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**This text does not replace the one published in the Official Gazette.**

**BOARD OF DIRECTORS RESOLUTION - RDC No. 260, DATED DECEMBER 21, 2018**

**(Published in the Federal Official Gazette No. 249, dated December 28, 2018)**

*It provides on the rules for conducting clinical trials with investigational Advanced Therapy Medicinal Products in Brazil, and other provisions.*

The **Board of Directors of the Brazilian Health Surveillance Agency**, in the use of the attribution conferred to it by art. 15, III and IV allied to art. 7, III and IV, of Law 9,782, dated January 26, 1999, and to art. 53, V, §§ 1 and 3 of the Internal Regulation approved in accordance with Annex I of the Board of Directors Resolution (RDC, in Portuguese) No. 255, dated December 10, 2018, decided to adopt the following Board of Directors Resolution, as resolved at a meeting held on December 11, 2018, and I, Chief Executive Officer, determine its publication.

**CHAPTER I  
INITIAL PROVISIONS**

**Section I  
Purpose**

Art.1 It defines the regulatory procedures and requirements for conducting clinical trials with investigational Advanced Therapy Medicinal Products (ATMP) in Brazil.

**Section II  
Scope**

Art.2 This Resolution applies to clinical trials with investigational ATMP, which will be conducted in Brazil, for the purpose of proving safety and/or efficacy.

Sole Paragraph. Marketing authorization and post-market authorization of ATMP should follow specific regulations.

Art.3 This Resolution does not apply to:

I - clinical trials with drugs addressed by RDC No. 9, dated February 20, 2015, and its amendments; and

II - clinical trials with medical devices addressed by RDC No. 10, dated February 20, 2015, and its amendments.



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**Section III**  
**Definitions**

Art. 4 For the purposes of this Resolution, the following definitions are adopted:

I - Audit: systematic and independent analysis of clinical trial activities and documents, to determine whether the activities were adequately performed, and the data recorded, analyzed and reported accurately, when complying with the protocol, sponsor's standard operating procedures (SOPs), Good Clinical Practices (GCP) and applicable regulatory requirements;

II - Good Practices on Human Cells<sup>1</sup>: part of the Quality Assurance that ensures that cells/ATMP are consistently handled and controlled, with quality standards appropriate for the intended use;

III - Good Clinical Practices (GCP): standards for planning, conducting, performing, monitoring, auditing, recording, analyzing and reporting clinical trials, to ensure that the reported data and the results have credibility and accuracy, and that the rights, integrity and confidentiality of study participants are protected;

IV - Good Laboratory Practices (GLP): a quality system that covers the entire organizational process and the conditions under which non-clinical studies are planned, developed, monitored, recorded, filed and reported;

V - Investigator's Brochure: compilation of clinical and non-clinical data on the investigational ATMP that is relevant to the study of that product in humans;

VI - Clinical Trial Site: a public, private or philanthropic organization, legitimately constituted and duly registered in the National Register of Health Establishments (CNES, in Portuguese), where clinical trials are conducted;

VII - Brazilian Research Ethics Committee (CONEP, in Portuguese): an independent collegiate body of advisory, deliberative, normative and educational nature, linked to the National Council of Health (CNS, in Portuguese) of the Ministry of Health, as defined by CNS Resolution No. 446, dated August 11, 2011, which has as its main attribution the assessment of the ethical aspects of researches involving humans and the coordination of the network of the local institutions' Research Ethics Committees;

VIII - Brazilian Biosafety Technical Commission (CTNBio, in Portuguese): a multidisciplinary consultative and deliberative board which aims to provide technical and advisory support to the Federal Government in formulating, updating and implementing the National Biosafety Policy for Genetically Modified Organisms (GMOs) and their derivatives, as well as in establishing technical safety standards and technical opinions on the authorization of activities involving research and commercial use of GMOs and their derivatives (construction, experimentation, cultivation, handling, transport, marketing, consumption, storage, release and disposal), based on the assessment of their zoo-phytosanitary, human health and environmental risk;

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<sup>1</sup> In this Resolution, the expression "Good Practices on Human Cells", translated from the version in Portuguese, is equivalent, at the same time, to "Good Cell Practices" and "Good Manufacturing Practices for Advanced Therapy Medicinal Products", in English.



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IX - Independent (or Research) Ethics Committee (CEP, in Portuguese): interdisciplinary and independent board of public relevance, of advisory, deliberative and educational nature, created to defend the interests of participants of researches involving humans in their integrity and dignity and to contribute with the development of researches within ethical standards;

X - Independent Data Monitoring Committee: an independent committee established to monitor safety data collected from one or more clinical trials for the issuance of recommendations on the continuation, modification or suspension of such trials;

XI - Active Substance: cells or substances that perform a necessary effect to the intended therapeutic activity, used in the production of the ATMP;

XII - Special Statement (CE, in Portuguese): document issued by Anvisa, of authorizing nature, required for the start of the clinical trial in Brazil and, where applicable, for the import or export of investigational ATMP;

XIII - Specific Special Statement (CEE, in Portuguese): document issued by Anvisa required for the import or export application for a clinical trial with a class I ATMP, to a clinical trial subject to the notification regimen, and for clinical trials with investigational ATMP in progress prior to the publication of this Resolution;

XIV- Clinical Trial Start Date: corresponds to the date of inclusion of the first clinical trial participant in the world;

