Clinical research from the perspective of integrity

Anamaria Gonçalves dos Santos Feijó [1], *Anelise Crippa* [2], *Andressa Daron Giordani* [3], *Natália Moreira Vieira* [4], *Carlos Isaia Filho* [5]

Abstract

All publications resulting from scientific research require compliance to ethical standards that characterize investigators' appropriate conduct, which translates into integrity in research. However, there is a distinct research modality known as "clinical research", which has been seeking to act with integrity in order to strengthen the basis of its activities carried out for the benefit of society as a whole. The purpose of this work was to identify the people involved in this process as well as their intended and actual role in the modern scenario. The search for and the discovery of new drugs will benefit the entire community, provided that public health policies are efficient – thereby standardizing people's access to those discoveries. Therefore, the concept of integrity in research must expand its horizons in order to also encompass clinical research, in which participants must be guided and charged to apply good practices in the various stages of research development, which will allow for comprehensive and successful research.

Keywords: Ethics research. Clinical trial. Legislation as topic. Human rights.

Resumo

Pesquisa clínica sob a ótica da integridade

Toda publicação advinda de pesquisa científica exige respeito aos padrões de ética que caracterizam a adequada conduta do investigador, o que se traduz em integridade na pesquisa. Porém, há distinta modalidade de pesquisa, conhecida como "pesquisa clínica", que vem buscando atuar de maneira íntegra visando fortalecer a base de seu agir em prol da sociedade em geral. A caracterização dos envolvidos e sua função ideal e real no cenário moderno foi o objetivo deste trabalho. A busca e descoberta de novas drogas beneficiarão toda coletividade, se as políticas de saúde pública forem eficazes, normatizando o acesso da população a essas descobertas. A integridade na pesquisa, portanto, precisa ampliar seus horizontes para abarcar também a pesquisa clínica, cujos partícipes devem ser orientados e cobrados quanto à boa prática nas diversas etapas de desenvolvimento do estudo, o que permitirá íntegra e exitosa investigação.

Palavras-chave: Ética em pesquisa. Ensaio clínico. Legislação como assunto. Direitos humanos.

Resumen

La investigación clínica desde la perspectiva de la integridad

Toda publicación resultante de la investigación científica debe respetar las normas éticas que caracterizan la adecuada conducta del investigador, lo cual se traduce en integridad en la investigación. Sin embargo, hay una modalidad distinta de investigación, conocida como "investigación clínica", que busca actuar de manera íntegra con el fin de fortalecer la base de su accionar para la sociedad en general. El objetivo de este trabajo fue la caracterización de los involucrados y su función ideal y real en el escenario moderno. La búsqueda y el descubrimiento de nuevas drogas beneficiarán a toda la colectividad, si las políticas de salud pública lograran ser eficaces, regulando el acceso de la población a estos descubrimientos. La integridad en la investigación, por lo tanto, necesita ampliar sus horizontes para abarcar también la investigación clínica, cuyos participantes deben estar orientados y advertidos en cuanto a la buena práctica en las diversas etapas de desarrollo del estudio, lo que permitirá una investigación íntegra y exitosa.

Palabras clave: Ética en investigación. Ensayo clínico. Legislación como asunto. Derechos humanos.

1. Doutora agsfeijo@isaia.com.br – Unidade de Pesquisa Clínica do Centro de Medicina Reprodutiva Dr. Carlos Isaia Filho **2. Doutora** anecrippa@gmail.com – Faculdade Cenecista de Osório (Facos), Osório/RS **3. Graduada** andressa@isaia.com.br – Unidade de Pesquisa Clínica do Centro de Medicina Reprodutiva Dr. Carlos Isaia Filho **4. Mestre** natalia@isaia.com.br – Unidade de Pesquisa Clínica do Centro de Medicina Reprodutiva Dr. Carlos Isaia Filho **5. Doutor** isaia@isaia.com.br – Unidade de Pesquisa Clínica do Centro de Medicina Reprodutiva Dr. Carlos Isaia Filho, Porto Alegre/RS, Brasil.

Correspondência
Anamaria Gonçalves dos Santos Feijó – Rua Padre Chagas, 66, conjunto 704, Moinhos de Vento CEP 90570-080. Porto Alegre/RS, Brasil.

Declaram não haver conflito de interesse.

Every publication coming from scientific research demands respect for the so-called "ethical standards" that should characterize the proper conduct of the investigator. The truthfulness and the non-fragmentation of the data, as well as the care regarding the correct indication of the authors, the lack of benefit to the investigators, the lack of plagiarism or self-plagiarism, among others, are factors that establish the ethically correct limits for the research to be considered to have integrity [1].

The lack of veracity of the data is characterized by fraudulent manipulation, aiming to achieve more convincing and, consequently, more interesting results, creating a greater chance of publication of the findings in a high impact journal. The division of a single research in several publications, the so-called "fragmentation of research", is another behavior that has been criticized and rejected by the scientific community [2].

Another matter pertinent to the topic "integrity in research" is the adequate identification of the authors. Garcia et al [3] remind us that being the author of an article or similar presupposes, more than just a legal right, but also a moral right of that author regarding that specific work, which must be respected. Working collaboratively in research may characterize co-authorship when physical and intellectual resources are shared, and this collaboration must be rigorously acknowledged [4]. There are cases, however, where authorship includes the names of persons who did not participate in the research, or omits the names of those that, in some way, contributed to the research [5], characterizing a serious ethical problem.

