

# Good Clinical Practices and Regulatory Aspects Concerning Cell Therapy Clinical Research

Bruna Zambonato<sup>1,2</sup>, Nathan Buggs<sup>1</sup>, Annelise Pezzi<sup>1,2</sup>, Vanessa Valim<sup>1,2</sup>, Alice Dahmer<sup>1,2</sup>, Filipe Sehn<sup>1,2</sup>, Ianaê Wilke<sup>1,2</sup>, Juliana Furlan<sup>2</sup>, Maria Aparecida Lima da Silva<sup>1</sup>, Bruna Amorin<sup>1,2,3</sup>, Lucia Silla<sup>1,2,4</sup>

<sup>1</sup> Celular Therapy Center of Hospital de Clínicas de Porto Alegre, Center for Experimental Research, Porto Alegre, Brazil.

<sup>2</sup> Post-graduation: Federal University of Rio Grande do Sul, Porto Alegre, Brazil.

<sup>3</sup> Centro Universitário Ritter dos Reis, Porto Alegre, Brazil.

<sup>4</sup> Hematology and Bone Marrow Transplantation of Hospital de Clínicas de Porto Alegre, Porto Alegre, Brazil.

**Abstract:** *When it comes to clinical research, the Good Clinical Practice (GCP) quality standard not only protects the safety, well-being and rights of participants enrolled in clinical trials, but also ensures the validity and reliability of data and results generated. As cell therapy (CT) research expands, it is necessary that studies involving this subject be conducted with the same care and standards that clinical research, involving conventional drugs, are currently being conducted. Additionally, cell therapy must work in accordance with current Good Manufacturing Practice (GMP), in order to maintain the quality of its products. The goal of this study, an exploratory literature review conducted at CTC-HCPA, is to review and discuss the good clinical practices and regulatory aspects of cell therapy research. These aspects rely not only on following the current parameters of GCP and GMP but also on acting in accordance with the legislation implemented in each country where the studies take place. Further, several resources are also necessary to ensure the quality of research data and products, such as authorized facilities, equipment able to generate reliable results, and a multidisciplinary team with wide knowledge of GCP/GMP quality standards and pertinent legislation.*

**Keywords:** Clinical Trial, Cell Therapy, Stem Cell, Protocols, Good Manufacturing Practices, Regulation, Law.

## 1. Introduction

Stem cell-based therapy is a topic currently in vast expansion, holding great promise for assessing a wide array of medical conditions. Stem cells, which are cells able to differentiate along several types of human tissues, are the subject of several current studies, given their therapeutic and regenerative potential<sup>(1,2)</sup>.

With the increase in the number of clinical trials involving cell therapy, in which the administered medications are cellular products with therapeutic potential, it is necessary the establishment of criteria which ensure that these potential therapies are being subject to the same quality standards as conventional drugs. It is of the utmost importance that we define correct dosage, safety, feasibility, possible adverse outcomes and benefits of these new therapeutic approaches. Clinical trials that aim to demonstrate the efficacy of stem cell-based or specific tissue-based cell therapies, such as infusion of lymphocytes, should act in accordance with the same guidelines of clinical research currently established, and should also always adopt the Good Clinical Practice (GCP) quality standard.

In the case of Brazil, studies evaluating cell therapy are relatively recent and not yet fully contemplated by current legislation, and, overall, these studies are regulated by technical standards issued by public agencies that govern the functioning of the cellular technology centers (CTCs) established in Brazil<sup>(3)</sup>. Therefore, it is important to discuss the Good Clinical Practices and regulatory aspects of cell therapy clinical research, which is the intent of this review.

This is an exploratory review, with a qualitative approach, which encompasses the characterization of clinical research, good clinical practices, good manufacturing practices, and

regulatory aspects, with an emphasis on cell therapy clinical research. The databases included were Library of Medicine (PubMed), Scientific Electronic Library Online (SciELO) and LILACS. The search terms used were “Clinical Trial”, “Cell Therapy”, “Stem cell”, “Protocols”, “Good Manufacturing Practice”, “Regulation”, “Law” and their combinations. Articles of all languages available online were included. Other resources were also reviewed, such as book chapters, the ClinicalTrials.gov website, web search, relevant legislation and other papers that were deemed helpful by the research group. Each source was fully reviewed and summarized before proceeding to the writing of this review.

## 2. Clinical Research and Good Clinical Practices

Clinical research is defined as a scientific investigation involving human beings with the aim of analyzing clinical, pharmacological, pharmacodynamic, pharmacokinetic effects and adverse outcomes of products being investigated<sup>(4)</sup>. The discussion of criteria concerning the ethics of experiments involving humans can be traced back to the Nuremberg Code, in 1947, including, among other important points, the necessity of informed consent. Ethical principles were improved in 1964 with the Declaration of Helsinki, and worldwide harmonization of research regulatory authorities occurred in 1990 with the creation of the International Conference on Harmonization, which was responsible for the implementation of the Good Clinical Practice quality standard in 1996<sup>(5)</sup>.