XV - Clinical Trial Start Date in Brazil: corresponds to the date of inclusion of the first clinical trial participant in Brazil;

XVI- Clinical Trial Termination Date: corresponds to the date of the last visit of the last clinical trial participant in the world;

XVII - Clinical Trial Termination Date in Brazil: corresponds to the date of the last visit of the last clinical trial participant in Brazil or other definition by the sponsor, expressly determined in the specific clinical trial protocol;

XVIII - Clinical Trial Protocol Deviation: any non-compliance with the procedures or requirements defined in the approved version of the clinical trial protocol, without major implications to the integrity of the trial, data quality or to the rights and safety of clinical trial participants;

XIX - Clinical Trial Dossier with Investigational Advanced Therapy Medicinal Product (DDCTA, in Portuguese): set of documents and information submitted to Anvisa comprising the process of clinical trials with Class II ATMP approvals;

XX - Simplified Clinical Trial Dossier with Investigational Advanced Therapy Medicinal Product (DSCTA, in Portuguese): set of documents and information submitted to Anvisa regarding clinical trials with Class I ATMP;

XXI - Clinical Trial: study in human volunteers, with the objective of discovering or confirming clinical effects; discovering or confirming the therapeutic effects; identifying any adverse events; and/or studying the absorption, distribution, mechanism of action, metabolism and excretion of the investigational ATMP to verify its safety and/or efficacy;

XXII - Adverse Event: any adverse clinical occurrence in a patient or clinical trial participant to whom an investigational ATMP has been administered, resulting in any



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unfavorable and unintended clinical signs, symptoms, infection or illness (including laboratory test results out of the reference range), whether related or not to the product;

XXIII - Serious Adverse Event: adverse clinical occurrence in a patient, related to the investigational ATMP, occurring at any dose, and resulting in one or more of the following outcomes:

- a) persistent or significant incapacity/disability;
- b) hospitalization of the patient or prolongation of existing hospitalization;
- c) congenital anomaly or birth defect;
- d) suspicion or transmission of infectious agent through ATMP;
- e) life-threatening;
- f) clinically significant event;
- g) death.

XXIV - Excipient: any component of the final product, intentionally added to its formulation, other than the active substance, impurities and packaging material;

XXV - Case Report Form (CRF): printed, optical or electronic document intended to record all the information on each clinical trial participant, including adverse events that, according to the protocol, must be reported to the sponsor;

XXVI - GCP Inspection: act of conducting official review of the documents, facilities, records and any other resources considered by the Health Authority to be related to the clinical trial and which may be found at the site where the trial is conducted, at the facilities of the sponsor and/or of the Contract Research Organization (CRO), or in other places that the authority deems appropriate;

XXVII - Raw Material: any substance, whether active or inactive, used in the production of the active substance and not intended to be part of the final product integrate the final product. Examples of raw materials are: culture media, growth factors, accessory cells and nucleic acids.

XXVIII - Starting Material: material used in the production of the ATMP that is part of the final product, including those of biological and non-biological origin. Examples of starting materials are: cells or tissues retrieved from a donor, supports and matrices or biomaterials combined with engineered cells;

XXIX - Monitoring: act of continuously reviewing the process of a Clinical Trial and ensuring that it is conducted, recorded and reported according to the clinical trial protocol, SOPs, GCP and the applicable regulatory requirements;

XXX - Clinical Trial Notification: information to be sent to Anvisa for the purpose of conducting post-marketing surveillance (phase IV clinical trials);

XXXI - Contract Research Organization (CRO): any company regularly installed in the national territory, contracted by the sponsor or sponsor-investigator that assumes, partial or totally, their attributions with Anvisa;

XXXII - Sponsor: individual or legal entity responsible for financing actions, infrastructure, human resources and institutional support related to the clinical trial, and responsible before Anvisa for the quality and integrity of the clinical trial data;

XXXIII - Investigator: qualified and trained person, responsible for the coordination and conduction of the clinical trial protocol, according to the descriptions contained therein. If the



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study is conducted by a group of individuals, the lead investigator of the group is called the principal investigator;

XXXIV - Sponsor-Investigator: qualified and trained person, responsible for coordinating and conducting the clinical trial protocol, according to the descriptions contained therein, with their own financial and material resources or those from national or international research funding entities. It is the individual responsible before Anvisa for the quality and integrity of the clinical trial data;

XXXV - Placebo: inert formulation, without active substances, administered to the clinical trial participant for the purpose of masking or being a comparator with the investigational ATMP;

XXXVI - Tissue Engineering Product: biological product consisting of human cells organized in tissues or organs that have properties that allow regenerating, reconstituting or replacing a human tissue or organ, in the presence or not of structural support consisting of biological or biocompatible material, and a) has been subjected to substantial manipulation; and/or (b) performs in the recipient a function distinct from that performed in the donor;

XXXVII - Advanced Therapy Medicinal Products (ATMP): advanced cellular therapy products, tissue engineering products and gene therapy products;

XXXVIII - Class I ATMP: advanced cellular therapy product submitted to minimal manipulation that performs in the recipient function distinct from that performed in the donor;

XXXIX - Class II ATMP: advanced cellular therapy product undergoing substantial manipulation, tissue engineering product and gene therapy product;

XL - Investigational ATMP: ATMP to be investigated in a clinical trial;