In order to minimize such misconduct, organizations such as the International Committee of Medical Journal Editors have already established criteria for authoring publications, with the objective of guiding authors and editors regarding this important issue. To be considered an author, the investigator needs to: 1) have contributed substantially to the elaboration and planning of the research, and to the collection or analysis and interpretation of the findings; 2) have drafted the article or made an important critical review; 3) have approved its final version [6].

It is equally essential that any conflict of interest - that is, when there is any relationship of interest between the investigator, or the institution or sponsor giving support to the research and the research itself - is always mentioned [7]. It also refers to those conflicts of interest that are described in the professional codes of ethics, which need to be respected by the different categories [8]. These conflicts of interest, if not duly mentioned, will certainly hinder the research undertaken, generating society's distrust towards the results obtained and disseminated [9].

Hank ten Have [10] argues that the first response to this problem should be transparency. The author affirms that the self-reporting solution to the conflict of interests is extremely limited since, being voluntary and there being no sanctions for not doing so, it will depend on the willingness of the investigators to report the situation [10]. Public doubt about the interests of investigators, prioritized to the detriment of what society asks for and needs, raises the question of fairness in relation to the benefits gained by those who do research [11]. In the investigation of new drugs, this matter needs to be clearly defined, since society will have many questions regarding the financial interests of the industry.

Plagiarism is the most common problem regarding integrity in research in the scientific community. The diverse and increasingly available technological tools allow access to third-party works without proper reference to the authors. This refers to the partial or total copying of texts written by others where, as Sanchez [12] points out, there is misappropriation of other people's ideas without reference to the proper source or correct credit being given to the author of the publication.

Another procedure, also considered inappropriate, is what is called "self-plagiarism". This would be the reproduction as something unpublished of something that was previously written by the author and produced in other publications [13]. There are publishers that agree to publish books that include some chapters that reproduce something that the same author has published previously, but it is necessary that this fact be well emphasized so as not to constitute self-plagiarism, but rather the reproduction of the same ideas or conclusions in another form of publication. In this case, the author must reference the original publication of the reproduced excerpt.

The situations described point out ethically incorrect attitudes whose occurrence many national and international universities are attempting to minimize starting with the investigator's training as a student. The search for integrity in research is the focus of the scientific community.

However, there is a distinct modality of research, known as clinical research, which has

been seeking to act with integrity in order to strengthen the basis of its action in favor of society as a whole. Each investigator must act within rigid methodological criteria, and their identification, as well as their ideal and real function in this scenario is an issue of unquestionable importance. However, this issue is still discussed very little in Brazil, thereby justifying this publication.

Addressing clinical research

What is clinical research?

The term "clinical research", so commonly used in the health and pharmaceutical fields, does not really have a formal legal or scientific definition. Important national documents seek to characterize the research, without, however, specifying the clinical trial. The Resolução 466/2012 [Resolution 466/2012] of the Brazilian National Health Council, for example, considers research as *a formal and systematic process aimed at producing, advancing knowledge and/or obtaining answers to problems through the use of a scientific method* [14]. Moreover, it clarifies research involving human beings as individual or collective research that includes the management of participants' data, biological materials or information [14].

The Good Clinical Practice (GCP) [15] document, published in 1996, ensures the safety, rights and well-being of study participants, setting the international standard for ethical and scientific excellence. It states that the terms "clinical trial" and "clinical study" are synonymous but do not allude to specific clinical research terminology. Clinical trial is indicated in the document "Good Clinical Practice: Document of the Americas", proposed at the IV Pan American Conference on Drug regulatory Harmonization on March 2005, as *a systematic study of drugs and/or medicinal specialties in human volunteers that strictly follows the guidelines of the scientific method* [16].

In fact, it is perceived that clinical research has been used as a synonym of clinical trial, and so we will use it in the course of this presentation.

What is the purpose of clinical research?

The objectives of clinical research, according to the "Document of the Americas" [16], would be to seek to know or to effectively confirm effects and identify adverse events of the investigated product, as well as to determine their effectiveness and safety by studying the pharmacokinetics of their active ingredients in controlled trials. These tests need to be conducted on humans so that, once their efficacy and safety are confirmed, the product's registration can be authorized by the competent authorities and thus be marketed as a new drug or new indication.

The well-known precautionary principle applies here, since the adequate use and the foreseeable consequence of science and technology appear, also in this context, as a way to guide ethically appropriate attitudes, avoiding abuses as they often happen and are reported in the written, spoken and televised press [17].

As Bergel [18] points out, nowadays one cannot speak of the right to health or life without addressing the right for access to medicines. The theme "access to medicines" is very broad and brings with it special conditions: adequate level of user information, drugs offered at reasonable cost, drugs available timeously to exercise their therapeutic function, quality drugs researched according to strict regulations that assure their safety and effectiveness.

In order to achieve these objectives, scientific and ethical solidity is required in the conduct of these clinical trials. This solidity also includes the keeping of the data obtained during the investigation, which can be confirmed at any time by regulatory agencies [16].

It is important to emphasize that the drug is the result of the combination of information and context in relation to a specific product [19]. Humet [20] also argues that medicines are essential goods, as they assist in controlling many infectious diseases, combating pain and other ailments, improving individuals' quality of life.