In Brazil, clinical research was first regulated by the Resolution #196 issued by the National Health Council (CNS), which approved guidelines and regulating norms for research involving human subjects<sup>(6)</sup>. The current active

regulation is the Resolution #466 of December 12, 2012, which is the latest periodic review of the previous Resolution issued in 1996<sup>(7)</sup>. Likewise, research in Brazil also acts in accordance with GCP specific guidelines, such as the Good Clinical Practices: Document of the Americas guideline<sup>(8)</sup> and the specific document regarding MERCOSUR nations<sup>(9)</sup>, ensuring that the studies obey international quality standards.

Good Clinical Practices are defined as a scientific and ethical international quality standard utilized in research that includes the participation of humans. This quality standard encompasses the planning and conduction of trials, as well as establishing standards for record keeping, monitoring, analysis and reports of clinical trials. This ensures that the data and results generated are valid and reliable, in addition to assuring the protection of human rights, such as safety and privacy, for the subjects enrolled<sup>(8)</sup>.

Good Clinical Practices guidelines ensure that all clinical research involving human beings act in accordance with quality standards. These guidelines, however, must always be utilized having in mind relevant ethical principles and pertinent legislation<sup>(10)</sup>. Likewise, according to GCP, the product being investigated must be produced complying with the Good Manufacturing Practices (GMP) standard quality.

Good Manufacturing Practices principles are related to the employment of adequate instruments and proceedings by capacitated professionals<sup>(11)</sup>. These practices secure the safety, purity, and efficacy of products. All aspects of production are contemplated: quality assurance, personnel, manufacturing facilities and equipment, documentation, production, quality control, and product tracking<sup>(12)</sup>. In Brazil, GMP of medications are regulated by Resolution N° 17 of 2010, issued by Brazil's National Health Surveillance Agency (ANVISA), and governs all operations involving drug manufacturing, including clinical trials, in order to ensure the quality of products<sup>(13)</sup>.

### 3. Clinical Research and Cell Therapy

Cell therapy is a modality of treatment that uses human cellular material and is currently under investigation for the treatment of a wide array of diseases. It is expected that in the future such therapy may treat diseases today deemed as incurable<sup>(14)</sup>.

Several clinical trials are being conducted utilizing cell therapy for the treatment of different disorders. Data from ClinicalTrials.gov demonstrate that there are about 226.000 studies currently registered on the website, and nearly 30.800 of these are clinical trials involving "Cell Therapy"<sup>(15)</sup>. It is worth mentioning, however, that the concept "Cell Therapy" encompasses hematopoietic stem cell transplantation (HSCT), which is the only modality of cell therapy that is currently recommended in guidelines, due to its widely recognized efficacy. When the search terms are limited to studies involving cell therapy and mesenchymal stem cells, for example, the number of registered trials is 586.

All products for advanced medicinal therapy (AMT), such as those used for gene therapy, somatic cell therapy, and tissue engineering, have been considered as drugs in Europe since 2001<sup>(12)</sup>. Cells are considered Advanced Therapy Medicinal Products (ATMP), and their manufacturing process is regulated by the European Regulation (EC 1394/2007), establishing rules for the authorization, supervision, and technical requirements regarding the summary of product characteristics, labeling, and package leaflets of ATMPs that are prepared according to industrial methods and in academic institutions. Likewise, they must be manufactured in compliance with Good Manufacturing Practice<sup>(11)</sup>.

In the United States, production of human cells, tissues, or cellular and tissue-based products (HCT/PS) must comply with current Good Tissue Practice requirements, under the Code of Federal Regulations (CFR). This includes regulation of processes such as facilities, environmental control, equipment, supplies, and reagents, recovery, processing and process controls, labeling controls, storage, shipment, distribution, and donor eligibility, screening and testing<sup>(11)</sup>.

In Australia, products made from or containing human tissues and cells, are controlled by a new regulatory framework since 2011. This framework categorizes biological products in four classes, according to the different levels of risk that each product poses. The classification is based on the amount of manipulation involved and the closeness of the intended use of cells or tissues to their standard biological function<sup>(16)</sup>. Nonetheless, despite the expansion of regulations regarding cell therapy in places like Europe and Australia, Von Tigerstrom (2015)<sup>(16)</sup> states that there are important obstacles on its path, such as the discrepancy between public perceptions and expectations about this new therapy and the current scientific evidence that supports it. This discrepancy may exist due to the fact that cell therapy is still a topic in development.

Many stem cell types are being used to address a wide array of medical disorders. Limbal stem cells have been registered as a product for eye burns in Europe and mesenchymal stem cells have been approved for pediatric graft versus host disease in Canada and New Zealand<sup>(17)</sup>. In the case of Japan, two new laws came into effect in 2014, allowing that studies with cell therapy in phase II may already receive market authorization for their product, as long as its efficacy and safety are properly demonstrated<sup>(18)</sup>. Despite the significant expansion of studies involving cell therapy, only a small number of them are demonstrating enough benefits to justify premature marketing approval. Yet, it is expected that a substantial increase in the number of registrations of new types of cell therapies may occur soon<sup>(17)</sup>.

