Ministry of Health - MS

National Health Surveillance Agency - ANVISA

RESOLUTION OF THE COLLECTIVE BOARD - RDC No. 9, OF FEBRUARY 20, 2015

(Published in DOU nº 41, of March 3, 2015)

Provides for the Regulations for carrying out clinical trials with medicines in Brazil.

Note: See Normative Instruction No. 20, of October 2, 2017.

The Collegiate Board of the National Health Surveillance Agency, in the use of the powers conferred on it by items III and IV, of art. 15 of Law No. 9,782, of January 26, 1999, item II and § 1 and 3 of art. 54 of the Internal Regulations approved under the terms of Annex I of Ordinance No. 354 of Anvisa, of August 11, 2006, and its updates, in view of the provisions of items III, of art. 2nd, III and IV, of art. 7th of Law No. 9,782, of 1999, in art. 35 of Decree no. 2015 adopts the following Resolution of the Collegiate Board of Directors and I, Deputy Chief Executive Officer, determine its publication:

CHAPTER I

INITIAL PROVISIONS

Section I

From the Objective

Art. 1 This Resolution aims to define the procedures and requirements for carrying out clinical trials with medicines, including the submission of the Medicines Clinical Development Dossier (DDCM) to be approved by Anvisa.

Section II

Scope

Art. 2 This Resolution is applicable to all clinical trials with medicines that will have all or part of their clinical development in Brazil for registration purposes.

Single paragraph. Clinical trials with medicines registered in Brazil must follow all provisions of this Resolution when providing subsidies for:

I- new therapeutic indication;

II- new route of administration;

III- new concentration;

IV- new pharmaceutical form;

V- expansion of use;

VI- new dosage;

VII - new associations; or

VIII- any post-registration change that requires clinical data, including registration renewal.

Art. 3 Post-marketing clinical trials (phase IV) are not the primary objective of this standard and are subject only to the Clinical Trial Notification, and must be initiated only after obtaining ethical approvals in accordance with current legislation.

I- except for the provisions of the **caput,** phase IV clinical trials involving vaccines and trials that aim to evaluate efficacy and safety for registration or renewal purposes, which are considered as phase III clinical trials;

II- in cases of phase IV clinical trials whose medicine already has a Drug Clinical Development Dossier (DDCM) approved by Anvisa, the Notification petition must be linked to the DDCM;

III- phase IV and observational clinical trials that are not part of a DDCM previously approved and involving import or export procedures, will be subject to Clinical Trial Notification and issuance of a Specific Special Notice (CEE) within 30 (thirty) calendar days, from the date of receipt of the notification by Anvisa,

IV- the Clinical Trial Notification must consist of the following documents:

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

b) proof of payment, or exemption, of the Security Inspection Fee Health Surveillance, through the Union Collection Guide (GRU);

c) clinical trial protocol in accordance with the GCP;

d) proof of registration of the clinical trial in the company's registration database *International Clinical Trials Registration Platform / World Health Organization (ICTRP/WHO)* or others recognized by *the International Committee of Medical Journals Editors (ICMJE);* e

~~e) Substantiated opinion from the Research Ethics Committee (CEP) issued to the first clinical trial center to forward the protocol for analysis by the CEP.~~ **~~(Revoked by Resolution-RDC~~ No. 205, of December 28, 2017)**

Art. 4 This Resolution is not applicable to bioequivalence and relative bioavailability studies, clinical trials with cosmetics, health products, foods, gene therapy and stem cells, which must follow specific regulations.

Art. 5 Anvisa may issue guidelines on the applicability of this Resolution for unforeseen cases of clinical trials with medicines.

Section III

From Settings

Art. 6 For the purposes of this Resolution, the following definitions are adopted:

I- Audit - systematic and independent analysis of activities and documents related to the study to determine whether the activities evaluated were performed and the data recorded, analyzed and reported accurately while complying with the protocol, standard operating procedures defined by the sponsor, Good Practices Clinics (BPC) and applicable regulatory requirements;

II- Good Clinical Practices (GCP) - standard for planning, conducting, carrying out, monitoring, auditing, recording, analyzing and reporting clinical trials that provides the guarantee that the data and results reported have credibility and accuracy, and that the rights, integrity and confidentiality of clinical trial participants are protected, in accordance with the GCP guidelines set out in Document of the Americas and Conference Good Clinical Practice Manual International Harmonization (Document E6);

III- Good Manufacturing Practices (GMP) - part of Quality Assurance that ensures that products are consistently produced and controlled, with quality standards appropriate for the intended use and required by registration;

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

V- Investigator's Brochure - compiled of clinical and non-clinical data on the experimental medicine(s), which are relevant to its study in human beings;