XLI - Advanced Cellular Therapy Product: biological product consisting of human cells or its non-chemically defined derivatives, with the purpose of obtaining therapeutic, preventive or diagnosing properties, through its main mode of action of metabolic, pharmacological and/or immunological nature, for autologous or allogeneic use in humans, and (a) has been submitted to substantial manipulation; and/or (b) performs in the recipient function distinct from that performed in the donor;

XLII - Gene Therapy Product: biological product whose active substance contains or consists of recombinant nucleic acid, to modify (regulate, repair, replace, add or delete) a genetic sequence or to modify the expression of a gene, for therapeutic, preventive or diagnostic purposes;

XLIII - Final Product: consists of the finished product that has completed all its production stages;

XLIV - Clinical Trial Protocol: document describing the objectives, context, the reasoning, design, methodology, statistical considerations and organization of the clinical trial;

XLV - Clinical Trial Protocol Violation: any noncompliance in the clinical trial protocol that may affect the quality of the data, which may compromise the integrity of the study or affect the safety or rights of the clinical trial participants.



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**Section IV  
Clinical Trial Site**

Art.5 The clinical trial site must have a Health Permit in force, issued by the competent state, city or Federal District Health Authority, except for establishments part of the Public Administration or instituted by it, to which the sole paragraph of art. 10 of Law 6,437, dated August 20, 1977, and legal state, city or Federal District complementary provisions apply.

Art.6 The clinical trial site must have adequate facilities to conduct the clinical trial protocol, regarding the physical infrastructure, equipment, instruments and human resources, and, where applicable, must follow the provisions of RDC No. 63, dated November 25, 2011, and its amendments.

**CHAPTER II  
RESPONSIBILITIES**

**Section I  
Responsibilities of the Sponsor and Sponsor-Investigator**

Art.7 The sponsor and the sponsor-investigator are assigned with the following responsibilities:

I - to prepare and submit the DDCTA or the DSCTA to Anvisa, for clinical trials with investigational ATMP in Brazil;

II - to implement and maintain Quality Assurance and quality control systems to ensure that clinical trials are documented and reported in accordance with GCP;

III - to select researchers, supplier establishments, cell processing centers and qualified clinical trial sites, thus ensuring the conduction of clinical trials in accordance with GCP;

IV - to ensure qualified professionals to supervise the general conduction of clinical trials, manage the data generated, conduct statistical analysis, and prepare reports;

V - to maintain data related to the clinical trial with the investigational ATMP in physical or digital file for a period of 10 (ten) years after the conclusion or discontinuation of the clinical trial or, in case of product registration, after the date of granting the respective registration;

VI - to ensure that the available investigational ATMP is in accordance with the RDC No. 214, dated February 07, 2018, which provides for Good Practices on Human Cells for therapeutic use and clinical research, and its amendments;

VII - to guarantee, where applicable, that the importation of the investigational ATMP is limited to the quantity required for the conduction of the clinical trial, as well as to distribute it only to the institutions informed in the clinical trial dossier and authorized by the respective ethics committees of the CEP/CONEP System;

VIII - to present evidence, where applicable, that the data obtained in non-clinical trials on the safety and efficacy of the investigational ATMP is sufficient to justify the human exposure in the population to be studied, by the route of administration and dosage chosen and for the duration of the proposed treatment;

IX - to provide medical care and follow-up to the participants affected by adverse events until their resolution or stabilization; and



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X - to promptly inform the investigators, if the clinical trial is to be terminated prematurely or suspended, for any reason.

Art.8 The sponsor or sponsor-investigator is responsible for the final destination of the investigational ATMP and other materials that may not be used in the clinical trial.

Art.9 The sponsor or sponsor-investigator must ensure that participation in any clinical trial with investigational ATMP is free of charge to all participants.

Art.10 The sponsor or sponsor-investigator is responsible for all expenses related to procedures and tests, especially those for diagnosis, treatment and hospitalization of the clinical trial participant and other actions necessary for the resolution of adverse events related to the clinical trials.

Art. 11 The sponsor or sponsor-investigator can contract a CRO to carry out the functions under his responsibility.

§1 Contracting referred to in the main section of this article does not waive the sponsor's and the sponsor-investigator's responsibility for the quality and integrity of the clinical trial data.

§2 Procedures related to the clinical trial, which are transferred to a CRO and assumed by the latter, must be specified by means of a formal document signed by the sponsor or sponsor-investigator, and by the CRO.

Art.12 If a clinical trial with a donated ATMP, already registered in Brazil, is carried out, and its outcomes involves proprietary interests, such as the inclusion of a new therapeutic indication in the product market authorization, the product donor shares the responsibilities with the sponsor or the sponsor-investigator of the trial.

**Section II**  
**Investigator's Responsibilities**

Art.13 The investigator must conduct the clinical trial according to the protocol agreed with the sponsor or sponsor-investigator, according to the GCP, as well as to the applicable regulatory and ethical requirements.

Art.14 The investigator must supervise the clinical trial and may delegate tasks to qualified personnel.

Sole Paragraph. The delegation referred to in the main section of this article does not imply mitigation of the investigator's responsibilities.

Art.15 The investigator may use the investigational ATMP only within the scope of the clinical trial authorized by Anvisa, by the CEP/CONEP System and, where applicable, by CTNBio.

Sole Paragraph. The storage and transportation of the product referred to in the main section of this article must occur according to the sponsor's or the sponsor-investigator's specifications and to applicable regulatory requirements.

Art.16 The investigator must provide medical care and follow-up to the participants affected by adverse reactions, until their resolution or stabilization.