Therefore, when talking about research aimed at producing a drug to be made available to a particular society, we are actually talking about politics, because access to this drug should always be discussed within the scope of collective health. *The Universal Declaration on Bioethics and Human Rights* [21] already stands for defending access to every medicine considered essential.

Documents that guide clinical research

Nuremberg Code

After the end of World War II, the atrocities committed against human beings led the great nations to propose, at the International Military Tribunal, in Nuremberg in 1946, the famous Nuremberg Code [22]. The document established basic

 http://dx.doi.org/10.1590/1983-80422018262237

standards of human research, emphasizing voluntary consent and valuing autonomy regarding what concerns scientific investigation. It aimed, then, at the cessation of what countries called the heinous crimes against humanity that occurred at the time of the Holocaust.

The document emphasized that the subjects' voluntary consent was absolutely essential for their participation in any research, and stressed the importance of the risk and benefit analysis of any research to be performed on human beings. In addition, it required that consent to participate in research be provided by persons legally able to do so, thereby protecting vulnerable individuals. This document sowed the idea of caring for those in vulnerable situations, as well as respecting those who participate in scientific research.

Declaration of Helsinki

The Declaration of Helsinki [23] is a document prepared by the World Medical Association in 1964 in Helsinki, Finland. This declaration is, in fact, the first and unprecedented effort of the world medical community to establish indispensable criteria to be followed in biomedical research. Based on the principles established in the Nuremberg Code, the Declaration became an international standard of conduct in this field. This document focuses on the priority of human well-being over science and society, as well as the caveat regarding the importance of free consent to be given by research participants.

In the area of clinical research, in which international multicenter trials are common, these patterns of conduct help in standardizing the steps to be followed based on the protocol. Even today, the Declaration of Helsinki is considered to be *the most influential set of principles governing medical research involving human subjects* [24] and has had seven revisions, since certain aspects required adaptations to the current context in which social, cultural, and even research patterns have undergone transformations.

It is important to note that Brazil is no longer a signatory to the Declaration of Helsinki, because our representatives strongly disagree with the way in which the document presents criteria both for access to the analyzed product after the study and for the use of placebos [25].

Regarding access to the drug researched after the conclusion of the clinical trial, there are controversies in the scientific community. Dainesi and Goldbaum [26] argue that the responsibility for supplying the drug investigated after the research should be analyzed on a case-by-case basis, since at the end of this research the drug tested is still experimental and must undergo safety and efficacy assessments. The Universal Declaration on Bioethics and Human Rights [21], in its article 15, emphasizes that benefits from scientific research must be shared with society, highlighting the importance of this act of sharing with developing countries. However, this document speaks of benefits in general and it is not possible, at this point of the clinical research, to dissociate risk from benefit.

Experimental medication used prematurely may present risks not yet known and not fully studied [27]. There are studies - such as that of Sofaer et al. [24], which presented clinical research performed with participants from the United States (USA) - that resulted in the almost unanimous opinion of the respondents regarding the obligation of investigators to provide information on research results at the end of the study. But there was no consensus on the availability of the drug tested at the end of the clinical investigation.

The *double standard* is another nephralgic point in the relationship between Brazil and *Helsinki*. There is awareness of the requirement to test an experimental drug with a placebo when there is no equivalent effective drug on the market. However, as pointed out by Schülklenk and Hare [28], from the point of view of ethics, a study could only be considered ethically correct if all participants had access to the trial drug or an equivalent medication already marketed, since the risk would be equally divided among all the participants.

However, the register of reference medicines varies between developed and developing countries, and therefore participants from the latter will not always have access to the drug considered as the gold standard. Therefore, similar research can be designed differently in different countries (trial drug vs. reference medication and trial drug vs. placebo), which has been considered unfair by many.

Belmont Report

The existence of the Declaration of Helsinki was not sufficient to curb abuses in research involving human beings, such as the research on syphilis in Tuskegee, Alabama (USA) [29]. The identification of these ethically unsuitable actions in US territory prompted the American Congress to appoint an official commission to determine the principles that

should guide the country's research, leading to the so-called Belmont Report [30].

Published in 1978, this report emphasized three basic principles that should be taken into account when dealing with research involving human beings [15]: 1) respect, which encompassed both respect for the person's autonomy and care for those who had their autonomy diminished; 2) beneficence, which advocated not to harm and minimize risks, maximizing benefits; and 3) justice, which advocated equal treatment for all. According to Clotet and Feijó [17], this document proposed a new method of reflection and action based on principles. This would influence new lines of argument and future conduct, as well as new documents regarding research involving human beings.

Guide to Good Clinical Practices

The ethical principles highlighted in the Belmont Report - respect for persons, beneficence, and justice - served as the basis, with the Declaration of Helsinki, for proposing a document that would guide clinical research in the United States, the well-known GCP [15]. This set of norms was recognized and adopted by the World Health Organization from 1995, as a formal recommendation to the affiliated countries. In 1996, following the International Conference on Harmonization (ICH) and the publication of the ICH Harmonized Tripartite Guideline [15], a landmark in the evolution of clinical research, a single standard of conduct was formalized for the United States, the European Union and Japan [31].

Adherence to the GCP is universally accepted as a fundamental requirement for scientific research involving human beings [31]. It is intended that good clinical practice ensures the safety and integrity of people who will engage in research as research participants, as well as seeks to obtain excellent results that will generate real contributions to individuals and society [32].

