication of RDC n. 9/2015[2] by Anvisa. Among the registered clinical trials, placebo is still widely used as the comparator and the Brazilian population is present in only a minority of studies. Finally, in view of this situation, it is imperative to strengthen pharmacovigilance actions in Brazil in order to understand the effectiveness and safety profiles of drugs after their use in the Brazilian population.

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Authors' Contribution

Silva JCRA - Conception, planning (study design), data acquisition, analysis and interpretation, and writing of the manuscript. Silva DLM - Conception, planning (study design) and writing of the manuscript. Capucho HC, Santana RS - Data acquisition, analysis, interpretation, and writing of the manuscript. Farinasso CM - Writing of the manuscript. All authors approved the final draft of the manuscript.

Conflict of Interest

Authors have no potential conflict of interest to declare, related to this study's political or financial peers and institutions.

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