In Brazil, manufacturing and usage of human cells and its derivatives for cell therapy and clinical research are regulated by Resolution #9, of March 16, 2010, which approves and establishes technical norms for the existence of cellular technology centers, called CTCs. These services must have adequate facilities, personnel, equipment, supplies, and reagents for the manufacturing of cell-derived products for the treatment of humans<sup>(3)</sup>.

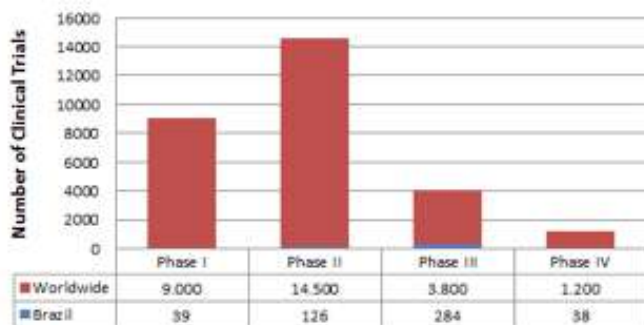
There are currently eight of these services functioning in Brazil, constituting the Cellular Therapy National Network (RNTC), together with fifty-two laboratories selected by the National Council for Scientific and Technological Development (CNPq) and by the Department of Science and Technology (DECIT) of the Ministry of Health<sup>(19)</sup>. One of these eight services is the CTC-HCPA, located at the Hospital de Clínicas de Porto Alegre, in the state of Rio Grande do Sul. The CTC-HCPA was created in 2008 and is responsible for the development of clinical research and therapies involving human stem-cell or tissue-specific cell-based products, especially those involving mesenchymal stem cells and natural killer cells.

#### 4. Good Clinical Practices and Cell Therapy

As pointed out, research with cell therapy, just like clinical research with conventional drugs, must obey a quality standard, acting in accordance with the GCP guidelines and pertinent legislation. In this manner, the safety of the participants of studies can be ensured, from the manufacturing of the products to the monitoring of patients' clinical responses.

##### Research Phases

New therapeutical approaches must have their safety and efficacy confirmed through a series of clinical trial phases. When it comes to cell therapy studies, just like in conventional pharmacological trials, the same criteria are applied, being necessary that the intervention is tested in all four phases of clinical trials. Data from ClinicalTrials.gov<sup>(15)</sup> shows that there are about 9,000 cell therapy phase I studies, 14,500 phase II studies, 3,800 phase III studies and 1,200 phase IV studies currently ongoing worldwide. In Brazil, of the almost 500 studies ongoing, 39 are phase I, 126 are phase II, 284 are phase III and 38 are phase IV studies, as shown in Graph 1. As mentioned before, however, these numbers include studies involving hematopoietic stem cell transplantation (HSCT), which is the only modality of cell therapy already widely utilized, and the only one with ongoing phase IV studies. There are no phase IV studies involving cell therapy with mesenchymal stem cells or natural killer cells<sup>(15)</sup>.



**Figure 1:** Cell Therapy Clinical Trials Worldwide and in Brazil

In Brazil, no kind of product or procedure that involves cell therapy other than HSCT has received marketing approval, so there are no phase IV studies. Also, there is no clear regulation of the nature of the cellular product, which is one of the reasons that currently there is not much private investment in such area<sup>(14)</sup>. Cell therapy may be regarded as

either a transplantation procedure or a type of medication. In the former case ANVISA would define the general requirements for safety and quality for performing the procedure, the evaluation of clinical efficacy and intended use would be responsibility of the Federal Councils of Medicine and Odontology, and commercialization would still be prohibited, but the procedure could be considered for patients, and the public or private health system would be able to charge for the costs of the procedure. In the latter case, cell therapy would receive market approval by ANVISA as clinical trials would be demonstrating its safety and efficacy, and commercialization would be authorized<sup>(20)</sup>. The current lack of clear definitions, however, is detrimental to the development of cell therapy, considering that uncertainties tend to discourage investments.

##### Protocol

Studies with cell therapy must follow a protocol written and signed by the investigator and the sponsor, as in conventional clinical trials, and there is no necessity for additional points other than the ones already pointed out in pertinent GCP guidelines. The protocol should contain (1) general information about the investigator and the sponsor, such as title of the protocol, names, titles, and addresses of investigators and monitors; (2) background information such as name and description of the investigational product, rationale of the study, summary of potential risks and benefits, and a statement that all pertinent GCP guidelines will be followed; (3) objectives of the trial, including a detailed description of the purpose of the trial and its hypotheses; (4) design of the trial, including measured primary and secondary outcomes, type of trial to be conducted, and a description of measures taken to minimize bias; (5) criteria for the selection and withdrawal of patients; (6) treatment of the subjects; (7) evaluation of outcomes, including safety evaluation; (8) description of the statistical methods used; (9) direct access to the original data; (10) quality control and quality assurance, including description of the ethical considerations related to the trial and the procedures for data entry and data management<sup>(8)</sup>. Moreover, any kind of modification of the protocol must be notified.