Document of the Americas

This document was proposed by countries from the American Continent that were not part of the ICH when the GCP was proposed, but which felt the need to establish universally accepted ethical and scientific principles in their territories, also based on the Declaration of Helsinki [16]. Its objective was to propose good clinical practice manuals that should guide both regulatory agencies and investigators, ethics committees and other bodies or individuals involved in clinical trials.

Resolução CNS 466/2012 [CNS Resolution 466/2012]

Revoking Resolução CNS 196/1996 [CNS Resolution 196/1996] [33], which established national guidelines for research involving human beings and created the National Research Ethics Commission (Comissão Nacional de Ética em Pesquisa - CONEP), the same Brazilian National Health Council (Conselho Nacional de Saúde - CNS) enacted Resolução CNS 466/2012 [CNS Resolution 466/2012] [14]. This document emphasizes the recognition and affirmation of the dignity, freedom and autonomy of the human being, and bases its principles on the Brazilian Federal Constitution [34] and on well-known international documents. These are, for example, *the Nuremberg Code* [22], *the Universal Declaration of Human Rights* [35], *the International Covenant on Economic, Social and Cultural Rights* [36], *the International Covenant on Civil and Political Rights* [37], *the Universal Declaration on the Human Genome* [38], *the International Declaration on Human Genetic Data* [39] *and the Universal Declaration on Bioethics and Human Rights* [21]. It should be noted that the *Declaration of Helsinki* [23] is not cited here, since Brazil, as we have seen, is no longer a signatory.

The Resolution incorporates some important terms for clinical research, such as free and informed consent - consent of a child, adolescent or legally incapable participant - and benefit of the research - direct or indirect benefit, immediate or subsequent, obtained by the research participant [14]. Item III.3 subparagraph (d) advises that it is necessary *to ensure that all participants at the end of the study have, provided by the sponsor, free and indefinite access to the best prophylactic, diagnostic and therapeutic methods that have proved effective* [14].

This is a discordant point between Brazil and the signatories of the Declaration of Helsinki [23]. CONEP has always required the maintenance of access to a trial drug, which has proven beneficial to the patient, as a general rule, according to CNS Resolution 466/2012 [14]. This position was in line with that proposed by the National Health Surveillance Agency (Agência Nacional de Vigilância Sanitária - ANVISA), which defended, in a meeting held in 2009, the provision of the trial product as an extension of the study. This guarantees the follow-up of the participant by the protocol and the delivery of the medication used in the original study, maintaining, through its perspective, control of the research and taking care of the safety of the individuals involved [26].

 http://dx.doi.org/10.1590/1983-80422018262237

Investigators

Usually, a physician becomes an investigator or sub-investigator of clinical research. Dentists can also be accepted as such, when the protocol covers their area of expertise. The principal investigators is also a physician or dentist, as this is the usual practice. However, the documents that guide the clinical research are not clear on this matter.

The GCP [15] is quite broad regarding this point and states that the investigator must have an academic qualification, training and experience to be responsible for the development of the study, taking into account the qualifications required by regulatory standards. It does not specify what academic training, nor does it require that only those with a medical degree be the principal investigators.

The same is true of the "Document of the Americas" [16]. CNS Resolution 466/2012 [14] is also generic in this regard and states only, in its item II.16, that the investigator responsible (not the physician) is the individual who is responsible for the coordination of the research and becomes co-responsible for the integrity and well-being of the research participants.

Returning to the GCP, the guide only refers to the profession of physician or dentist in item 4.3.1, where it indicates that a qualified medical investigator or sub-investigator should be the one that will answer for the study's medical decisions. It stresses that dentists should also be responsible for clinical research in their field. Ambiguity can be perceived here: practice calls for and even requires the figure of the physician (or dentist) as the principal investigator in clinical research, but the norms do not state this, seeming to accept that a person with another qualification can fulfill this role. This is a point that requires more specific definition in the regulatory documents, since the practice must follow formal guidelines and never be guided only by conduct considered habitual.

The sponsor is defined as the person responsible for the implementation and maintenance of the guarantees and quality control, in order to ensure correct conduct of the clinical study according to the protocol, the GCP and the current regulatory standards. The compilation and documentation of the data coming from the investigation are functions of the study's sponsor [15,35], as well as the choice of the research centers and the drafting and establishment of agreements with them, guaranteeing their unrestricted access to all the research data. In addition, the sponsor must ensure adherence to the protocols by the various investigators, which will be ensured by monitoring and recorded in specific reports.

By definition of our CNS Resolution 466/2012, the sponsor is *an individual or legal entity, public or private that supports the research, through actions of financing, infrastructure, human resources or institutional support* [14]. The sponsor is the partner that, as a rule, aims to profit from research, but who must respect the ethical limits as well as the effectiveness of the product. For this to happen, the sponsor relies on the role of the monitor, which assists in ethically conducting the study, verifying the accuracy of the data and certifying the rights and well-being of the participants [15,40].

The Contract Research Organizations (CROs) are entities to which the sponsor delegates or with whom he or she shares the responsibilities of ensuring the smooth running of clinical research [16]. These organizations may design the research project, recruit subjects, monitor research, or collect data, it being only necessary that their role be previously defined in a contract signed with the sponsor.

