COLLEGIATE BOARD RESOLUTION – RDC No. 506 OF 27 MAY 2021

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Provides for the rules to conduct clinical trials with investigational Advanced Therapy Medicinal Products in Brazil and gives other provisions.

The Collegiate Board of Directors of the Brazilian Health Regulatory Agency, in the use of the attributions vested in it under Article 15, items III and IV, combined with Article 7, items III and IV, of Law no. 9,782 of 26 January 1999, and Article 53, item V, paragraphs 1 and 3, of the Internal Regulation approved by Annex I of Collegiate Board Resolution – RDC no. 255 of 10 December 2018, adopts the following Collegiate Board Resolution, as decided upon in a meeting held on 11 December 2018, and I, the Director-President, determine its publication.

CHAPTER I

INITIAL PROVISIONS

Section I

Objective and Scope

Article 1. This Resolution defines the regulatory procedures and requirements to conduct clinical trials with investigational advanced therapy medicinal products in Brazil.

Article 2. This Resolution applies to clinical trials with investigational advanced therapy medicinal products, which will be developed in Brazil, for the purposes of proving safety, efficacy, or safety and efficacy.

Sole paragraph. Marketing authorization and post-marketing authorization of advanced therapy medicinal products must follow the provisions in Collegiate Board Resolution – RDC no. 505 of 27 May 2021, or its updates.

Article 3. This Resolution does not apply to:

I – clinical trials with medicinal products provided for in Collegiate Board Resolution – RDC no. 9 of 20 February 2015, or its updates; and

II – clinical trials with medical devices provided for in Collegiate Board Resolution – RDC no. 10 of 20 February 2015, or its updates.

Section II

Definitions

Article 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 were recorded, analyzed, and reported accurately, when complying with the protocol, the sponsor's Standard Operating Procedures (SOPs), the Good Clinical Practices (GCP) and the applicable regulatory requirements;

II – Good Practices on Human Cells[1]: part of the Quality Assurance that ensures cells and advanced therapy medicinal products 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, in order to ensure that the reported data and results have credibility and accuracy, and that the rights, integrity, and confidentiality of clinical trial participants are protected;

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

V – Investigator's Brochure: compilation of clinical and non-clinical data related to an investigational advanced therapy medicinal product that is relevant to the study of that product's use 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 of 11 August 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 collegiate body that aims at providing 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, transportation, commercialization, consumption, storage, release, and disposal), based on the assessment of their zoo-phytosanitary, human health, and environmental risk;

IX – Research Ethics Committee (CEP, in Portuguese): interdisciplinary and independent collegiate board of public relevance, of advisory, deliberative, and educational nature, created

[1] In this Resolution, the expression "Good Practices on Human Cells", translated from the original version in Portuguese, is equivalent to both "Good Cell Practices" and "Good Manufacturing Practices for Advanced Therapy Medicinal Products", in English.

to defend the interests of participants of researches involving humans in their integrity and dignity, and to contribute towards the development of research within ethical standards;

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

XI – Active Component: cells or substances that perform a necessary effect to the intended therapeutic activity, used in the manufacture of the advanced therapy medicinal product;

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 request to import or export investigational advanced therapy medicinal products;

XIII – Specific Special Statement (CEE, in Portuguese): document issued by Anvisa required for the import or export request for a clinical trial subject to the notification regimen, and for clinical trials with investigational advanced therapy medicinal products in progress prior to the publication of this Resolution;

XIV – clinical trial start date: it corresponds to the date of inclusion of the first clinical trial participant in the world;

XV – clinical trial start date in Brazil: it corresponds to the date of inclusion of the first clinical trial participant in Brazil;

XVI – clinical trial termination date: it corresponds to the date of the last visit of the last clinical trial participant in the world;

XVII – clinical trial termination date in Brazil: it 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 Development Dossier of Investigational Advanced Therapy Medicinal Product (DDCTA, in Portuguese): set of documents and information comprising the process of approval of clinical trials with Class II advanced therapy medicinal products;