VI- Clinical Trials Center - public or private organization, legitimately constituted, duly registered in the National Registry of Health Establishments (CNES), in which clinical trials are carried out;

VII- Research Ethics Committee (CEP) - interdisciplinary and independent collegial body, of public relevance, of a consultative, deliberative and educational nature, created to defend the interests of research participants in their integrity and dignity and to contribute to the development of research within of ethical standards;

VIII- Independent Safety Monitoring Committee - independent committee, established to monitor specific safety data collected from one or more clinical trials at defined intervals.
Recommends to the sponsor whether a study should be continued, modified, or stopped;

IX- Special Communication (CE) - document of an authorizing nature, issued by Anvisa, after analysis and approval by the DDCM, and can be used in import or export requests for a clinical trial;

X- Specific Specific Notice (EEC) - Document, issued by ANVISA, necessary for the request for import or export to a clinical trial subject to the notification regime or to a clinical trial subject to that described in the
Chapter X (Transitional Provisions) of this standard;

XI- Bill of lading - document issued, on the date of shipment of the good or product, by the carrier or consolidator, constituting the international transport contract and proof of the disposition of the good or product to the importer;

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

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

XIV- Clinical Trial End Date **-** corresponds to the date of the last visit of the last clinical trial participant in the world or another definition by the sponsor, expressly determined in the specific clinical trial protocol;

XV- Termination date of the clinical trial in Brazil- corresponds to the date of the last visit of the last clinical trial participant in Brazil or other definition of the sponsor, expressly determined, in the specific clinical trial protocol;

XVI- Deviation from the clinical trial protocol - any non-compliance with the procedures or requirements defined in the approved version of the clinical trial protocol, without major implications for the integrity of the trial, the quality of the data or the rights and safety of the clinical trial participants;

XVII- Document delegating import responsibility -
document issued by the research sponsor, indicating the authorized importer and the responsibilities relating to the transportation and clearance of imported goods;

XVIII- Document for Import of Product(s) under investigation of the Medicinal Clinical Development Dossier (DDCM): Document issued by
Anvisa, necessary for requesting import or export for a clinical trial, in cases of non-compliance with the DDCM;

XIX- Clinical Drug Development Dossier (DDCM) –
compiled of documents to be submitted to Anvisa with the purpose of evaluating the steps inherent to the development of an experimental medicine with a view to obtaining information to support the registration or post-registration changes of said product;

XX- Specific Dossier for each Clinical Trial - compiled of documents to be submitted to Anvisa with the purpose of obtaining information regarding clinical trials, to be conducted in Brazil, which are part of the Plan of
Development of the Experimental Medicine;

XXI- Amendment to the clinical trial protocol - any proposal to modify an original clinical trial protocol, always presented with the justification that motivated it, and such amendment may be substantial or not;

XII- Clinical trial - research conducted on human beings with the aim of discovering or confirming the clinical and/or pharmacological effects and/or any other pharmacodynamic effect of the experimental drug and/or identifying any adverse reaction to the experimental drug and/or studying absorption , distribution, metabolism and excretion of the experimental drug to verify its safety and/or effectiveness;

XXIII- Adverse Event (AE) - any adverse medical occurrence in a patient or clinical trial participant to whom a pharmaceutical product was administered and which does not necessarily have a causal relationship to the treatment.
As a result, an AE can be any unfavorable and unintended sign, symptom, or illness (including results outside the reference range) associated with the use of an investigational product, whether related to it or not;

XXIV- Serious Adverse Event - one that results in any adverse experience with medicines, biological products or devices, occurring at any dose and resulting in any of the following outcomes:

a) death;

b) threat to life;

c) persistent or significant incapacity/disability;

d) requires hospitalization or prolonged hospitalization;

e) congenital anomaly or birth defect;

f) any suspicion of transmission of an infectious agent through a medicine or;

g) clinically significant event.

XXV- Unexpected Adverse Event - event not described as an adverse reaction in the experimental drug brochure or leaflet.

XXVI- Case Report Form - printed, optical or electronic document intended to record all information about each clinical trial participant that, according to the clinical trial protocol, must be reported to the sponsor;

XXVII- Inspection - The act by a regulatory authority of conducting an official review of documents, facilities, records and any other resources considered by the authority to relate to the clinical trial and which may be located where the trial is conducted, in facilities of the sponsor, Representative Organization for Clinical Research (ORPC), or other locations that the regulatory authority deems appropriate;

XXVIII- Active Pharmaceutical Ingredient (IFA) - any substance introduced into the formulation of a pharmaceutical form that, when administered to a patient, acts as an active ingredient. Such substances may exert pharmacological activity or other direct effects on the diagnosis, cure, treatment or prevention of a disease, and may also affect the structure and functioning of the human body;