##### Informed Consent

When it comes to the informed consent, besides the points already included in GCP guidelines, there are a few elements that, when pertinent, should be included in the informed consent document. It is important to include (1) information regarding the risks for the donor of the cellular material and the potential benefits for the receiver of the material, (2) information regarding which tests will be used to evaluate the eligibility of the donor, (3) explicit permission to use the donor's medical history for research purposes, (4) explicit permission to the laboratory in charge of the material to provide qualitative and quantitative data to the investigators, and (5) permission to store samples for future use and to discard samples that do not conform with criteria for storage or future use<sup>(3)</sup>. The latter aspect must be underlined since that particular cell therapy might not have the desired effect.

##### Funding

Academic institutions fund most current trials involving cell therapy. Thus, investigators not only have to conduct the research, complying with good clinical practices but also



must take over sponsor responsibilities. In Brazil, public institutions for the promotion of research can provide funds, but these processes are often complicated and available in limited periods of time. Hospitals where the trials take place may provide funds, however, those are often insufficient. A study has shown that, in the year of 2014, about of 70% of the clinical trials involving cell therapy were sponsored by academic or public institutions, while 30% were sponsored by private institutions<sup>(21)</sup>.

### **Product Tracking**

Product tracking is a crucial point in cell therapy clinical research. It is essential to record which supply was used to manufacture each product, in order to ensure that, if any unexpected outcome occurs, it is possible to identify the source of the problem and correct it.

To ensure the safety of cell products for allogeneic or autologous use, all samples collected for cell therapy purposes must undergo the same screening process as blood samples undergo for blood donation, depending on local legislation. In Brazil, the ANVISA Board Resolution #34 of the year of 2014 determines that all kind of activities involving blood products and transfusions needs to have its products screened for a series of infectious diseases: syphilis, Chagas disease, hepatitis B (HBsAg, anti-HBc and viral DNA detection), hepatitis C (anti-HCV and viral DNA detection), HIV types 1 and 2 (anti-HIV and viral DNA detection), HTLV types 1 and 2, and, in endemic regions, cytomegalovirus and malaria<sup>(22)</sup>.

All supplies and reagents employed in the production of cell products must be sterile, apyrogenic, non-cytotoxic, and, if possible, disposable. Furthermore, it is important that all supplies have their origin, expiration date and lot number correctly documented. All manufactured products must have a cryopreserved sample so that it is possible to perform quality control tests in the future, if needed<sup>(3)</sup>. Besides, the production and storage of any cellular material must be in accordance with the Good manufacturing practices guidelines.

## **5. Good Manufacturing Practices and Cell Therapy**

Good manufacturing practices (GMP) are a series of practices required to guarantee the quality and safety of manufactured products, providing minimum requirements that ensure the correct identity, strength, quality, and purity of products<sup>(23)</sup>. Cells expanded in culture must also be produced in accordance with GMP to guarantee safety, reproducibility, and efficacy of possible therapies with them<sup>(24)</sup>. Thus, just as with manufacturing of conventional drugs, production of cellular products must abide by all points of GMP to guarantee the sterility and safety of the product<sup>(25)</sup>.

Facilities designed for cell production must obey several points to guarantee that they are acting in accordance with GMP. The environment must be standardized and continually monitored, and there must be specific parameters of air filtration and ventilation, temperature, humidity, and

pressure. It is necessary that there is a restricted number of air particles and colony-forming units<sup>(24)</sup>.

Cell production requires processes such as changing cell culture media, transferring cultures to larger devices and centrifugation, which require cell manipulations that may hinder the aseptic conditions needed for cellular products. Thus, one of the key points in large-scale production of clinical-grade cell products is the development of closed systems<sup>(11)</sup>. Along these lines, closed system bioreactors may prove to be a useful way of translating research-based experimental procedures into scalable cell production processes. Bioreactors are closed and automated systems designed for cellular expansion, and their use is an important technique for increasing GMP compliance and safety of cell expansion for cell therapy purposes<sup>(26)</sup>.

Another key aspect of cell expansion is quality control. To guarantee the safety and efficacy of manufactured products, it is crucial that manufacturers demonstrate their purity<sup>(11)</sup>. Quality control of the product must be ensured by performing a series of tests, such as microbiological screening tests, genetic control, total cell count and viability, immunophenotyping, functional assays, and, when appropriate, pyrogenicity testing, and HLA typing<sup>(3)</sup>.

Moreover, the final product must undergo further testing to have its safety certified. The limit storage time for the cell products should be determined based on stability testing of the final product<sup>(25)</sup>. For the approval for clinical use, the product must be enclosed in its final package, and it is necessary that it explicitly contains information regarding criteria for its utilization, a statement that all GMP procedures were observed, and possible adverse effects of the utilization of the product<sup>(3)</sup>.

### **Storage of Cell Products**

As mentioned above, one important aspect of cell therapy research is the correct storage of manufactured products. In Brazil, this process can be done either by one of the eight authorized cell technology services (CTCs) or by individual investigators, which will be responsible for producing, storing, and providing the studied cellular material. Along these lines, it is crucial the availability of biorepositories and biobanks.