XX – Simplified Dossier for Clinical Trial with Investigational Advanced Therapy Medicinal Product (DSCTA, in Portuguese): set of documents and information comprising the process submitted to Anvisa regarding clinical trials with Class I advanced therapy medicinal products;

XXI – clinical trial: research conducted in humans, with the objective of discovering or confirming clinical effects; discovering or confirming therapeutic effects; identifying any adverse events; and/ or studying the absorption, distribution, mechanism of action, metabolism, and excretion of the investigational advanced therapy medicinal product, in order 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 advanced therapy medicinal product has been administered, resulting

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

XXIII – serious adverse event: adverse clinical occurrence in a patient, related to the investigational advanced therapy medicinal product, 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 the advanced therapy medicinal product;

e) threat to life;

f) clinically significant event;

g) death.

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

XXV – Case Report Form (CRF): printed, optical, or electronic document intended to record all 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 an official review of documents, facilities, records, and any other resources considered by the health authority to be related to the clinical trial and that 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 component and not intended to be an integral part of the final product, such as culture media, growth factors, accessory cells, and nucleic acids.

XXVIII – starting materials: materials used in the production of the advanced therapy medicinal product, which are part of the final product, including those of biological and non-biological origin, such as 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 purposes of conducting post-marketing (phase IV) clinical trials;

XXXI – Contract Research Organization (CRO): any company regularly installed in Brazilian territory, contracted by the sponsor or sponsor-investigator, which takes their attributions with Anvisa, either in part or in total;

XXXII – sponsor: individual or legal entity responsible for financing actions, infrastructure, human resources, and institutional support related to the clinical trials, and responsible before Anvisa for the quality and integrity of 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 study is conducted by a group of individuals, the lead investigator of the group is called the main 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 clinical trial data;

XXXV – placebo: inert formulation, without active components, administered to the clinical trial participant for the purposes of masking or being a comparator with the investigational advanced therapy medicinal product;

XXXVI – tissue engineering product: biological product consisting of human cells organized in tissues or organs presenting 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 submitted to substantial manipulation; and/ or

b) performs in the recipient a function distinct from that performed in the donor;

XXXVII – advanced therapy medicinal products: advanced cellular therapy products, tissue engineering products, and gene therapy products;

XXXVIII – class I advanced therapy medicinal product: advanced cellular therapy product submitted to minimal manipulation that performs in the recipient a function distinct from that performed in the donor;

XXXIX – class II advanced therapy medicinal product: advanced cellular therapy product submitted to substantial manipulation, tissue engineering product, and gene therapy product;

XL – investigational advanced therapy medicinal product: advanced therapy medicinal product to be investigated in a clinical trial;

XLI – advanced cellular therapy product: biological product consisting of human cells or its non-chemically defined derivatives, intended to obtain therapeutic, preventive, or diagnostic 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 a function distinct from that performed in the donor;

XLII – gene therapy product: biological product whose active component contains or consists of recombinant nucleic acid, intended to alter (regulate, repair, replace, add, or delete) a genetic sequence or to alter the expression of a gene, for therapeutic, preventive, or diagnostic purposes;

XLIII – final product: it 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.

Section IV

Clinical Trial Site

Article 5. The clinical trial site must have a health permit in force, issued by the competent state, municipal, or Federal District health authority, except for the establishments that are part of the Public Administration or instituted by it, in accordance with the sole paragraph of Article 10 of Law 6,437 of 20 August 1977, and legal state, municipal, or Federal District complementary provisions.

Article 6. The clinical trial site must have adequate facilities to conduct the clinical trial protocol, regarding physical infrastructure, equipment, instruments, and human resources, and, where applicable, must comply with the provisions of Collegiate Board Resolution – RDC no. 63 of 25 November 2011 or its updates.