XXIX- Investigator - person responsible for conducting a clinical trial at the location where the trial is conducted. If the study is conducted by a group of people, the investigator is the leader of the group and will be called the principal investigator;

XXX- Investigator-Sponsor - natural person responsible for conducting and coordinating clinical trials, alone or in a group, carried out under their immediate direction independently, developed with the investigator's own financial and material resources, national or international funding entities to research, from private entities and other non-profit entities;

XXXI-Experimental medicine - pharmaceutical product being tested, object of DDCM, to be used in the clinical trial, with the purpose of obtaining information for its registration or post-registration;

XXXII- Monitoring - the act of continually reviewing the process of a clinical trial and ensuring that it is conducted, recorded and reported in accordance with the protocol, standard operating procedures, GCP and applicable regulatory requirements;

XXXIII- Clinical Research Representative Organization (ORPC) - every company regularly installed in the national territory contracted by the sponsor

or by the sponsor-researcher, who partially or totally assumes, together with Anvisa, the sponsor's duties;

XXXIV- Sponsor - person, company, institution or organization responsible for initiating, managing, controlling and/or financing a clinical study;

XXXV- Placebo – formulation without pharmacological effect, administered to the clinical trial participant for the purpose of masking or being a comparator;

XXXVI- Product under investigation - experimental medicine, placebo, active comparator or any other product to be used in the clinical trial;

XXXVII- Clinical Trial Protocol - document that describes the objectives, design, methodology, statistical considerations and organization of the trial. It also provides the context and rationale for the clinical trial;

XXXVIII- Annual report - annual document containing specific information about the conduct of a specific clinical trial in centers in Brazil, in accordance with the clinical protocol and the GCP;

XXXIX- Investigational drug development safety update report - harmonized periodic report containing safety and development information on an experimental drug;

XL- Final report - document containing specific information about the conduct of a specific clinical trial in all centers participating in the study, in accordance with the clinical protocol and GCP;

XLI- Active substance - is the substance with pharmacological effect for activity intended therapy, used in the production of a specific biological product;

XLII- Clinical trial protocol violation - deviation of clinical trial protocol that may affect data quality, compromise the integrity of the study or that may affect the safety or rights of clinical trial participants;

CHAPTER II

RESPONSIBILITIES

Art. 7 The responsibilities listed in this chapter cover those defined in Good Clinical Practices, without prejudice to other ethical and legal responsibilities.

Section I

Sponsor Responsibilities

Art. 8 The sponsor is responsible for the information necessary for the correct execution of the DDCM, through the selection of qualified investigators and centers, thus ensuring that clinical trials are conducted in accordance with protocols and GCP.

Art. 9 The sponsor must use qualified professionals to supervise the general conduct of clinical trials, manage data, conduct statistical analysis and prepare reports.

Art. 10. The sponsor must ensure that quality assurance and quality control are implemented in all areas of the institutions involved in the development of the experimental medicine.

Art. 11. The sponsor must keep clinical trial data on file, physical or digital, for a period of 5 (five) years after the last approval of a registration request in Brazil.

Single paragraph. In case of discontinuation of clinical development or its completion not followed by a registration request, the sponsor must keep the clinical trial data in a physical or digital file for at least 2 (two) years after the discontinuation of clinical development or formal conclusion of this development.

Art. 12. The sponsor is responsible for all expenses related to procedures and exams, especially those related to diagnosis, treatment and hospitalization of the clinical trial participant, and other actions necessary to resolve adverse events related to the clinical trial.

Art. 13. The sponsor must ensure that the data obtained on the safety and efficacy of the experimental medicine are sufficient to support human exposure through the proposed route of administration, the chosen dosage, the duration of the proposed treatment and in the population to be studied.

Art. 14. The sponsor must ensure that the experimental drug, modified comparator drug and placebo, when used, are manufactured in accordance with GMP and are coded and labeled in a way that protects masking, if applicable, and characterizes them as investigational products clinic.

Single paragraph. In studies using active comparators, the sponsor you must use those manufactured in accordance with GMP.

Art. 15. The sponsor is responsible for importing the amount necessary to carry out the clinical trial.

Art. 16. The sponsor is responsible for distributing the product(s) under investigation only to the institutions informed in the Clinical Trial submission form contained in the Specific Dossier for each Clinical Trial and authorized by the Research Ethics Committees.

Art. 17. The sponsor is responsible for the final destination of medicines and products that were not used in the clinical trial.

Art. 18. The sponsor must ensure adequate monitoring and auditing of clinical trials.

Art. 19. The sponsor must immediately inform those involved in the trial, when it is terminated prematurely or suspended for any reason.

Art. 20. The sponsor may transfer its functions to an ORPC.

§1º The transfer referred to in the **caput** does not eliminate liability final approval from the sponsor for the quality and integrity of the clinical trial data.