The orientation for the creation of interdisciplinary colleges, with a public function, of an advisory, deliberative and educational character with the intention of defending the interests of research participants appears in Brazil. This type of body, research ethics committees (REC), was created by CNS Resolution 196/1996 [33], which preceded the current CNS Resolution 466/2012, and had and has the function of approving and monitoring the various stages of research involving human beings in Brazilian territory.

On the other hand, CONEP, according to CNS Resolution 466/2012, is defined as a *collegiate body of an advisory, deliberative, normative, educational and independent nature, linked to the Brazilian National Health Council/Ministry of Health* [42]. It should be noted that there is in this document a large concern with emphasizing the close link between RECs and CONEP, forming the REC/CONEP system (in Portuguese: sistema CEP/Conep).

ANVISA is the authority, created by Lei 9.782/1999 [Law 9,782/1999], that has the primary function of protecting the health of the Brazilian population through *hygienic control of the production and consumption of products and services subject to health surveillance, including environments, processes, inputs and related technologies* [41]. In clinical trials, it is incumbent

upon ANVISA to evaluate both the protocol and its implementation for allowing, or not, the registration of the product under investigation, as well as the renewal of that registration.

According to CNS Resolution 466/2012 [14], a research participant is one who, informed and voluntarily, or under the clarification and authorization of his or her legal guardian(s), agrees to participate in research, including clinical trials. It should be noted that the document brings, for the first time, the term "research participant" instead of the term "research subject", as recommended in CNS Resolution 196/1996. This participation, however, should be free of charge - there might be an exception in Phase I or bioequivalence studies.

How does integrity fit into clinical research?

Clinical research, as can be seen, is performed by several contributors, each with their own specific responsibility. In fact, integrity in clinical research will be the sum of the proper conduct of all who participate in its elaboration and attainment. For this, some aspects should be highlighted or even modified so that one can be assured that this proper conduct will be adopted by all.

It is imperative that the principal investigator, as well as his/her team, have knowledge and mastery of the research protocol through its thorough and prior analysis. This is because, in the eagerness to start clinical trials, many inclusionary and exclusionary criteria may be neglected, becoming a serious problem for the integrity of the investigation. The researcher can only accept responsibility for research if he or she can effectively follow all of its steps.

The researcher's readiness to take all responsibility for the study to its end, not accepting to defraud the research when signing it without effectively accompanying it, is the correct attitude and is demanded by good practice. This point is already stressed in the new addendum to the GCP [42] published in June 2015. It is important to note that the first ethical endorsement of the clinical trial must be given by the principal investigator, and it is not acceptable that this responsibility be transferred only to the institutional RECs.

Currently, all activities to be developed in a given study should be planned in the budget and defined in advance, as the GCP already predicates. The investigator responsible must pass on the value of a given procedure to the person who actually executed it, and not accept that persons linked academically or functionally to him or her - such as scholarship holders or trainees - execute the procedure for free, as if these tasks were inherent to the function.

The budget is approved by the institutional REC, and every person in the team must have access to the document.

It is also up to the researcher, along with the study coordinator, to take care of the process of free and informed consent, which must be registered in the source documents. This consent must be renewed at each visit, since the consent process cannot be restricted to the simple signing of an informed consent form (ICF) at the time of the participant's first visit to the center.

There is a tendency to understand the signature of the ICF as a safeguard for the research participants and for the other people involved in the process, which de-characterizes the real importance of informed consent. In this regard, Hossne questions quite perceptively: *does the obtaining of the consent term make ethically acceptable a proposal that is ethically unacceptable?* [43]. Here the importance of the consent process is noted, not simply the signature of a document. This is extremely important in any research, including clinical research.

The sponsor is certainly the most interested party in clinical research results, since renewal of registration or the introduction of a new drug into the market means profit for the sponsor. However, ethical care must be prioritized. First, the sponsor should have social advantages (better dosage, better cost for the patient) in mind, in addition to financial ones. Secondly, the sponsor should be responsible for the implementation and maintenance of quality assurance and control systems to ensure proper data management, generation and documentation, according to protocol, GCP [15], and applicable regulatory standards.

For this to be possible, greater concern should be inculcated in the sponsors to avoid different interpretations in protocol analysis by different centers (in the case of multi-center research), which generally happens, since the usual initialization visits do not comply with this aspect.

The plurality of habits, customs and cultures in our country, or between different countries, contributes to accentuate these different interpretations. The training and harmonization program among research centers for multicenter studies appears as an attempt to address this difficulty, which is reflected in *recruitment problems, inclusion failures, follow-up losses, and data*

 http://dx.doi.org/10.1590/1983-80422018262237

inconsistencies, jeopardizing the development and results of the study [44].

The choice of centers is another task that must be undertaken with great care by the sponsor, with clear and transparent criteria, supporting the critical and demanding analysis of the monitor, who will carry out the qualification visit of the centers. This guarantee is essential for the proper and ethically correct choice of the places where the research will be carried out. This same care should be applied in choosing the coordinating center, as well as in the choice of the Contract Research Organization (CRO), if the sponsor opts to hire such a service.

Although documents such as the GCP [15] accept the mediation of the CROs, in the USA there are criticisms of these organizations. Some authors, such as Hank ten Have [10], point out as a negative aspect of the US clinical research scenario the hiring (and high cost) of these CROs. The author [10] says that these organizations have set up a true clinical trial industry, strengthening the model of "outsourcing" and the image of clinical research as a business. National supervisory bodies need to be attentive to the role that Brazilian CROs have been playing in the clinical research scenario.