CHAPTER II

RESPONSIBILITIES

Section I

Responsibilities of the Sponsor and Sponsor-Investigator

Article 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 advanced therapy medicinal products in Brazil;

II – to implement and maintain quality assurance and quality control systems to ensure that the clinical trials conducted are documented and reported in accordance with the GCP;

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

IV – to ensure that qualified professionals 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 advanced therapy medicinal products 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 marketing authorization, after the date the respective marketing authorization was granted;

VI – to ensure that the investigational advanced therapy medicinal product to be made available is in accordance with Collegiate Board Resolution – RDC no. 508 of 27 May 2021, which provides for Good Practices on Human Cells for therapeutic use and clinical research, or its updates;

VII – to guarantee, where applicable, that the import of the investigational advanced therapy medicinal product is limited to the quantity required for the conduction of the clinical trial, as well as it is distributed 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 advanced therapy medicinal product 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

X – to promptly inform the investigators, in case the clinical trial is to be terminated prematurely or suspended, for any reason.

Article 8. The sponsor or sponsor-investigator is responsible for the final destination of the investigational advanced therapy medicinal product and other materials that may not be used in the clinical trial.

Article 9. The sponsor or sponsor-investigator must ensure that participation in any clinical trial with investigational advanced therapy medicinal products is free of charge for all participants.

Article 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.

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

Paragraph 1. The contract referred to in the caption 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.

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

Article 12. In case of conduction of a clinical trial with a donated advanced therapy medicinal product already granted a marketing authorization in Brazil, the outcomes of which involve proprietary interests, such as the inclusion of a new therapeutic indication in the product marketing authorization, the product donor shares the responsibilities with the sponsor or the sponsor-investigator of the trial.

Section II

Investigator's Responsibilities

Article 13. The investigator must conduct the clinical trial in accordance with the protocol agreed with the sponsor or sponsor-investigator, the GCP, and the applicable regulatory and ethical requirements.

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

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

Article 15. The investigator may use the investigational advanced therapy medicinal product only within the scope of the clinical trial authorized by Anvisa, the CEP/CONEP system and, where applicable, CTNBio.

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

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

Sole Paragraph. The medical care and follow-up referred to in the caption of this article must be provided by the sponsor or sponsor-investigator, without any cost to the participant.

Article 17. In case 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

Article 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 the following:

I – management of adverse events;

II – management of the clinical trial protocol;

III – data management and traceability;

IV – training of personnel involved in the conduction of the clinical trial;

V – quality assurance of the clinical trial;

VI – audit and monitoring of the clinical trial; and

VII – waste management.

Article 19. The institution to which the sponsor-investigator is linked may delegate the responsibilities provided for in Article 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 taken by each of the parties.

Sole Paragraph. The activities listed in items V and VI of Article 18 of this Resolution cannot 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

Article 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.

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

Paragraph 2. The DSCTA or the DDCTA must be submitted to Anvisa in the cases where there is the intention of conducting clinical trials with investigational advanced therapy medicinal products in Brazil.

Paragraph 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 dossier of clinical trial to be conducted in Brazil.

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

I – information on the product classification, through the completion of an investigational advanced therapy medicinal product classification form, available on Anvisa website; and

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

Article 22. Upon receipt of the DSCTA, Anvisa shall have 30 (thirty) days to analyze the dossier and express its opinion on the approval, rejection, or elaboration of requirements regarding the application.

Paragraph 1. The period referred to in the caption of this article may be extended for an equal period, upon justification and technical reasoning.

Paragraph 2. In case Anvisa does not express its opinion in up to 30 (thirty) days after the date it received the DSCTA, and there is no pertinent justification and technical reasoning to extend the period to do so, the clinical development may be initiated after the pertinent ethical approvals.

Paragraph 3. Only clinical trials related to the DSCTA and listed in the Special Statement (CE) shall be approved and may be initiated.

Article 23. Upon receipt of the DDCTA, Anvisa shall have 180 (one hundred and eighty) calendar days to analyze the dossier and express its opinion on the approval, rejection, or elaboration of requirements regarding the application.

Paragraph 1. The period referred to in the caption of this article may be extended for an equal period, upon justification and technical reasoning.