§2° Any functions related to the clinical trial that are transferred to an ORPC and assumed by it must be specified in writing in a document signed by the sponsor and ORPC.

Section II

Investigator Responsibilities

Art. 21. The investigator must conduct the clinical trial in accordance with the protocol agreed with the sponsor, with the GCP, with the applicable and current regulatory and ethical requirements.

Art. 22. The investigator must personally supervise the clinical trial, and may only delegate tasks, but not responsibilities.

Art. 23. The investigator must allow monitoring, audits and inspections to be carried out.

Art. 24. The investigator must ensure adequate medical assistance to clinical trial participants regarding any adverse events related to the clinical trial, including clinically significant laboratory values, without any cost to the participant.

Art. 25. The investigator must promptly inform participants in the clinical trial when it is terminated prematurely or suspended for any reason, in addition to ensuring appropriate therapy and follow-up for participants.

Art. 26. The investigator is responsible for using the products under investigation only within the scope of the clinical trial and storing them as specified by the sponsor and in accordance with applicable regulatory requirements.

Section III

Responsibilities of the Investigator-Sponsor

Art. 27. In the case of a clinical trial developed by an investigator-sponsor, the institution with which he/she has a link will be the primary sponsor.

§1 The primary sponsor may delegate responsibilities to the investigator, who will be responsible for conducting the clinical trial at the institution, and, in this case, the investigator-sponsor will be the secondary sponsor.

§2 In case of delegation of responsibilities and activities, a document writing must be signed between the parties.

§3 The primary sponsor cannot delegate quality assurance activities, audits and monitoring of clinical trials to the investigator-sponsor, but can delegate them to an ORPC.

§4 The primary sponsor must present its own or outsourced structure with at least the following units:

I - management of adverse events;

II - project management;

III - data management;

IV - training;

V - information technology;

VI - quality assurance and;

VII - monitoring.

§5º The institution referred to in the **caput** must be the one in which the clinical trial will be realized.

§6 The responsibilities listed in this article do not exclude the provisions of Sections I and II of this chapter cover sponsor and investigator responsibilities.

Art. 28. In the case of donating medicines already registered in Brazil to carry out a clinical trial, the donor will be the sponsor if there is an agreement to transfer or own the data obtained in the research to the donor.

Art. 29. In the case of donating medicines not registered in Brazil to carry out a clinical trial, the donor shares the responsibilities of sponsor.

Section IV

The Structure of the Clinical Trial Center

Art. 30. The clinical trial center must have adequate facilities to conduct the protocol, regarding the physical structure, equipment, instruments and

human resources, and also be consistent with the clinical trial population, such as the elderly, children, people with special needs, among others.

Art. 31. The institution's management must be notified about the conduct of the clinical trial.

CHAPTER III

REQUIREMENTS FOR SUBMISSION OF THE DOSSIER OF CLINICAL DRUG DEVELOPMENT (DDCM)

Art. 32. The documentation presented in the DDCM must guarantee the safety and rights of participants in all phases of clinical development, the quality of the experimental medicine and the data obtained in the clinical phases of development, so that they allow an assessment of the effectiveness and medication safety.

Art. 33. The DDCM can be presented to Anvisa at any stage of the drug's clinical development, for one or more phases of clinical trials.

Section I

General Requirements for the Request

Art. 34. The sponsor must submit a DDCM to Anvisa only if it intends to carry out clinical trials with medicines in national territory.

Single paragraph. For the purposes of analyzing the DDCM, it must be registered by the at least one specific clinical trial dossier to be carried out in Brazil.

Art. 35. A single Special Notice (CE) will be issued by DDCM mentioning all clinical trials to be conducted in Brazil.

Single paragraph. Only clinical trials listed in the CE may be initiated in the country respecting other ethical approvals.

Art. 36. After receiving the DDCM, Anvisa will evaluate it within 90 (ninety) calendar days.

§1° If there is no response from Anvisa within 90 (ninety) calendar days after receipt of the DDCM by Anvisa, clinical development may begin after the relevant ethical approvals.

§2° In cases of non-manifestation, Anvisa will issue a Document to Import of Product(s) under investigation of the Medicines Clinical Development Dossier (DDCM), to be presented at the customs clearance site, for

import or export of product(s) under investigation, necessary to conduct the clinical trial.

§3 Except for the provisions of the **caput** and §1, clinical development submissions that fall into at least one of the following situations: national development, clinical development of biological products - including vaccines - and clinical development in phase I or phase II. For these cases, the technical area will evaluate the DDCM within 180 (one hundred and eighty) calendar days after receipt of the DDCM by Anvisa and the clinical study can only be started after approval from Anvisa.