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Sole Paragraph. The medical care and follow-up mentioned in the main section of this article must be supported by the sponsor or sponsor-investigator, without any cost to the participant.

Art.17 If the clinical trial is terminated prematurely or suspended for any reason, the investigator must inform to the participants the reason for the decision, as well as ensure them the necessary medical follow-up.

**Section III  
Responsibilities of the institution to which the sponsor-investigator is linked**

Art. 18 The institution to which the sponsor-investigator is linked must guarantee, by means of its own infrastructure or an outsourced qualified infrastructure, the accomplishment of at least:

- I - management of adverse events;
- II - management of the clinical trial protocol;
- III - data management and traceability;
- IV - training of personnel involved in the execution of the clinical trial;
- V - quality assurance of the clinical trial;
- VI - audit and monitoring of the clinical trial; and
- VII - waste management.

Art.19 The institution to which the sponsor-investigator is linked may delegate the responsibilities provided for it in the art. 18 of this Resolution to the sponsor-investigator, by means of a written document signed between the parties, which explicitly states the responsibilities and obligations assumed by each of the parties.

Sole Paragraph. The activities listed in items V and VI of art. 18 of this Resolution may not be delegated to the sponsor-investigator but may be delegated to a CRO.

**CHAPTER III  
GENERAL REQUIREMENTS FOR SUBMISSION TO ANVISA**

**Section I  
General Requirements for submission of the DSCTA, the DDCTA and the  
Clinical Trial Notification**

Art.20 The DSCTA or the DDCTA must be submitted, for the purposes of its regularization with Anvisa, by the sponsor, by the sponsor-investigator or by the CRO, for one or more phases of clinical trials.

§1 The person responsible for submitting the DSCTA or DDCTA, whether sponsor, sponsor-investigator or CRO, must also be responsible for all the subsequent submissions to Anvisa, related to the initial dossier.

§2 The DSCTA or the DDCTA must be submitted to Anvisa in cases that it is intended to conduct clinical trials with investigational ATMP in Brazil.

§3 For the purposes of analysis of the DSCTA or the DDCTA, the sponsor, sponsor-investigator or the CRO must protocol with Anvisa at least 1 (one) specific clinical trial dossier to be conducted in the country.





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Art.21 The person responsible for submitting the DSCTA or the DDCTA may request from Anvisa:

Information on product classification, through the completion of an investigational ATMP classification form, available on Anvisa website; and

Meeting with the competent technical area of the Agency, with a view to previously present and discuss the documentation to be submitted.

Art.22 After submission of the DSCTA to Anvisa, the clinical trial may be initiated with the sponsor or Sponsor-investigator being fully responsible for compliance with all the requirements set forth in this Resolution and other applied regulations, remaining subject to other applicable ethical and regulatory approvals.

Sole Paragraph. Anvisa will have 30 (thirty) calendar days counted from the submission of the DSCTA, for the issuance of the respective Specific Special Statement (CEE).

Art.23 Upon receipt of the DDCTA, Anvisa will have 180 (hundred-eighty) calendar days to analyze the dossier and express its opinion on the approval, non-approval or formulation of requirements in face of the application.

§1 The period referred to in the main section of this article may be extended for an equal period, upon justification and technical reason.

§2 Only clinical trials related to the DDCTA and listed in the Special Statement (CE) will be approved and may be initiated.

Art.24 Anvisa will issue the CE for each DDCTA and the CEE for each DSCTA, mentioning the clinical trials approved and able to be conducted in Brazil.

Art.25 At any time, after the issuance of the CE or CEE, Anvisa may request from the sponsor, sponsor-investigator or CRO, any other information it deems necessary for the product's classification, evaluation and monitoring of the clinical development, under penalty of suspension or cancellation of the clinical trial.

Art.26 No clinical trial may be initiated in Brazil without the technical opinion issued by the CEP/CONEP System or, in the case of a clinical trial involving GMOs, without the technical opinion on biosafety risk assessment issued by CTNBio, as provided by Law 11,105 of March 24, 2005, and its amendments.

## **Section II**

### **Content and format of DSCTA for Class I Advanced Therapy Medicinal Products**

Art.27 The DSCTA to be submitted to Anvisa must be composed of the following documents:

I - proof of payment of the Health Surveillance Inspection Fee (TFVS, in Portuguese), upon Federal Tax Liability Payment Form (GRU, in Portuguese), or proof of exemption;

II - clinical investigation plan for the class I investigational ATMP containing the following information:

- a. product description;
- b. possible mechanism of action;
- c. route of administration;



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- d. indications to be studied;
- e. overall objectives and planned duration for clinical development; and
- f. summary description, for each planned clinical trial, of the design, endpoints, population to be studied, hypothesis, participant inclusion/exclusion criteria, estimated number of participants, intended statistical planning and, where applicable, comparators, collection forecast and storage conditions for biological material.

III - specific clinical trial dossier to be performed in Brazil, which must be filed for each clinical trial, containing the following documents:

- a. clinical trial submission form, available on Anvisa website, duly completed;
- b. clinical trial protocol, according to the GCP; and
- c. proof of registration of the clinical trial in the "International Clinical Trials Registration Platform/World Health Organization" (ICTRP/WHO), the Brazilian Clinical Trials Registry (ReBEC, in portuguese) databases, or databases from another entity recognized by the "International Committee of Medical Journals Editors" (ICMJE).