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

Article 24. Anvisa shall issue an CE for each DDCTA and each DSCTA, mentioning the clinical trials approved and able to be conducted in Brazil.

Article 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 and for the assessment and monitoring of the clinical development intended, under possible penalty of suspension or cancellation of the clinical trial.

Article 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 for by Law 11,105 of 24 March 2005, or its updates.

Section II

Content and Format of DSCTA for Class I Advanced Therapy Medicinal Products

Article 27. The DSCTA to be submitted to Anvisa must be comprised 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);

II – clinical investigation plan for the class I investigational advanced therapy medicinal product, 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 the duration planned for the clinical development; and

f) summary description, for each planned clinical trial, of the design, endpoints, population to be studied, hypotheses, selection criteria (inclusion/ exclusion), estimated number of participants, intended statistical planning and, where applicable, comparators, estimated collection, and storage conditions for biological materials.

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

a) clinical trial submission form, available on Anvisa website, duly completed;

b) clinical trial protocol, in accordance with 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, for the establishments located in Brazilian territory involved in the production of the investigational advanced therapy medicinal product, or an equivalent document issued by a foreign competent authority, in case the product is not manufactured in Brazil.

Article 28. If a new specific dossier is proposed for a clinical trial to be carried out in Brazil, the respective documentation must be submitted in the form of an application secondary to the DSCTA process, upon original proof of payment of the Health Surveillance Inspection Fee (TFVS) through the Federal Tax Liability Payment Form (GRU), or proof of exemption therefrom.

Article 29. Forms with clinical trial start and termination dates in Brazil must be submitted, in the form of an application secondary to the DSCTA process, in up to 30 (thirty) calendar days counting from each start and termination date.

Section III

Content and Format of the DDCTA for Class II Advanced Therapy Medicinal Products

Article 30. The DDCTA to be submitted to Anvisa must be comprised of the following documents:

I – proof of payment of the Health Surveillance Inspection Fee (TFVS), upon Federal Tax Liability Payment Form (GRU);

II – clinical investigation plan for the investigational advanced therapy medicinal product, 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 the duration planned for the clinical development; and

f) summary description, for each planned clinical trial, of the design, endpoints, population to be studied, hypotheses, selection criteria (inclusion/ exclusion), estimated number of participants, intended statistical planning and, where applicable, comparators, estimated collection, and storage conditions for biological materials.

III – investigator's brochure containing the following information:

a) description of the product, including composition;

b) biological and toxicological effects on animals and humans, where applicable;

c) information on safety and efficacy in humans, obtained from clinical trials already conducted, when available; and

d) possible risks and adverse events related to the use of the investigational product.

IV – production dossier of the investigational advanced therapy medicinal product containing the following information:

a) identification and addresses of all establishments involved in the production of the investigational advanced therapy medicinal product, including the active component;

b) copy of regularization document issued by the health authority in Brazil, for the establishments located in Brazilian territory involved in the production of the investigational advanced therapy medicinal product, or an equivalent document issued by a foreign competent authority, in case the product is not manufactured in Brazil;

c) list of all starting materials used in the production of the investigational advanced therapy medicinal product including, in the case of gene therapy product, the materials necessary for the production of vectors and for the genetic manipulation of the cells;

d) list of the raw materials used in the production of the investigational advanced therapy medicinal product, including the name of the material, manufacturer, quantity used in the process, pharmacopoeia recommendations, or specifications of in-house materials or technologies, including the documentation on the quality controls used;

e) list of the equipment used in the process;

f) information on the selection of the donor of starting and raw materials of human origin, including clinical, social, and laboratory screening, physical evaluation, and other relevant assessments, in accordance with Collegiate Board Resolution – RDC no. 508 of 27 May 2021, or its updates;

g) documentation regarding the control of transmissibility of spongiform encephalopathies (TSEs), in accordance with the provisions of Collegiate Board Resolution – RDC no. 508 of 27 May 2021 and Collegiate Board Resolution – RDC no. 305 of 14 November 2002, or their updates;

h) overall description of the product's manufacturing process, containing:

1. detailed information on all stages, including the ones of selection of the cell population of interest, cell culture, transformation through physical-chemical and/ or biological agents;

2. detailed information on all stages of production of vectors, where applicable; and

3. detailed information on the production stages of excipients, where applicable.

i) characterization of the active component, 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 component;

k) overall description of the final investigational advanced therapy medicinal product, 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 that 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;

n) description of the comparator product or comparator treatment, where applicable, including information that ensure the maintenance of their characteristics;

o) model of label of the investigational product; and

p) critical analysis of non-clinical studies that contribute towards the safety of the clinical development proposed, as well as information on the sites where such studies were conducted, on where their records are available for consultation, including a statement that each study was conducted in accordance with the GLP or, in cases of noncompliance with the GLP, technical justification for such exception.

V – specific dossier of the clinical trial to be performed in Brazil, submitted for each clinical trial, in the form of an application secondary to the DDCTA process, containing the following documents:

a) clinical trial submission form, available on Anvisa website, duly completed;

b) clinical trial protocol, in accordance with 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).

Article 31. If a new specific dossier is proposed for a clinical trial to be carried out in Brazil, the respective documentation must be submitted in the form of an application secondary to the DSCTA process, upon original proof of payment of the Health Surveillance Inspection Fee (TFVS) through the Federal Tax Liability Payment Form (GRU), or proof of exemption therefrom.

Article 32. Forms with clinical trial start and termination dates in Brazil must be submitted, in the form of an application secondary to the DSCTA process, in up to 30 (thirty) calendar days counting from each start and termination date.

Section IV

Notification of Post-Marketing (Phase IV) Clinical Trial with Advanced Therapy Medicinal Products

Article 33. Post-marketing (phase IV) clinical trials with advanced therapy medicinal products are subject to the notification regimen without the need for DSCTA or DDCTA submission.

Paragraph 1. The clinical trials referred to in the caption of this article do not require an authorization from Anvisa, and they remain subject to other applicable ethical approvals.

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

Article 34. The post-marketing (phase IV) clinical trial notification 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, in accordance with 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 databases from another entity recognized by the "**International Committee of Medical Journals Editors**" (ICMJE).

Sole Paragraph. For import or export purposes, Anvisa shall have 30 (thirty) calendar days, counting from the receipt of the Notification referred to in this Section, to issue the respective CEE.

Article 35. This section only applies to post-marketing (phase IV) clinical trials, except for all other post-marketing surveillance studies to be provided for in specific regulation on the marketing authorization of advanced therapy medicinal products, to be published by Anvisa.

CHAPTER IV

AMENDMENTS TO DDTCA AND DSCTA

Section I

Substantial alterations

Article 36. For the purposes of this Resolution, substantial alterations consist of:

I – inclusion of unexpected or different clinical trial protocol compared to that established in the clinical investigational plan of the investigational advanced therapy medicinal product;

II – exclusion of clinical trial protocol; or

III – alteration that potentially impacts the quality or safety of the investigational advanced therapy medicinal product, active comparator, or placebo.

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

Sole Paragraph. The secondary application shall be linked to the respective DDCTA or DSCTA process, upon original proof of payment of the Health Surveillance Inspection Fee (TFVS) through the Federal Tax Liability Payment Form (GRU), or proof of exemption therefrom.

Article 38. Substantial alterations:

I – to the DDCTA may only be implemented after approval by Anvisa;

II – to the DSCTA may be implemented after the submission of the secondary application regarding the intended substantial alteration, and the sponsor or sponsor-investigator is fully

responsible for complying with all requirements set forth in this Resolution and related regulations, remaining subject to other applicable ethical and regulatory approvals.

Article 39. Upon receipt of the secondary application regarding the substantial alteration in the DDCTA, Anvisa shall have 60 (sixty) calendar days to analyze the application and express its opinion on the approval, rejection, or elaboration of requirements regarding the application.