Art. 37. The DDCM can be submitted by the sponsor, sponsor-investigator or ORPC.

§1º The person responsible for the DDCM before Anvisa must be the same for all subsequent submissions related thereto.

§2 Submissions via ORPC can only be made when the sponsor does not have a headquarters or branch in Brazil.

§3 The submission of the DDCM of a sponsor-investigator must be made by through the primary sponsor.

Section II

The Content and Format of the Request

Art. 38. The DDCM submitted to Anvisa must consist of the following documents:

I - Petition form duly completed, according to model available on the Anvisa website;

II - proof of payment, or exemption, of the Security Inspection Fee Health Surveillance, through the Union Collection Guide (GRU);

III - Medicine Development plan containing a description of the following topics:

a) IFA or active substance;

b) category of medicine (synthetic, biological, herbal or radiopharmaceutical);

c) therapeutic class;

d) route of administration;

e) mechanism of action;

f) indications to be studied;

g) general objectives and planned duration for clinical development; It is

h) information about phase, design, outcomes, comparators, objectives, population to be studied, hypothesis(es), estimated number of participants and statistical planning for each planned clinical trial.

IV - Investigator's brochure containing a description of the following topics:

a) experimental medicine;

b) formulation;

c) pharmacological and toxicological effects of the experimental medicine on animals and humans, when applicable;

d) safety and efficacy information in humans obtained from clinical trials already carried out; It is

e) possible risks and adverse events related to the experimental drug, based on previous experience, as well as special precautions or monitoring to be followed during development.

V - a summary of safety aspects based on previous experience in humans with the experimental medicine (for example, expanded access and compassionate use programs), as well as post-marketing experience in other countries, if applicable;

VI- information regarding the interruption of development or withdrawal from the market of the experimental medicine in any country, for reasons of safety or failure of efficacy, if applicable. The countries where access was discontinued must be identified, as well as the reasons for the interruption/ withdrawal of the product;

VII - Experimental Medicine dossier containing the following documents:

a) description of the API or active substance, including:

1. physicochemical, organoleptic and biological characteristics;

2. name and address of the manufacturer;

3. general method of obtaining;

4. validated analytical methodology and acceptable limits to guarantee identity, quality and purity; It is

5. results of stability studies.

b) description of the experimental medicine, including:

1. list of all active and inactive components with their respective functions, including those not present in the finished medicine;

2. quantitative composition;

3. General description of manufacturing and packaging process with information about the capacity of the equipment;

4. the analytical methodology and acceptable limits to guarantee identity; It is

5. results of stability studies that ensure the use of the experimental medicine in planned clinical trials.

c) description of the placebo, when applicable, including:

1. composition;

2. organoleptic characteristics;

3. manufacturing process; It is

4. analytical controls.

d) description of the comparator medicine when it is modified to carry out the clinical trial, including information that ensures the maintenance of the original characteristics of the medicine;

e) documentation regarding the control of transmissibility of Encephalopathies Transmissible Spongiform Diseases (TSE), according to current health standards or justifications for the exemption from this document;

f) label model(s) of the product(s) under investigation;

g) critical analysis of non-clinical pharmacological and toxicological studies that guarantee safety for carrying out the proposed clinical development and information on the locations where these studies were conducted, as well as where their records are available for consultation, including a statement that each study was carried out in compliance with GLP or justification for absence.

Description of known risks regarding the experimental medicine based on toxicological studies in animal models or *in vitro* tests already carried out or therapeutic class studied; risk/benefit assessment related to the development plan;

h) critical analysis of clinical trials already carried out, if applicable, including the basis of efficacy and safety. Description of the risks already known regarding the experimental medicine based on clinical trials already carried out or therapeutic class studied; risk/benefit assessment related to the development plan;

i) if the experimental drug is already registered in Brazil, only the information that supports the proposed post-registration changes must be submitted to the DDCM;

j) in cases where a sponsor-investigator wishes to carry out a clinical trial with a medicine that already has a DDCM approved by Anvisa, he or she may use the information already sent by the holder of the initial DDCM, if he or she authorizes it, without the need for resubmission all documentation. When authorization from the initial holder is not presented, the sponsoring researcher must submit all information to Anvisa through updated and indexed literature that supports the proposed development rationale;

VIII - specific dossier for each clinical trial to be carried out in Brazil. These dossiers must be filed in the form of individual processes, for each clinical trial. Each process must be linked to the DDCM and submitted by the sponsor or ORPC. The dossier must consist of the following documents:

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

b) proof of payment, or exemption, of the Security Inspection Fee Health Surveillance, through the Union Collection Guide (GRU);

c) clinical trial protocol in accordance with the GCP;

d) proof of registration of the clinical trial in the company's registration database *International Clinical Trials Registration Platform / World Health Organization (ICTRP/ WHO)* or others recognized by *the International Committee of Medical Journals Editors (ICMJE);* e

e) ~~Substantiated opinion from the Research Ethics Committee (CEP) issued to the first clinical trial center to forward the protocol for analysis by the CEP.~~ **~~(Revoked by Resolution – RDC nº 205, of December~~ 28, 2017)**

Art. 39. All documentation filed manually, including compliance with requirements, must be accompanied by a copy in electronic media (pdf or word file).