IV - copy of regularization document issued by the Health Authority in Brazil, if the investigational ATMP is manufactured in the national territory, or an equivalent document issued by competent authority overseas, if the product is not of national production.

Art.28 If a new specific clinical trial dossier to be carried out in the country is proposed, the respective documentation must be filed in the form of a petition secondary to the DSCTA process, upon proof of payment of the GRU, or proof of exemption of the TFVS.

Art.29 Formulary with clinical trial start and termination dates in Brazil must be filed, in the form of a petition secondary to the DSCTA process, within 30 (thirty) calendar days counted from each start and termination date.

### **Section III**

#### **Content and format of the DDCTA for Class II Advanced Therapy Medicinal Products**

Art.30 The DDCTA to be submitted to Anvisa must be composed of the following documents:

- I - proof of payment of the TFVS, upon GRU, or proof of exemption;
- II - clinical investigation plan for the investigational ATMP, containing the following information:
  - a. product description;
  - b. possible mechanism of action;
  - c. route of administration;
  - d. indications to be studied;
  - e. overall objectives and planned duration for clinical development; and
  - f. summary description, for each planned clinical trial, of the design, endpoints, population to be studied, hypothesis, participant inclusion/exclusion criteria, estimated number of participants, intended statistical planning and, where applicable, comparators, collection forecast and storage conditions for biological material.
- III - investigator's brochure containing the following information:
  - a. description of the product, including composition;



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- b. biological and toxicological effects on animals and humans, where applicable;
- c. information on safety and efficacy in humans, obtained from clinical trials already performed, when available; and
- d. possible risks and adverse events related to the use of the investigational product.

IV - production dossier of the investigational ATMP containing the following information:

- a. identification and address of all establishments involved in the production of the investigational ATMP, including the active substance;
- b. copy of regularization document issued by the Health Authority in Brazil, if the investigational ATMP is manufactured in the national territory, or an equivalent document issued by competent authority overseas, if the product is not of national production;
- c. list of all starting materials used in the production of the investigational ATMP including, in the case of gene therapy product, those intended to produce vectors and for the genetic manipulation of the cells;
- d. list of raw materials used in the production of the investigational ATMP, including the name of the material, manufacturer, quantity, recommendations of the pharmacopoeia or specifications of in-house materials or technologies, including the documentation on quality controls used;
- e. list of equipment used in the process;
- f. information on the selection of the donor of starting and raw material of human origin, including clinical, social and laboratory screening, physical evaluation, and other relevant evaluations, according to the RDC No. 214, dated February 7, 2018, and its amendments;
- g. documentation regarding the control of transmissibility of spongiform encephalopathies (TSEs), in accordance with the provisions of the RDC No. 214, dated February 7, 2018 and RDC No. 305, dated November 14, 2002, and their amendments;
- h. overall description of the product's production process, containing:
  - 1. detailed information of all stages, including the steps for selection of the cell population of interest, cell culture, transformation by physical-chemical and/or biological agents;
  - 2. detailed information on all stages of production of the vectors, where applicable; and
  - 3. detailed information on the production stages of the excipients, where applicable.
- i. characterization of the active substance, including, where appropriate, its identity, quantity, purity, viability, potency, karyology and sterility;
- j. description of the validated analytical methodologies for the characterization of the active substance;
- k. overall description of the final investigational ATMP, containing, where appropriate, information on composition and characterization, including identity, quantity, purity, viability, potency, karyology and sterility, as well as information on excipients and impurities;
- l. results from stability studies to ensure the use of the product in the planned clinical trials;
- m. description of placebo, where applicable, including composition, organoleptic characteristics, manufacturing process and analytical controls;



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- n. description of the comparator product or comparator treatment, where applicable, including information to ensure the maintenance of its characteristics;
- o. model of label of the investigational product; and
- p. critical analysis of non-clinical studies that contribute to the safety of the proposed clinical development, as well as information on the sites where these studies were conducted, on where their records are available for consultation, including statement that each study was conducted in accordance with GLP or, in cases of non-compliance with GLP, technical justification for this exception.

V - specific clinical trial dossier to be performed in Brazil, filed for each clinical trial, in the form of a secondary petition to the DDCTA process, containing the following documents:

- a. clinical trial submission form, available on Anvisa website, duly completed;
- b. clinical trial protocol, according to the GCP;
- c. proof of registration of the clinical trial in the International Clinical Trials Registration Platform/World Health Organization (ICTRP/WHO), the Brazilian Clinical Trials Registry (ReBEC) databases, or database from another entity recognized by the "International Committee of Medical Journals Editors" (ICMJE).

Art.31 If a new specific clinical trial dossier to be carried out in the country is proposed, the respective documentation must be filed in the form of a secondary petition to the DDCTA process, upon proof of payment, through a GRU, or proof of exemption of TFVS.

Art.32 Formulary with clinical trial start and termination dates in Brazil must be filed, in the form of a petition secondary to the DSCTA process, within 30 (thirty) calendar days counted from each start and termination date.

#### **Section IV**

##### **Phase IV Clinical Trial Notification with ATMP (post-marketing)**

Art.33 Post-marketing clinical trials (phase IV) with ATMP are subject to the reporting regimen without the need for DSCTA or DDCTA submission.

§1 The clinical trials referred to in the main section of this article do not require an authorization from Anvisa, remaining subject to other applicable ethical approvals.