The veracity of the data is another factor of extreme relevance. It will be these data that will substantiate the acceptance of the new drug's effectiveness by the sponsor and the regulatory agents. Unfortunately, fabrication or falsification of data has been happening in research as a whole. Authors such as Steneck [45] call attention to the need for professional self-discipline (and not an increased number of regulations) as a way to minimize misconduct.

In fact, this line of thought appeals to the investigator's scale of values, to his/her internal moral law, as guiding the proper conduct in research, which also applies to clinical trials. Here the monitoring action appears as an extremely important task to aid in the verification of the data. Although the GCP [15] states that monitoring of all clinical trial phases is necessary, it does not specify the nature and extent of such monitoring. The monitor can do this work face-to-face, focusing on the pages that have a greater chance of errors, but can also use remote monitoring to verify - especially in large databases - biases, fraud and badly calibrated equipment, bringing important information to the sponsor [46].

ANVISA is responsible for systematizing the analysis of the clinical trial protocols after the analysis and approval of the EPCs, carried out concomitantly with CONEP, whenever necessary [47]. However, ANVISA needs research centers committed to these clinical trials to guarantee quality, effectiveness and safety of studies. ANVISA could therefore organize a national register of qualified research centers, which would undergo periodic audits to certify the quality required by the agency.

Another important contributor in maintaining the integrity of clinical studies is REC. When CNS Resolution 196/1996 was made official, several national institutions had difficulty in implementing and providing adequate infrastructure to the RECs that were formed [48]. Currently, CNS Resolution 466/2012, in item X.1, sub-item 3.b, when referring to the REC's responsibilities, states that the committee must follow the development of the projects, through semi-annual reports from the researchers and other monitoring strategies, according to the risk inherent in the research [14].

This monitoring responsibility of the REC is, unfortunately, usually restricted to receiving and, possibly, analyzing these reports. It is observed, however, that our official norm foresees and gives room to strategies for monitoring of the centers. In clinical trials, perhaps more than in basic research, risk is intrinsic to the process, as it refers to the analysis of new interventions. These researches could be analyzed more closely by the RECs, thereby establishing a stronger link with the investigators.

The partnership is also highlighted in item VII of CNS Resolution 466/2012, in which the document officially establishes the REC/CONEP system (in Portuguese: sistema CEP/Conep), emphasizing the collaborative nature of the work [49]. The legislation allows the use of the proper interrelationship mechanisms, tools and instruments, in order to set up a system that allows truly cooperative work, aiming at the protection of research participants in a coordinated and decentralized manner.

Final considerations

Clinical trials have been considered as an important aggregating factor in the economy of the countries participating in them (through job creation, and scientific and technological development), as well as in the sciences (through scientific information) and in public health (via benefits to participants and to the population) [53]. One cannot, therefore, forget ethical principles when they are attained.

It is possible to affirm, then, that clinical research is inserted (or should be inserted) in this

context: the search for improving society's quality of life based, also, on the development of specific drugs that are researched with rigid standards both by the investigators and by industry, as well as inspected by specific official bodies. One of the driving forces behind this type of investigation is the search for and discovery of new drugs that will benefit the whole community.

It cannot be denied that society will benefit from these investigations if public health policies are truly effective, normalizing and socializing the population's access to these findings [51].

Therefore, integrity in research, so widely spoken about in universities nowadays, must broaden its horizons to also embrace clinical research. All those involved in this type of research need to be guided and charged to apply good practices in the various stages of research development, which will allow sound and successful studies to be achieved.