§1 Electronic documents must allow textual search.

§2 Submission of electronic media applies until Anvisa adopts information technology tools that allow electronic submission of the requested documents.

Art. 40. Forms for the start and end date of the clinical trial in Brazil must be filed in the form of a secondary petition to the corresponding clinical trial dossier process, within 30 (thirty) calendar days after each start and end date.

Art. 41. Anvisa may, at any time, request other information that it deems necessary for evaluating and monitoring clinical development.

CHAPTER IV

SUBSTANTIAL CHANGES TO THE DDCM

Art. 42. Substantial modifications to the DDCM must be filed and await a response from Anvisa before implementation, respecting the deadlines established in Art. 36.

Single paragraph. Modifications to the DDCM must be submitted to Anvisa in the form of a secondary petition attached to the respective DDCM process to which it is linked.

Art. 43. For the purposes of this Resolution, substantial modifications consist of in:

I - inclusion of clinical trial protocol(s) not foreseen or different from those previously established in the initial development plan,

II - exclusion from clinical trial protocol(s) or,

III - changes that potentially impact the quality or safety of the experimental medicine, active comparator or placebo.

Art. 44. Modifications to the DDCM arising from recommendations or alerts issued by health authorities must be notified before being implemented and may be executed, regardless of Anvisa's prior statement.

Art. 45. Modifications to the DDCM not considered substantial must be presented to Anvisa as part of the Safety Update Report for the development of the experimental medicine.

CHAPTER V

AMENDMENTS TO THE CLINICAL TRIAL PROTOCOL

Art. 46. All amendments to a clinical trial protocol must be presented to Anvisa, identifying the part of the protocol to be modified and its justifications.

Single paragraph. Any amendment must be implemented only after obtaining ethical approvals in accordance with current legislation.

Art. 47. Substantial amendments to clinical trial protocols must be filed and await a response from Anvisa before implementation, respecting the deadlines established in Art. 36.

§1 Substantial amendments must be submitted to Anvisa in the form of a secondary petition attached to the process of the respective clinical trial protocol to which it is linked.

§2° ~~The petition for substantial amendments must contain the new protocol and the Consubstantiated Opinion of the Research Ethics Committee (CEP) issued to the first clinical trial center to forward the protocol for analysis by the CEP.~~

§2° The petition for substantial amendments must contain the new protocol.
(Wording given by Resolution – RDC nº 205, of December 28, 2017)

§3 Amendments that aim to eliminate immediate risks to the safety of clinical trial participants are excluded from the provisions of the **caput .** These can be implemented and notified to Anvisa immediately.

Art. 48. For the purposes of this Resolution, an amendment will be considered substantial when at least one of the following criteria is met:

I- change in the clinical trial protocol that interferes with the safety or physical or mental integrity of the participants;

II- change in the scientific value of the clinical trial protocol.

Art. 49. Amendments to the clinical trial protocol not considered substantial must be presented to Anvisa as part of the annual clinical trial protocol monitoring report.

CHAPTER VI

SUSPENSIONS AND CANCELLATIONS

Art. 50. The sponsor may cancel or suspend a DDCM or clinical trial at any time, as long as the appropriate technical-scientific justifications are sent, as well as a monitoring plan for participants in the clinical trial(s) already initiate(s).

§1 Once a DDCM has been cancelled, no clinical trial related to it will be may be continued in the country.

§2 If a DDCM or clinical trial is canceled for safety reasons, the sponsor must technically and scientifically justify the reasons for cancellation and present measures to minimize/mitigate risk to participants in the clinical trial(s).).

§3 Suspensions and cancellations of clinical trials or DDCM must be submitted to Anvisa in the form of a secondary petition attached to the respective process.

Art. 51. The sponsor must notify Anvisa of the decision to suspend or cancel a clinical trial or DDCM. After a decision to suspend or

cancellation, the sponsor must notify Anvisa within a maximum period of 15 (fifteen) calendar days.

Art. 52. In cases of temporary suspension of the clinical trial or DDCM as an immediate safety measure, the sponsor must notify Anvisa within 7 (seven) calendar days from the date of suspension, justifying the reasons.

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

Art. 53. Requests to reactivate suspended clinical trial protocols or DDCM must be forwarded to Anvisa accompanied by the appropriate justifications so that the trial(s) can be restarted.