Biorepository is a term that encompasses repositories that collect and store biospecimens for future use and is usually associated with a specific group of investigators and a specific research project, and the material can usually only be used for the specific purposes that it was collected. Biobank is a type of biorepository that usually belongs to an institution and is shared among several research projects in a collaborative manner<sup>(27)</sup>.

## **6. Role of the Multidisciplinary Team in Cell Therapy Research**

As in clinical trials involving conventional drugs, the multidisciplinary team approach is a key step to guarantee the professionalism and reliability needed for cell therapy trials. The GCP guidelines state that the presence of a multidisciplinary team with adequate expertise and different

sets of skills is essential<sup>(8)</sup>. In Brazil, the regulation of cell therapy services requires a multidisciplinary team composed of members from different healthcare professions with specialized skills and expertise, and subject to continuing education<sup>(3)</sup>.

#### **Physician**

The physician plays an important role in cell therapy research, not only because of the clinical evaluation of the subjects of trials, but also because patients enrolled in cell therapy trials usually have bad prognosis diseases, and the patient's health care providers need to be integrated with the research team. One of the obstacles that may be present is that the health care provider often is not acquainted with the regulations and procedures related to cell therapy, not being fully aware of the necessary monitoring of the patient. This is intensified in multicentric studies, when the health care providers and the research team are more subject to miscommunication. The integration of the teams is essential for the adequate conduction of cell therapy trials.

#### **Manufacturing and Quality Control Team**

The manufacturing and quality control team has a major role in the development of cell therapy research. Professionals from different specialties may perform this function, as long as properly trained. This team must be able to collect biological samples from donors and execute properly the steps of processing the samples, transporting them, manufacturing the final cellular products and delivering them their final destination. All these steps must be performed in accordance with GMP guidelines to ensure the safety and conformity to quality standards. Overall, it is crucial a process control approach, comprising all steps of manufacturing, from the collection of the donor's cellular material to the final step of providing the product. All equipment must be constantly verified to ensure their reliability and validity, Standard Operating Procedures (SOPs) must be elaborated and updated, and it is essential the compliance with all the required quality assurance, quality control, and product liberation tests.

#### **Clinical Research Associates**

Monitoring is an important requirement in clinical trials in order to be compliant with GCP recommendations. In sponsored pharmacological trials, sponsor-indicated Clinical Research Associates (CRAs) must oversee the conduction of the trial through regular visits, reviewing protocols and records, and evaluating possible obstacles or unexpected outcomes. In academic research, it is up to the research team to provide such oversight activities. It is important to mention that, in academic research, nurses can reliably perform the CRA role. As demonstrated by Aguiar and Camacho (2010)<sup>(28)</sup> in a case report of a clinical trial in which their role as nurses and CRAs included oversight of protocols and records, assistance in the implementation of the study, control of potential biases, and assurance of the patients' well-being and rights.

#### **Nurse**

The role of the nurse in clinical research is a subject of great interest, in spite of being still incipient. These professionals are used to standardized and organized work structures, being able to perform the CRA role with excellence,

ensuring the adequate conduction of trials<sup>(28)</sup>. Besides, they may prove to be useful assets to the research team, being able to perform patient recruitment, obtain informed consent, perform infusion procedures, monitor the patients and ensure that all of the requirements of GCP guidelines are satisfied. The nurse is also qualified to be the mediator between research teams and the health care providers of the patient, which can be especially useful in multicentric studies, as mentioned before, ensuring that all of the peculiarities particular to the patient subject of cell therapy clinical trials are receiving adequate attention.

#### **Cell Therapy In Brazil**

The only modality of cell therapy that is routinely used both worldwide and in Brazil is HSCT<sup>(14)</sup>. This type of transplantation is the only kind of cell therapy that has its efficacy widely recognized and is recommended in a vast number of guidelines. Data from ClinicalTrials.gov<sup>(15)</sup> demonstrates that, in Brazil, there are several trials being conducted related to the search terms "cell therapy" and "stem cell". When trials involving HSCT are excluded from the search, most of the cell therapy trials involve mesenchymal stem cells for the treatment of several conditions, such as graft-versus-host disease (GVHD), aplastic anemia, chronic spinal cord injury, glaucoma, amyotrophic lateral sclerosis (ALS) and lipodystrophy. There is one trial using natural killer cells for the treatment of refractory acute myeloid leukemia, registered by our team. As mentioned before, it is important to notice that all cell therapy trials in Brazil must be conducted in accordance with GCP, GMP, and pertinent legislation, but there are no specific laws considering the design and conduction of cell therapy trials

#### **Regulation**

The federal constitution of Brazil<sup>(29)</sup> established in Article 199, fourth paragraph, the foundation of all regulations involving human tissues and cellular material in Brazil:

[...]

*Paragraph 4. The law shall provide for the conditions and requirements which facilitate the removal of organs, tissues and human substances for the purpose of transplants, research and treatment, as well as the collection, processing and transfusion of blood and its by-products, all kinds of sale being forbidden.*

[...]