Referências

1. Shinkai RS. Integridade na pesquisa e ética na publicação. Sci Med. 2011;21(1):2-3.
2. Brasil. Conselho Nacional de Desenvolvimento Científico e Tecnológico. Relatório da Comissão de Integridade de Pesquisa do CNPq [Internet]. Brasília: CNPq; 2011 [acesso 1º nov 2016]. Disponível: http://bit.ly/1PeyLNu
3. Garcia CC, Martrucelli CRN, Rossilho MMF, Denardin OVP. Autoria em artigos científicos: os novos desafios. Rev Bras Cir Cardiovasc [Internet]. 2010 [acesso 1º nov 2016];25(4):559-67. Disponível: http://bit.ly/2ArlDRL
4. Vanz SAS. As redes de colaboração científica no Brasil (2004-2006) [tese]. Porto Alegre: Universidade Federal do Rio Grande do Sul; 2009.
5. Domingues E. Autoria em tempos de "produtivismo acadêmico". Psicol Estud [Internet]. 2013 [acesso 1º nov 2016];18(2):195-8. Disponível: http://bit.ly/2AqQVrG
6. International Committee of Medical Journal Editors. Recommendations for the conduct, reporting, editing, and publication of scholarly work in medical journals [Internet]. [s.l.]: ICMJE; dez 2016 [acesso 20 ago 2017]. Disponível: http://bit.ly/1ToLU4m
7. Camanho GL. Editorial: conflito de interesse. Rev Bras Ortop [Internet]. 2009 [acesso 1º nov 2016];44(2):1. Disponível: http://bit.ly/2AE9bAq
8. Chamon W, Melo Jr LAS, Paranhos Jr A. Declaração de conflito de interesse em apresentações e publicações científicas. Arq Bras Oftalmol [Internet]. 2010 [acesso 2 nov 2016];73(2):107-9. Disponível: http://bit.ly/2ADv6rO
9. Massud M. Conflito de interesses entre os médicos e a indústria farmacêutica. Rev. bioét. (Impr.). 2010;18(1):75-91.
10. ten Have H. Pesquisa médica: como recuperar a confiança. Medicina CFM: revista de humanidades médicas. 2014;(5):48-55.
11. Angell M. A verdade sobre os laboratórios farmacêuticos. 4ª ed. Rio de Janeiro: Record; 2009.
12. Sanchez OP, Innarelli PB. Desonestidade acadêmica, plágio e ética. GV Executivo [Internet]. 2012 [acesso 1º out 2016];11(1):46-9. Disponível: http://bit.ly/2AOmUp8
13. Sauthier M, Almeida Filho AJ, Matheus MP, Fonseca PML. Fraude e plágio em pesquisa e na ciência: motivos e repercussões. Referência [Internet]. 2011 [acesso 29 out 2016];3(3):47-55. Disponível: http://bit.ly/2AlI1xN
14. Conselho Nacional de Saúde. Resolução CNS nº 466, de 12 de dezembro de 2012. Aprova diretrizes e normas regulamentadoras de pesquisas envolvendo seres humanos [Internet]. 2013 [acesso 1º nov 2016]. Disponível: http://bit.ly/1mTMIS3
15. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. ICH Harmonised Tripartite Guideline. Guideline for good clinical practice E6(R1). 10 jun 1996.
16. Organização Pan-Americana da Saúde. Boas práticas clínicas: documento das Américas [Internet]. Washington: OMS; 2005 [acesso 2 nov 2016]. 88 p. Disponível: http://bit.ly/2zJdM0I
17. Clotet J, Feijó A. Bioética: uma visão panorâmica. In: Clotet J, Feijó AGS, Oliveira MG, coordenadores. Bioética: uma visão panorâmica. Porto Alegre: EDIPUCRS; 2005. p. 9-20.
18. Bergel SD. El derecho de acceso a los medicamentos: su reconocimiento y las barreras puestas a su ejercicio. In: Casado M, Luna F, coordenadoras. Cuestiones de bioética en y desde Latinoamérica. Navarra: Civitas; 2012. p. 333-48.
19. Rossi F. Enfermedades de alto impacto social, enfermedades olvidadas, medicamentos de alto costo y ARV. In: Bermúdez J, Oliveira MA, Esher A. Acceso a medicamentos: derecho fundamental, papel del estado. Rio de Janeiro: Fiocruz; 2004. p. 193.
20. Humet C. Responsabilidade social e saúde. In: Casado M. Sobre a dignidade e os princípios: análise da declaração universal sobre bioética e direitos humanos. Porto Alegre: EDIPUCRS; 2013. p. 425-38.
21. Organização das Nações Unidas para a Educação, a Ciência e a Cultura. Declaração universal sobre bioética e direitos humanos [Internet]. Paris: OMS; 2006 [acesso 1º nov 2016]. 12 p. Disponível: http://bit.ly/1TRJFa9