Single paragraph. The clinical trial(s) or DDCM may be restarted only after approval by Anvisa.

Art. 54. Anvisa may, at any time, cancel or suspend the DDCM or any linked clinical trial, if it deems that the approval conditions have not been met or if there are reports of safety or efficacy that significantly affect the participants in the clinical trial or affect the scientific validity of data obtained, informing the sponsor of the reasons.

CHAPTER VII

SECURITY MONITORING AND ALERTS

Section I

Adverse Event Monitoring

Art. 55. The sponsor must monitor all adverse events, including non-serious adverse events, during the development of the experimental drug.

Art. 56. The sponsor or Independent Safety Monitoring Committee must systematically collect and evaluate aggregated data on adverse events occurring in the clinical trial, submitting the results of this evaluation to Anvisa in the safety update report for the development of the experimental drug.

Art. 57. The sponsor must establish a monitoring plan to detection of late adverse events, justifying the proposed period.

Single paragraph. In the case of pregnancy, the investigator and sponsor must accompany the mother and child.

Subsection I

Immediate Measures

Art. 58. In the event of a serious adverse event occurring during the conduct of the clinical trial at any stage of drug development, the sponsor and the investigator must adopt immediate safety measures to protect the clinical trial participants against any imminent risk.

Single paragraph. In the case of a serious adverse event to be notified, it will be necessary to inform which measures were adopted, the action plan in the event of new events of the same nature, data on the location where the service was provided, along with other data requested in the notification form, especially those that enable the traceability of the event and the affected participant.

Art. 59. The notification of unexpected serious adverse events, whose causality is possible, probable or defined, does not depend on the submission of the Investigator's Brochure, amendments, reports or early termination of the clinical trial.

Art. 60. The development of a phase III clinical trial must be monitored by Independent Safety Monitoring Committees and their recommendations must be reported to Anvisa by the sponsor.

Single paragraph. In cases where there is no constitution of Independent Safety Monitoring Committees, justifications must be provided.

Subsection II

Reporting Adverse Events by the Investigator

Art. 61. The investigator must communicate the occurrence of all adverse events to the sponsor, providing any requested information and expressing his opinion regarding the causality between the adverse event and the product under investigation.

Single paragraph. Adverse events or abnormalities in laboratory test results that affect participant safety must be reported to the sponsor in accordance with GCP and protocol.

Art. 62. All adverse events must be treated and affected participants monitored by the main investigator and his team until their resolution or stabilization.

Subsection III

Sponsor's Notification of Adverse Events

Art. 63. The sponsor must notify Anvisa, through a specific electronic form, of unexpected serious adverse events occurring in the national territory, the causality of which is possible, probable or defined in relation to the product under investigation.

Single paragraph. The sponsor must maintain all detailed records of adverse events reported by investigators. Anvisa may request such records at any time.

Art. 64. The sponsor must inform the investigators involved in the clinical trial about unexpected serious adverse events, the causality of which is possible, probable or defined, and adopt procedures for updating the investigator's brochure, in addition to reassessing the risks and benefits for the participants.

Subsection IV

Deadlines

Art. 65. The investigator must inform the sponsor about serious adverse events within 24 (twenty-four) hours from the date of knowledge of the event.

Art. 66. The sponsor must ensure that all relevant information about adverse events mentioned in Art. 63 that are fatal or life-threatening are documented and notified to Anvisa, via electronic form, within a maximum of 7 (seven) days calendar from the date the sponsor became aware of the case.

Single paragraph. Additional information on the monitoring of adverse events mentioned in the **caput** must be included in the form within 8 (eight) calendar days from the date of notification.

Art. 67. All other unexpected serious adverse events, whose causality is possible, probable or defined in relation to the products under investigation must be notified to Anvisa within 15 (fifteen) calendar days from the sponsor becoming aware of the case.

Section II

From Monitoring Reports

Subsection I

From Clinical Trial Protocols Monitoring Reports

Art. 68. The sponsor must send Anvisa annual monitoring reports containing the following information, exclusively from Brazilian centers, in tabulated form, for each clinical trial protocol:

I- title of the clinical trial;

II- protocol code;

III- recruitment *status* of clinical trial participants;

IV- breakdown of the number of participants recruited per center;

V- number and description of deviations and protocol violations per center; It is

VI- description of all adverse events that occurred per center during the evaluated period, identifying the clinical trial participants with the codes used in the Case Report Form adopted in the clinical trial protocol.

§1 The annual clinical trial protocol monitoring report must be submitted to Anvisa in the form of a secondary petition attached to the respective protocol process to which it is linked.

§2 The annual report must be filed within a maximum period of 60 (sixty) calendar days, with the start date of the clinical trial in Brazil as an annuality reference.