Being in the highest hierarchical level of legislation, all subsequent regulations of cellular material and human tissues must abide by the cited points, such as the prohibition of any kind of sale of these products. It is worth mentioning, however, that federal legislation does not contemplate any specific regulation for cell therapy research and procedures. Exceptions are Law #9,434/1997<sup>(30)</sup>, which provides requirements for the removal of organs or human tissues for transplantation purposes, and Law #11,105/2005<sup>(31)</sup>, which provides safety requirements for any kind of activity that involves genetically modified organisms and their derivatives. Other than those laws, regulation of cell therapy procedures and research is performed mostly by technical resolutions issued by the National Health Surveillance Agency (ANVISA) or the National Health Council (CNS).

There are seven technical regulations issued so far by the National Health Surveillance Agency (ANVISA), which have implications on the manipulation of cellular material. The ANVISA Board Resolution (RDC) #56/2010<sup>(32)</sup> regulates laboratories that process progenitor hematopoietic cells; RDC #9/2011<sup>(3)</sup> provides requirements for the functioning of cell technology services (CTCs); RDC #23/2011<sup>(33)</sup> provides requirements for Banks of Germ Cells and Tissues (BCTGs); RDC #19/2012<sup>(34)</sup>, which revokes and changes some articles in RDC #56/2010; RDC # 34/2014<sup>(22)</sup>, which provides good practices for any kind of activity that involves human blood; RDC #72/2016<sup>(35)</sup>, which makes changes in RDC #23/2011, and RDC #75/2016<sup>(36)</sup>, which makes changes in RDC #34/2014.

Fundamentally, these resolutions provide frameworks and technical requirements for the operation of cell therapy services. However, they cannot provide specific regulations regarding the clinical application of cell therapy and its goals, considering that they are not federal laws approved by the National Congress of Brazil, and the Federal Constitution, as already mentioned, explicitly requires that these aspects must be regulated by federal laws, not technical resolutions issued by public agencies<sup>(23,29)</sup>. It is important to have in mind that, as stated by the Brazilian Federal Constitution, no one shall be obliged to do or refrain from doing something except by virtue of law. A technical norm, such as those issued by ANVISA or the CNS, under Brazilian legislation, is only able to specify technical procedures regarding federal laws, but is not able to interfere with it.

The National Congress of Brazil, thus, has the power to create laws. However, its operations are frequently behind schedule, because the process of creating a law is often arduous and imposes several bureaucratic requirements, and there is a huge discrepancy between the pace of technological advances in health care and the processing of laws. For this reason, it is crucial that legislators delegate these functions to public agencies such as ANVISA and the CNS, which can issue resolutions containing more accurate technical specifications. Brazilian Biosafety Law (Law #11,105/2005)<sup>(31)</sup>, for example, is a federal law regarding genetically modified organisms (GMOs) which assigns to prospective technical norms the duty of establishing the regulation of GMOs, an assignment usually done only by federal laws. This is a potential model that could be followed by a federal law regulating cell therapy.

## 7. Final Considerations

Compliance with international quality standards such as GCP and GMP as well as pertinent legislation is a major factor in ensuring the reliability and safety of potential new therapeutic possibilities. It is necessary to emphasize, however, that cell therapy clinical trials must also be subject to such approach. The complexity intrinsic to such interventions requires that all possible measures be taken to ensure the safety of these trials and the reliability of data generated. It is crucial that research teams performing such trials act in accordance with international quality standards, utilizing validated equipment and supplies, and having a capacitated multidisciplinary team.

## 8. Acknowledgements

The study received financial support from the Research and Event Incentive Fund of Hospital de Clínicas de Porto Alegre (FIPE-HCPA) and The National Council for Scientific and Technological Development (CNPq). The authors declare no conflicts of interest.