§2 If a post-marketing clinical trial (phase IV) is related to an investigational ATMP that already has DSCTA or DDCTA approved by Anvisa, the notification protocol must be linked to the original DSCTA or DDCTA process.

Art.34 The post-marketing clinical trial notification (phase IV) must consist of the following information:

I - clinical trial submission form duly completed, according to the model available on Anvisa website;

II - clinical trial protocol, according to the GCP;

III - proof of registration of the clinical trial in the "International Clinical Trials Registration Platform/World Health Organization" (ICTRP/WHO), the Brazilian Clinical Trials Registry (ReBEC, in Portuguese) databases, or database from another entity recognized by the "International Committee of Medical Journals Editors" (ICMJE).



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Sole Paragraph. For the import or export purposes, Anvisa will have 30 (thirty) calendar days, counted from the receipt of the notification referred to in this Section, for the issuance of the respective CEE.

Art.35 This section only applies to post-marketing clinical trials (phase IV), except for all other post-marketing surveillance studies to be disciplined in a specific Resolution, for the marketing authorization of ATMP, published by Anvisa.

**CHAPTER IV  
AMENDMENTS TO DDCTA AND DSCTA**

**Section I  
Substantial changes**

Art.36 For the purposes of this Resolution, substantial changes consist of:

I - inclusion of not foreseen or of a different clinical trial protocol compared to that established in the clinical investigational plan of the investigational ATMP;

II - exclusion of clinical trial protocol; or

III - change that potentially impacts the quality or safety of the investigational ATMP, active comparator, or placebo.

Art.37 The request for a substantial change to the DDCTA and DSCTA must be submitted to Anvisa in the form of a secondary petition to the original process, according to the model made available by the Agency.

Sole Paragraph. The secondary petition will be linked to the respective DDCTA or DSCTA process, upon proof of payment of the TFVS, upon GRU, or proof of exemption.

Art.38 Substantial changes:

I - to the DDCTA, may only be implemented after Anvisa's approval;

II - to the DSCTA, may be implemented after the submission of the secondary petition regarding the intended substantial change, with the sponsor or sponsor-investigator being fully responsible for compliance with all requirements set forth in this Resolution and related regulations, remaining subject to other applicable ethical and regulatory approvals.

Art.39 Upon receipt of the secondary petition regarding a substantial change in the DDCTA, Anvisa will have 60 (sixty) calendar days to analyze the application and express its opinion on the approval, non-approval or formulation of requirements in face of the application.

Sole Paragraph. The period referred to in the main section of this article may be extended for an equal period, upon justification and technical reason.

Art.40 Changes to the DDCTA resulting from safety recommendations or alerts related to the clinical trial, issued by international Health Authorities, must be notified to Anvisa and may be executed independently of the prior manifestation by the Agency.

**Section II  
Amendments to the clinical trial protocol**



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Art.41 For the purposes of this Resolution, an amendment will be considered substantial when it modifies the scientific value of the clinical trial protocol or interferes in the safety of the participants, according to a specific manual available on Anvisa website.

Art.42 Any amendment referred to in this Resolution may only be implemented after obtaining the respective ethical approvals, in compliance with current legislation.

Art.43 The request for a substantial amendment to the DDCTA and the DSCTA must be submitted to Anvisa in the form of a secondary petition to the original process, according to the model made available by the Agency.

Sole Paragraph. The secondary petition will be linked to the respective DDCTA or DSCTA process, upon original proof of payment of the TFVS, upon GRU, or proof of exemption.

Art.44 Substantial amendments:

I- to the DDCTA, may only be implemented after Anvisa's approval;

II - to the DSCTA, may be implemented after the submission to Anvisa of a secondary petition regarding the intended amendment, with the sponsor or sponsor-investigator being fully responsible for compliance with all requirements set forth in this Resolution and related regulations, remaining subject to other applicable ethical and regulatory approvals.

§1 Upon receipt of the secondary petition regarding a substantial amendment to the DDCTA, Anvisa will have 60 (sixty) calendar days to analyze the request and express its opinion on the approval, non-approval or formulation of requirements in face of the application.

§2 The period referred to in §1 of this article may be extended for an equal period, upon justification and technical reason.

§3 Substantial amendments aimed at eliminating immediate risks to the participants' safety must be notified to Anvisa, but must be implemented immediately, regardless of the prior manifestation by the Agency.

Art.45 Amendments to the clinical trial protocol not considered substantial must be presented to Anvisa as part of the annual clinical trial protocol monitoring report.

**Section III**  
**Suspensions and Terminations**

Art.46 The sponsor or sponsor-investigator may terminate or suspend the DDCTA, the DSCTA or the clinical trial, at any time, upon presentation of technical-scientific and/or financial justifications, as well as presentation of the monitoring plan for the participants in the clinical trials already initiated.

§1 As the DDCTA or DSCTA is terminated, no clinical trial related to it may be continued in the country.

§2 If DDCTA, DSCTA or clinical trial is terminated for safety reasons, the sponsor or the sponsor-investigator must justify technically and scientifically the reasons for the cancellation, as well as present the respective measures for risk minimization/mitigation to the study participants.



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Art.47 The sponsor or sponsor-investigator must notify Anvisa, in the form of a secondary petition, within a maximum period of 15 (fifteen) calendar days from the decision to suspend or terminate a clinical trial, DDCTA or DSCTA.

Sole Paragraph. Suspended clinical trials, DDCTA or DSCTA may only be restarted after Anvisa's authorization.