 http://dx.doi.org/10.1590/1983-80422018262237

22. Trials of war criminals before the Nüremberg Military Tribunals [Internet]. Washington: US Government Printing Office; 1949 [acesso 2 nov 2016]. v. 2, p. 181-2. Disponível: http://bit.ly/2BFtoUt
23. Associação Médica Mundial. Declaração de Helsinque da Associação Médica Mundial: princípios éticos para pesquisa médica envolvendo seres humanos [Internet]. Fortaleza: WMA; 2013 [acesso 1º nov 2016]. Disponível: http://bit.ly/2kgnPpS
24. Sofaer N, Thiessen C, Goold SD, Ballou J, Getz KA, Koski G *et al*. Subjects' views of obligations to ensure post-trial access to drugs, care, and information: qualitative results from the experiences of participants in clinical trials (EPIC) study. J Med Ethics [Internet]. 2009 [acesso 29 out 2016];35(3):183-8. Disponível: http://bit.ly/2At1oD8
25. Conselho Nacional de Saúde. Comissão Nacional de Ética em Pesquisa. Análise técnica da Comissão Nacional de Ética em Pesquisa sobre o Projeto de Lei nº 200/2015 [Internet]. 2015 [acesso 16 jun 2016]. Disponível: http://bit.ly/2jlvWgM
26. Dainesi SM, Goldbaum M. Fornecimento de medicamento investigacional após o fim da pesquisa clínica: revisão da literatura e das diretrizes nacionais e internacionais. Rev Assoc Med Bras. 2011;57(6):710-6.
27. Dainesi SM. Como fazer valer a máxima da ética médica *primum non nocer* ao oferecer continuidade de tratamento com drogas experimentais a pacientes de pesquisa clínica? Rev Assoc Med Bras. 2009;55(3):237-8.
28. Schüklenk U, Hare D. Questões éticas na pesquisa internacional e em estudos multicêntricos. RECIIS. 2008;2(1 Suppl):S19-30.
29. Brandt AM. Racism and research: the case of the Tuskegee Syphilis Study. Hastings Cent Rep. 1978;8:21-9
30. US Government. The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. The Belmont Report: ethical principals and guidelines for the protection of human subjects of research [Internet]. 1979 [acesso 2 nov 2016];4-6. Disponível: http://bit.ly/2uvrnZO
31. Laranjeira LN, Marcílio CS, Guimarães HP, Avezum Á. Boas práticas clínicas: padrão de pesquisa clínica. Rev Bras Hipertens. 2007;14(2):121-3.
32. Zucchetti C, Morrone FB. Perfil da pesquisa clínica no Brasil. Rev HCPA. 2012;32(3):340-7.
33. Conselho Nacional de Saúde. Resolução 196 versão 2012 [Internet]. 2012 [acesso 14 dez 2016]. Disponível: http://bit.ly/2ieEDe3
34. Brasil. Constituição da República Federativa do Brasil de 1988 [Internet]. Diário Oficial da União. Brasília; 5 out 1988 [acesso 5 dez 2017]. Disponível: http://bit.ly/1bJYlGL
35. Organização das Nações Unidas. Declaração Universal dos Direitos Humanos [Internet]. 1948 [acesso 14 dez 2016]. Disponível: http://uni.cf/2sXdl3e
36. Brasil. Decreto nº 591, de 6 de julho de 1992. Atos internacionais. Pacto internacional sobre direitos econômicos, sociais e culturais. Promulgação [Internet]. Diário Oficial da União. Brasília, 7 jul 1992 [acesso 14 dez 2016]. Disponível: http://bit.ly/2AGqQHU
37. Organização das Nações Unidas. Pacto internacional sobre os direitos civis e políticos [Internet]. 1966 [acesso 14 dez 2016]. Disponível: http://bit.ly/2zsQSxH.
38. Organização das Nações Unidas para a Educação, a Ciência e a Cultura. Declaração universal sobre o genoma humano e os direitos humanos: da teoria à prática [Internet]. Paris: Unesco; 1997 [acesso 14 dez 2016]. Disponível: http://bit.ly/2oNe3x4
39. Organização das Nações Unidas para a Educação, a Ciência e a Cultura. Declaração internacional sobre os dados genéticos humanos [Internet]. Paris: Unesco; 2004 [acesso 14 dez 2016]. Disponível: http://bit.ly/2oDqgUt
40. Cesar MB, Laranjeira LN, Guimarães HP, Avezum Á, Piegas LS. Processos de iniciação em pesquisa clínica: responsabilidades do investigador e do patrocinador. Rev Bras Hipertens. 2008;15(2):100-3.
41. Agência Nacional de Vigilância Sanitária. Institucional [Internet]. c2016 [acesso 1º nov 2016]. Disponível: http://bit.ly/2AnEuit
42. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. ICH Harmonised Guideline. Integrated addendum to ICH E6(R1): guideline for good clinical practice E6(R2) [Internet]. 2015 [acesso 2 nov 2016]. Disponível: http://bit.ly/1L4YlA2
43. Hossne WS. Dos referenciais da bioética: a vulnerabilidade. Bioethikos. 2009;3(1):41-51. p. 48.
44. Unidade de Pesquisa Clínica do Centro de Saúde Reprodutiva Carlos Isaia Filho. Programa de capacitação e harmonização de centros de pesquisa para estudos multicêntricos [Internet]. Porto Alegre: CSRCIF; c2014 [acesso 2 nov 2016]. Disponível: http://bit.ly/2kiZsJq
45. Steneck NH. Fostering integrity in research: definitions, current knowlege, and future directions. Sci Eng Ethics [Internet]. 2006 [acesso 2 nov 2016];12:53-74. Disponível: http://bit.ly/2idz8MB
46. Olsen R, Bihlet AR, Kalakou F, Andersen JR. The impact of clinical trial monitoring approaches on data integrity and cost: a review of current literature. Eur J Clin Pharmacol. 2016;72(4):399-412.
47. Nishioka SA. Regulação da pesquisa clínica no Brasil: passado, presente e futuro. Prática Hospitalar. 2006;8(48):17-26.
48. Kipper DJ. Ética na pesquisa envolvendo seres humanos. In: Casado M, Luna F, coordenadoras. Cuestiones de bioética en y desde Latinoamérica. Navarra: Civitas; 2012. p. 349-70.
49. Novoa PCR. What changes in research ethics in Brazil: Resolution no. 466/12 of the National Health Council. Einstein [Internet]. 2014 [acesso 1º nov 2016];12(1):vii-x. Disponível: http://bit.ly/2icTB44

50. Silva CF, Ventura M, Castro CGSO. Perspectivas bioéticas sobre justiça nos ensaios clínicos. Rev. bioét. (Impr.) [Internet]. 2016 [acesso 1º nov 2016];24(2):292-303. Disponível: http://bit.ly/2kinapl
51. Bergel SD. Diez años de la declaración universal sobre bioética y derechos humanos. Rev. bioét. (Impr.) [Internet]. 2015 [acesso 29 out 2016];23(3):446-55. Disponível: http://bit.ly/2iLgkYS

Participation of the authors

Anamaria Gonçalves dos Santos Feijó was responsible for the conception, research and bibliographical revision, as well as for the drafting of the original text. Anelise Crippa, Andressa Daron Giordani and Natália Moreira Vieira assisted in the bibliographic review and did the critical analysis of the content. Carlos Isaia Filho participated in the orientation of the topic, critical analysis of the content and final revision of the text. All authors have approved the final version of this article.

Recebido: 4.11.2016
Revisado: 1º. 9.2017
Aprovado: 9.10.2017

Update