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

Article 40. Alterations in the DDCTA resulting from safety recommendations or warnings related to the clinical trial, issued by international health authorities, must be notified to Anvisa and may be executed regardless of the prior manifestation by the Agency.

Section II

Amendments to the clinical trial protocol

Article 41. For the purposes of this Resolution, an amendment shall be considered substantial when it alters 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.

Article 42. Any amendment referred to in this Resolution may only be implemented after the grant of the respective ethical approvals, in compliance with the legislation in force.

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

Sole Paragraph. The secondary application shall be linked to the respective DDCTA or DSCTA process, upon original proof of payment of the Health Surveillance Inspection Fee (TFVS) through the Federal Tax Liability Payment Form (GRU), or proof of exemption therefrom.

Article 44. Substantial amendments:

I – to the DDCTA may only be implemented after approval by Anvisa;

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

Paragraph 1. Upon receipt of the secondary application regarding a substantial amendment to the DDCTA, Anvisa shall have 60 (sixty) calendar days to analyze the request and express its opinion on the approval, rejection, or elaboration of requirements regarding the application.

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

Paragraph 3. Substantial amendments intended to eliminate immediate risks to the participants' safety must be notified to Anvisa, but must be implemented immediately, regardless of the prior manifestation by the Agency.

Article 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 Cancellations

Article 46. The sponsor or sponsor-investigator may cancel 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 the follow-up plan for the participants in the clinical trials already initiated.

Paragraph 1. After cancellation of the DDCTA or DSCTA, no clinical trial related to it may be continued in Brazil.

Paragraph 2. If the DDCTA, the DSCTA or the clinical trial is cancelled for safety reasons, the sponsor or the sponsor-investigator must technically and scientifically justify the reasons for the cancellation and present the respective measures to minimize/ mitigate risks to the study participants.

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

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

Article 48. The sponsor or sponsor-investigator must notify Anvisa, in the form of a secondary application, 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 such decision.

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

Article 49. Anvisa may, at any time, suspend or cancel 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 trial participants, or the scientific validity of the data obtained. The sponsor or the sponsor-investigator must be informed in a reasoned and justified manner.

CHAPTER V

SAFETY MONITORING AND WARNINGS

Section I

Monitoring of Adverse Events

Article 50. The sponsor and sponsor-investigator, or the CRO, must monitor all adverse events, including non-serious ones, during the clinical trial of an investigational advanced therapy medicinal product.

Article 51. The sponsor, sponsor-investigator, CRO, or the Independent Safety Monitoring Committee must systematically collect and assess pooled data of adverse events that occurred during the clinical trial, submitting the results of such assessment to Anvisa as part of the annual follow-up reports of the investigational advanced therapy medicinal product development.

Article 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 an opinion on the possible causality between the adverse event and the investigational product.

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

Paragraph 2. The affected participants must be follow-up by the main investigator and his/ her team, until their stabilization or adverse event resolution.

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

Paragraph 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 occurred, whose causality is possible, probable, or confirmed in relation to the investigational product.

Paragraph 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 counting from the date the sponsor or sponsor-investigator became aware of the case.

Paragraph 3. The notification of other serious adverse events occurred must be carried out within a maximum period of 15 (fifteen) calendar days counting from the date the sponsor or sponsor-investigator became aware of the case.

Paragraph 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.

Article 54. The sponsor and the sponsor-investigator must establish a monitoring plan to detect late adverse events, justifying the proposed period.

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

Article 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, and adopt the procedures to update the investigator's brochure, in addition to reassessing the risks and benefits to participants.

Article 56. The development of a phase III clinical trial must be accompanied by Independent Safety Monitoring Committees, and their recommendations must be reported to Anvisa by the sponsor, sponsor-investigator, or CRO.

Section II

Follow-up Reports and Final Report

Article 57. The sponsor, sponsor-investigator, or CRO must submit to Anvisa, in the form of an application secondary to the DSCTA or DDCTA, Annual Follow-up 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 – number of participants recruited per site;

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

V – description of all adverse events occurring per site in the assessed period, identifying the clinical trial participants through the codes used in the Case Report Form (CRF) adopted in the clinical trial protocol; and

VI – alterations to DSCTA and DDCTA not considered substantial.