Art.48 The sponsor or sponsor-investigator must notify Anvisa, in the form of a secondary petition, within a maximum period of 7 (seven) calendar days, the temporary suspension as an immediate safety measure of the clinical trial, DDCTA or DSCTA, justifying the reasons for this decision.

Sole Paragraph. The reasons, scope, discontinuation of treatment and suspension of participants recruitment must be clearly explained in the temporary suspension notification.

Art.49 Anvisa may, at any time, suspend or terminate the DDCTA, the DSCTA or any clinical trial linked thereto, if it considers that the approval conditions have not been met, or if there are safety or efficacy reports that significantly affect the clinical trials participants or the scientific validity of data obtained. The sponsor or the sponsor-investigator must be informed in a reasoned and justified manner.

**CHAPTER V  
SAFETY AND ALERTS MONITORING**

**Section I  
Monitoring of Adverse Events**

Art.50 The sponsor and sponsor-investigator or the CRO, must monitor all adverse events, including the non-serious ones, during the clinical trial of an investigational ATMP.

Art.51 The sponsor, sponsor-investigator, CRO or the Independent Data Monitoring Committee must systematically collect and evaluate pooled adverse event data that occurred during the clinical trial, submitting the results from this evaluation to Anvisa as part of the annual clinical trial monitoring reports of the investigational ATMP.

Art.52 The investigator must communicate the occurrence of all adverse events to the sponsor, sponsor-investigator or CRO and provide all the information requested, as well as manifest the possible causality between the adverse event and the investigational product.

§1 All adverse events must be recorded on the Case Report Form (CRF) and must be processed.

§2 The affected participants must be accompanied by the principal investigator and his/her team, until their stabilization or the resolution of the adverse event.

Art.53 In the event of a serious adverse event occurring during the conduct of the clinical trial, at any stage of development of the investigational ATMP, the sponsor, sponsor-investigator or the CRO and the investigator must adopt immediate safety measures, in order to protect the other clinical trial participants from any imminent risk.

§1 The sponsor, the sponsor-investigator or the CRO must report to Anvisa, by means of a specific form available on Anvisa website, the serious adverse events that have occurred, whose causality is possible, probable or confirmed in relation to the investigational product.





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§2 Serious adverse events that lead to death or are life-threatening must be notified to Anvisa, through a specific form available on Anvisa website, within a maximum period of 7 (seven) days from the acknowledgement date of the case by the sponsor or sponsor-investigator.

§3 The notification of other serious adverse events occurred must be carried out within a maximum period of up to 15 (fifteen) calendar days from the acknowledgement of the case by the sponsor or the sponsor-investigator.

§4 The sponsor and the sponsor-investigator must keep all detailed records of the adverse events reported by the investigators, and Anvisa may, at any time, request such records.

Art.54 The sponsor and the sponsor-investigator must establish a monitoring plan for the detection of late adverse events, justifying the proposed period.

Sole Paragraph. In the case of pregnancy, the investigator and the sponsor-investigator, or the investigator and the sponsor must monitor the mother and the child.

Art.55 The sponsor or sponsor-investigator must inform the investigators involved in the clinical trial of the adverse events whose causality is possible, probable or confirmed, as well as adopting the procedures for updating the investigator's brochure, and reassessing the risks and benefits to participants.

Art.56 The development of a phase III clinical trial must be accompanied by Independent Data Monitoring Committee, and its recommendations must be reported to Anvisa by the sponsor, by the sponsor-investigator or by the CRO.

**Section II  
Clinical trial Monitoring Reports and Final Report**

Art.57 The sponsor, sponsor-investigator or CRO must submit to Anvisa, in the form of a secondary petition to the DSCTA or DDCTA, annual monitoring reports, tabulated for each clinical trial protocol, containing the following information:

I - title of the clinical trial;

II - recruitment status of clinical trial participants;

III - listing of the number of participants recruited per site;

IV - number and description of deviations and clinical trial protocol violations, per site;

V - description of all adverse events occurring per site in the assessed period, identifying the clinical trial participants by the codes used in the CRF adopted in the clinical trial protocol; and

VI - modifications to DSCTA and DDCTA not considered substantial.

Sole Paragraph. The annual monitoring report must be submitted within a maximum period of 60 (sixty) calendar days, having as an annuality reference the clinical trial start date in Brazil.

Art.58 Upon completion of the activities of a clinical trial in all participating countries, the responsible for submitting the DDCTA and DSCTA must submit to Anvisa, in the form of a





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secondary petition, within 12 months of the clinical trial termination date, the final clinical trial report containing the following information:

I - title of the clinical trial;

II - number of participants recruited and number of participants withdrawn from the clinical trial;

III - description of patients included in each statistical analysis and of those who were excluded from the efficacy analysis;

IV - demographic region of the participants recruited in the clinical trial;

V - overall statistical analysis;

VI - number and description of clinical trial protocol deviations and violations;

VII - list of all adverse events with causality assessment, occurring by participants;

VIII - results obtained in the measurement of the endpoints, for each clinical trial participant; and

IX - justification for the suspension or termination of the clinical trial in Brazil or worldwide, when applicable.

Art.59 The sponsor or sponsor-investigator must submit annually to Anvisa, the Safety Update Reports of the investigational ATMP, by means of a secondary petition to the DSCTA or DDCTA.