## References

- [1] Au P, Hursh DA, Lim A, Jr MCM, Oh SS, Schneider BS, et al. FDA Oversight of Cell Therapy Clinical Trials FDA Oversight of Cell Therapy Clinical Trials. *Sci Transl Med.* 2012;4(149).
- [2] Trounson A, et al. The rapid advance of stem cell clinical trials for a broad. *BMC Med.* 2011;9(52).
- [3] ANVISA. RESOLUÇÃO DE DIRETORIA COLEGIADA - RDC Nº9, DE 14 DE MARÇO DE 2011 [Internet]. 2011. Available from: [http://portal.anvisa.gov.br/documents/33880/2568070/rd\\_c0009\\_14\\_03\\_2011.pdf/47a01eaf-f568-44b4-b551-0b106baea474](http://portal.anvisa.gov.br/documents/33880/2568070/rd_c0009_14_03_2011.pdf/47a01eaf-f568-44b4-b551-0b106baea474)
- [4] Zucchetti C, Morrone FB. Perfil da Pesquisa Clínica no Brasil. *Rev HCPA.* 2012;32(3):340–7.
- [5] Goldim JR. Diretrizes, Normas e Leis em Pesquisa em Saúde: Seres Humanos [Internet]. 2015. Available from: <https://www.ufrgs.br/bioetica/diraber.htm>
- [6] MS. Resolução nº 196/96 [Internet]. 1996. Available from: [http://www.aids.gov.br/sites/default/files/anexos/legislacao/1996/51388/resolu\\_o\\_196\\_96\\_cns\\_26201.pdf](http://www.aids.gov.br/sites/default/files/anexos/legislacao/1996/51388/resolu_o_196_96_cns_26201.pdf)
- [7] MS. Resolução nº 466, de 12 de dezembro de 2012 [Internet]. 2012. Available from: <http://conselho.saude.gov.br/resolucoes/2012/Reso466.pdf>
- [8] (OPAS) ORGANIZAÇÃO PAN-AMERICANA DA SAÚDE. Boas Práticas Clínicas: Documento das Américas [Internet]. IV CONFERÊNCIA PAN-AMERICANA PARA HARMONIZAÇÃO DA REGULAMENTAÇÃO FARMACÊUTICA. 2005. Available from: [http://www.anvisa.gov.br/medicamentos/pesquisa/boaspraticas\\_america.pdf](http://www.anvisa.gov.br/medicamentos/pesquisa/boaspraticas_america.pdf)
- [9] MERCOSUL. Boas Práticas Clínicas Grupo Mercado Comum (MERCOSUL) - Resolução nº 129/96 [Internet]. 1996. Available from: <https://www.ufrgs.br/bioetica/bpcmerco.htm>
- [10] ICH. GUIDELINE FOR GOOD CLINICAL PRACTICE - ICH HARMONISED TRIPARTITE GUIDELINE [Internet]. 1996. Available from: [http://www.ich.org/fileadmin/Public\\_Web\\_Site/ICH\\_Products/Guidelines/Efficacy/E6/E6\\_R1\\_Guideline.pdf](http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6/E6_R1_Guideline.pdf)
- [11] Sensebé L, Bourin P, Tarte K. Good manufacturing practices production of mesenchymal stem/stromal cells. *Hum Gene Ther* [Internet]. 2011 Jan;22(1):19–26. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/21028982>
- [12] de Girolamo L, Lucarelli E, Alessandri G, Antonietta Avanzini M, Ester Bernardo M, Biagi E, et al. Mesenchymal stem/stromal cells: a new cells as drugs'' paradigm. Efficacy and critical aspects in cell therapy. *Curr Pharm Des* [Internet]. 2013;19(13):2459–73. Available from:



- [https://www.researchgate.net/publication/234030221\\_Mesenchymal\\_StemStromal\\_Cells\\_A\\_New\\_Cells\\_as\\_Drugs\\_Paradigm\\_Efficacy\\_and\\_Critical\\_Aspects\\_in\\_Cell\\_Therapy%5Cnhttp://www.ncbi.nlm.nih.gov/pubmed/23278600%5Cnhttp://www.pubmedcentral.nih.gov/articlerender.f](https://www.researchgate.net/publication/234030221_Mesenchymal_StemStromal_Cells_A_New_Cells_as_Drugs_Paradigm_Efficacy_and_Critical_Aspects_in_Cell_Therapy%5Cnhttp://www.ncbi.nlm.nih.gov/pubmed/23278600%5Cnhttp://www.pubmedcentral.nih.gov/articlerender.f)
- [13] ANVISA. Resolução RDC nº 17, de 16 de abril de 2010 [Internet]. 2010. Available from: [http://189.28.128.100/dab/docs/legislacao/resolucao17\\_16\\_04\\_10.pdf](http://189.28.128.100/dab/docs/legislacao/resolucao17_16_04_10.pdf)
- [14] Narahashi L, Carvalho ACC de, Araújo HP de. Regulamentação das terapias celulares no Brasil Stem Cell Therapy Regulations in Brazil. *Visa em debate*. 2015;3(3):19–24.
- [15] U.S. National Institutes of Health. CLINICAL TRIALS [Internet]. 2016. Available from: <https://clinicaltrials.gov/>
- [16] Von Tigerstom B. Revising the regulation of stem cell-based therapies: critical assessment of potential models. *Food Drug Law J* [Internet]. 2015;70(2):315–37. Available from: null
- [17] Trounson A, McDonald C. Cell Stem Cell Stem Cell Therapies in Clinical Trials: Progress and Challenges. 2015; Available from: <http://dx.doi.org/10.1016/j.stem.2015.06.007>
- [18] Konomi K, Tobita M, Kimura K, Sato D. New Japanese Initiatives on Stem Cell Therapies. Vol. 16, *Cell Stem Cell*. 2015. p. 350–2.
- [19] RNTC - Rede Nacional de Terapia Celular. A RNTC [Internet]. 2016. Available from: <http://www.rntc.org.br/>
- [20] Galli MC. Regulatory Aspects of Gene Therapy and Cell Therapy Products: A Global Perspective [Internet]. 2015. 230 p. Available from: <https://books.google.com/books?id=oliQCgAAQBAJ&pgis=1>
- [21] BERSENEV A. Cell therapy trials - 2014 Report [Internet]. 2015. Available from: <http://celltrials.info/2015/01/22/2014-report/>
- [22] ANVISA. RESOLUÇÃO DA DIRETORIA COLEGIADA – RDC Nº 34, DE 11 DE JUNHO DE 2014 [Internet]. 2014. Available from: [http://portal.anvisa.gov.br/documents/10181/2867975/%281%29RDC\\_34\\_2014\\_COMP.pdf/ddd1d629-50a5-4c5b-a3e0-db9ab782f44a](http://portal.anvisa.gov.br/documents/10181/2867975/%281%29RDC_34_2014_COMP.pdf/ddd1d629-50a5-4c5b-a3e0-db9ab782f44a)
- [23] Gee A. Cell Therapy - cGMP Facilities and Manufacturing [Internet]. 2009. Available from: <http://link.springer.com/10.1007/b102110>
- [24] Roseti L, Serra M, Bassi A. Standard Operating Procedure for the Good Manufacturing Practice-Compliant Production of Human Bone Marrow Mesenchymal Stem Cells. In 2014 [cited 2016 Nov 3]. p. 171–86. Available from: [http://link.springer.com/10.1007/7651\\_2014\\_103](http://link.springer.com/10.1007/7651_2014_103)
- [25] Astori G, Soncin S, Cicero V Lo, Siclari F, Sürder D, Turchetto L, et al. Bone marrow derived stem cells in regenerative medicine as advanced therapy medicinal products. *Am J Transl Res*. 2010;2(3):285–95.
- [26] Electric G. Cell expansion [Internet]. 2016. Available from: <https://promo.gelifesciences.com/GL/XURI/expansion.html#WDMuIS0rKM8>
- [27] Ashton-Prolla P, Clausell N, Fernandes MS, Matte U, Bittelbrunn AC, Hemesath MP, et al. BIOBANCO DO HOSPITAL DE CLÍNICAS DE PORTO ALEGRE: ASPECTOS TÉCNICOS, ÉTICOS, JURÍDICOS E SOCIAIS. *Rev HCPA*. 2009;
- [28] de Aguiar DF, Camacho KG. O cotidiano do enfermeiro em pesquisa clínica: um relato de experiência. *Rev da Esc Enferm*. 2010;44(2):526–30.
- [29] Brazil. Constitution of the Federative Republic of Brazil [Internet]. Documentation and Information Center. 1988. Available from: <http://english.tse.jus.br/arquivos/federal-constitution>
- [30] BRASIL. Lei nº 9.434, de 4 de Fevereiro de 1997. 1997.
- [31] BRASIL. Lei nº 11.105, de 24 de Março de 2005. 2005.
- [32] ANVISA. Resolução RDC nº 56, 16 de dezembro de 2010 [Internet]. 2010. Available from: <http://adcon.rn.gov.br/ACERVO/Suvisa/doc/DOC00000000117397.PDF>
- [33] ANVISA. RESOLUÇÃO DA DIRETORIA COLEGIADA – RDC Nº 23, DE 27 DE MAIO DE 2011 [Internet]. 2011. Available from: [http://portal.anvisa.gov.br/documents/10181/2954258/RDC\\_23\\_2011\\_COMP.pdf/ba335341-5993-4843-83dc-f23681690514](http://portal.anvisa.gov.br/documents/10181/2954258/RDC_23_2011_COMP.pdf/ba335341-5993-4843-83dc-f23681690514)
- [34] ANVISA. RESOLUÇÃO DA DIRETORIA COLEGIADA - RDC Nº 19, DE 23 DE MARÇO DE 2012. [Internet]. 2012. Available from: [http://portal.anvisa.gov.br/documents/33880/2568070/rdc0019\\_23\\_03\\_2012.pdf/5430d064-a8f2-49fb-a7f4-7be8090b01de](http://portal.anvisa.gov.br/documents/33880/2568070/rdc0019_23_03_2012.pdf/5430d064-a8f2-49fb-a7f4-7be8090b01de)
- [35] ANVISA. RESOLUÇÃO - RDC Nº - 72, DE 30 DE MARÇO DE 2016 [Internet]. 2016. Available from: [http://portal.anvisa.gov.br/documents/33880/2568070/RDC\\_72\\_2016.pdf/14b66550-3af2-4761-a439-2140c33043cd](http://portal.anvisa.gov.br/documents/33880/2568070/RDC_72_2016.pdf/14b66550-3af2-4761-a439-2140c33043cd)
- [36] ANVISA. Resolução - RDC nº 75, de 2 de maio de 2016 [Internet]. 2016. Available from: [http://portal.anvisa.gov.br/documents/10181/2782609/%281%29RDC\\_75\\_2016.pdf/bb01cd39-cb70-48d6-9126-d359999f25a6](http://portal.anvisa.gov.br/documents/10181/2782609/%281%29RDC_75_2016.pdf/bb01cd39-cb70-48d6-9126-d359999f25a6)