Sole Paragraph. The Annual Follow-up Report must be submitted within a maximum period of 60 (sixty) calendar days, having the clinical trial start date in Brazil as annual reference.

Article 58. Upon completion of the activities of a clinical trial in all participating countries, the person responsible for submitting the DDCTA and DSCTA must submit to Anvisa, in the form of a secondary application, within 12 months from 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, occurred with the clinical trial participants;

VIII – results obtained from the measurement of the endpoints, for each clinical trial participant; and

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

Article 59. The sponsor or sponsor-investigator must submit annually to Anvisa, the Safety Update Reports of the investigational advanced therapy medicinal product, as an application secondary to the DSCTA or DDCTA.

Sole Paragraph. The report referred to in the caption of this article must be submitted in up to 60 (sixty) calendar days, having the date Anvisa approved the DDCTA or DSCTA, or a date determined in the international development, as annual reference.

CHAPTER VI

INSPECTIONS

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

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

I – the suspension of the clinical trial;

II – the cancellation of the trial at the uncompliant clinical trial site;

III – cancellation of the trial in all clinical trial sites in Brazil;

IV – invalidation of data from uncompliant clinical trial sites; or

V – invalidation of clinical trials not complying with the GCP.

Article 62. Anvisa may conduct Good Practices on Human Cells inspections in the production of the investigational advanced therapy medicinal product, in order to verify the information contained in the DDCTA or the DSCTA, as well as to ensure compliance with Collegiate Board Resolution – RDC no. 508 of 27 May 2021, or its updates.

CHAPTER VII

IMPORT AND EXPORT

Article 63. The import and export of goods and products to be used in a clinical trial with investigational advanced therapy medicinal products must be subject to supervision by the competent health authority at the site of clearance or shipment.

Paragraph 1. The provisions of Collegiate Board Resolution – RDC no. 172 of 12 September 2017, or its updates, are not applied to the goods and products referred to in the caption of this article.

Paragraph 2. For the purposes of the inspection referred to in this article, the health authority at the site of clearance must verify the publication of CEs or CEEs related to the goods and products to be imported or exported, accordingly.

Article 64. The packing, packaging, documentation, and transportation of the biological material to be used in a clinical trial with investigational advanced therapy medicinal products must be carried out in order to ensure and maintain the integrity of such products, in an appropriate and exclusive container for the purposes of export and import, at the appropriate temperature, and

duly identified, in accordance with Collegiate Board Resolution – RDC no. 504 of 27 May 2021 and the Collegiate Board Resolution – RDC no. 508 of 27 May 2021, or their updates.

Sole Paragraph. The importer or exporter is responsible for the compliance with the provisions set forth in the caption of this article.

CHAPTER VIII

FINAL AND TRANSITIONAL PROVISIONS

Article 65. Any material of human origin obtained in Brazil used in the manufacture of advanced therapy medicinal products must be obtained free of charge, through free, spontaneous, and informed donation, in compliance with the provisions of Collegiate Board Resolution – RDC no. 508 of 27 May 2021, or its updates.

Article 66. Failure to comply with the provisions contained in this Resolution constitutes a health infraction, pursuant to Law no. 6,437 of 20 August 1977, without prejudice to the applicable civil, administrative, and criminal liabilities.

Article 67. Omitted or complementary cases shall be settled in the light of other Brazilian regulations and international guidelines related to the subject addressed by this Resolution.

Article 68. The following are hereby revoked:

I – Collegiate Board Resolution – RDC no. 260 of 21 December 2018, published on the Federal Official Gazette of 28 December 2018; and

II – Collegiate Board Resolution – RDC no. 453 of 17 December 2020, published on the Federal Official Gazette of 23 December 2020.

Article 69. This Resolution enters into force on 1 July 2021.

ANTONIO BARRA TORRES

Director-President