Sole Paragraph. The reports referred to in the main section of this article must be submitted within 60 (sixty) calendar days, having as an annuality reference the approval date of the DDCTA or DSCTA by Anvisa, or a date determined in the international development.

## **CHAPTER VI**

### **INSPECTIONS**

Art.60 Anvisa may conduct inspections at the sponsor, at the institution to which the sponsor-investigator is linked, at the CRO, as well as in the clinical trial sites.

Art.61 Depending on the conclusion of the GCP inspection, Anvisa may determine:

I - the suspension of the clinical trial;

II - the termination of the trial at the non-compliant clinical trial site;

III - termination of the trial in all clinical trial sites in Brazil;

IV - invalidation of data from non-compliant clinical trial sites; or

V - invalidation of clinical trials under non-compliance with GCP.

Art.62 Anvisa may conduct Good Practices on Human Cells inspections in the production of the investigational ATMP, in order to verify the information contained in the DDCTA or the DSCTA, as well as to ensure compliance with the RDC No. 214, dated February 7, 2018, and its amendments.



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**CHAPTER VII**  
**IMPORTS AND EXPORTS**

Art.63 The importation and exportation of goods and products to be used in a clinical trial with investigational ATMP must be subject to supervision by the Health Authority at the place of clearance or shipment.

§1 The provisions of the RDC No. 172, dated September 12, 2017, and its amendments, must not apply to the goods and products referred to in the main section of this article.

§2 For the purposes of the inspection referred to in this article, the Health Authority at the place of clearance must verify the publication of CEs or CEEs, related to the goods and products to be imported or exported.

Art.64 The packing, packaging, documentation and transportation of biological material to be used in a clinical trial with investigational ATMP must be performed in order to ensure and maintain the integrity of these products, in an appropriate and exclusive container for the purpose of export and import, with the appropriate internal temperature and duly identified, in accordance with the RDC No. 20, dated April 10, 2014, and the RDC No. 214, of 2018, and their amendments.

Sole Paragraph. It is the importer's or exporter's responsibility to comply with the provisions of the main section of this article.

**CHAPTER VIII**  
**FINAL AND TRANSIENT PROVISIONS**

Art.65 Any material of human origin obtained in Brazil used in the production of ATMP must be obtained free of charge, by free, spontaneous and informed donation, in compliance with the provisions of the RDC No. 214, of 2018, and its amendments.

Art.66 In the case of clinical trials with investigational ATMP approved by the CEP/CONEP System and already in progress in Brazil at the time of publication of this Resolution, the sponsor or sponsor-investigator must submit, within 90 (ninety) days from the publication date of this Resolution, the DSCTA, DDCTA or Clinical trial notification, observing the requirements applicable, according to Sections II, III and IV of Chapter III of this Resolution.

§1 The clinical trials with investigational ATMP described in the main section of this article may be continued, regardless of Anvisa's approval, and the sponsor or sponsor-investigator is fully responsible for compliance with all the requirements set forth in this Resolution and in related regulations, remaining subject to other applicable ethical and regulatory approvals.

§2 At any time, Anvisa may request other information that it deems necessary for the classification of the product, evaluation and monitoring of the intended clinical trial development, remaining the clinical trial under the possibility of suspension or cancellation.

Art.67 Subsection III of art. 6 of the RDC No. 214, of 2018, is now in force with the following wording:

"III - Gene Therapy Product."

Art.68 The subsection XXVI of art. 7 of the RDC No. 214, of 2018, is now in force with the following wording:



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"XXVI - Gene Therapy Product: biological product whose active component contains or consists of recombinant nucleic acid, to modify (regulate, repair, replace, add or delete) a genetic sequence or to modify the expression of a gene, for therapeutic, preventive or diagnostic purposes".

Art.69 Art. 64 of the RDC No. 214, of 2018, is now in force with the following wording:

"Art.64 In the case of Gene Therapy Product, the records of the tests of identity, integrity, purity and potency related to the line of mother cells and vector must be kept." (NR)

Art.70 Subsection III of art. 87 of the RDC No. 214, of 2018, is now in force with the following wording:

"III - cells and ATMP processing; and the production of gene therapy vectors or manipulation of Gene Therapy Products demands dedicated rooms or isolated environments (by using isolators technology), as determined in art. 157 hereof;"

Art.71 The main section of art. 139 of the RDC No. 214, of 2018, is now in force with the following wording:

"Art.139 The blood samples for donor's laboratorial screening, as well as aliquots referred to in subsections I to III of art. 167 of this Resolution, must be collected:"

Art.72. §2 and subsection I of art. 158 of the RDC No. 214, of 2018, are now in force with the following wording:

"§2 Vectors and Gene Therapy Products must not be produced or manipulated in the same room as other types of cells or ATMP (Advanced Cellular Therapy Products or Tissue Engineering Products), and:

I - manipulation of Gene Therapy Product can be performed within the same room or area used to produce vector, provided there is an approved protocol for environment cleaning and disinfection ensuring the non-occurrence of cross-contamination; and"

Art.73 Failure to comply with the provisions of this Resolution constitutes a health infraction, according to Law 6.437, dated August 20, 1977, without prejudice to the applicable civil, administrative and penal liabilities.

Art.74 Omitted or complementary cases will be settled in the light of other national norms and international guidelines related to the subject addressed by this Resolution.

Art.75 This Resolution enters into force 60 (sixty) days after the date of its publication.

**WILLIAM DIB**