Art. 69. After completion of the activities of a clinical trial in all participating countries, for any reasons, the sponsor must submit to Anvisa
a final report containing, at a minimum, the following information:

I- title of the clinical trial;

II- protocol code;

III- breakdown of the number of participants recruited and removed from the clinical trial;

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

V- demographic description of participants recruited in the clinical trial;

VI- statistical analysis;

VII- number and description of deviations and violations of the protocol;

VIII- list of all adverse events and laboratory abnormalities with causality assessment occurred by participants;

IX- the results obtained in measuring the outcomes for each participant in the clinical trial; It is

X- rationale for the premature termination of development in Brazil or in the world, when applicable.

§1 The final clinical trial protocol report must be submitted to Anvisa in the form of a secondary petition attached to the respective protocol process to which it is linked.

§2 The final report must be filed within 12 (twelve) months of the end date of the clinical trial.

Subsection II

From the Investigational Drug Development Safety Update Report

Art. 70. The sponsor must send annual reports to Anvisa investigational drug development safety update.

Single paragraph. Annual reports must be filed within a maximum period of 60 (sixty) calendar days with the annuality reference being the date of approval of the DDCM by Anvisa or the date determined in international development.

CHAPTER VIII

INSPECTIONS

Section I

Inspections to Verify Compliance with Good Clinical Practices

Art. 71. With the aim of guaranteeing the protection of the rights, safety and well-being of clinical trial participants, as well as the accuracy and reliability of the data to be obtained or submitted for health registration, Anvisa may carry out inspections in BPC in clinical trial centers, sponsor, ORPC, laboratories and other institutions involved in the development of the experimental medicine to verify the degree of adherence to current Brazilian legislation and compliance with GCP, in addition to ensuring the rights and duties that concern the scientific community and the State.

§1º GCP inspections will follow the guidelines harmonized in the Document of the Americas, Manual of Good Clinical Practices of the International Conference on Harmonization (Document E6) and in specific GPC inspection standards published by Anvisa.

§2 Depending on the result of the BPC inspection, Anvisa may determine:

I- the temporary interruption of the clinical trial;

II- the definitive cancellation of the clinical trial at the center in question;

III- the definitive cancellation of the clinical trial in all centers in Brazil;
or

IV- the invalidation of data from centers and clinical trials that
do not comply with GCP.

Section II

Inspections to Verify Compliance with Good Manufacturing Practices of Products Under Investigation

Art. 72. Anvisa may carry out GMP inspections of the experimental medicine or product under investigation produced or modified by the sponsor in order to verify the chemical, production and quality control information informed in the DDCM and whether the medicine is sufficiently safe to allow administration to clinical trial participants.

CHAPTER IX

IMPORTATION

Art. 73. The import of products under investigation for exclusive use in clinical trials must only be subject to inspection by the health authority in office at the place of clearance.

Single paragraph. Exception from this situation are products under investigation subject to special control which, in addition to inspection at the clearance site, must have prior authorization for shipment by the responsible technical area at Anvisa.

Art. 74. The following documents must be presented upon arrival of the product under investigation in the national territory:

I - copy of the Special Announcement (CE), Specific Special Announcement (CEE) or Document for Import of Product(s) under investigation of the Dossier of Clinical Development of Medicines (DDCM) issued by the competent technical area of Anvisa at its headquarters;

II – in cases of imports carried out by others than the holder of the DDCM, a copy of the document delegating import responsibilities must be presented;

III - term of responsibility for imports intended for clinical research set out in health regulations for imported goods and products;

IV - copy of the bill of lading; It is

V - copy of the commercial invoice.

Art. 75. The competent health authority in office at the place of clearance of the product under investigation will verify compliance with the service

to packaging, transport and storage indications, in accordance with specific information in the CE, CEE, or Document for Import of Product(s) under investigation of the Medicinal Product Clinical Development Dossier (DDCM) in addition to that provided by the manufacturer or sponsor.

Single paragraph. In external or transport packaging used for movement of products covered by this Chapter must include:

a) number of the CE, CEE or Document for Import of Product(s) under investigation of the Medicinal Product Clinical Development Dossier (DDCM) to which the product under investigation is submitted;

b) quantity of imported material;

c) information on special storage precautions, such as temperature, humidity and luminosity;

d) information on physical form or pharmaceutical form relating to the presentation of the medicine;

e) information on the expiration date of the medicine and, when applicable, the medical device; It is

f) batch number or serial number.

Art. 76. The qualitative information and specifications of the products under investigation to be used in the clinical trial will be informed in the Special Communication (CE), in the Special Specific Communication (CEE) and in the Document for Import of Product(s) under investigation of the Dossier of Clinical Drug Development (DDCM).

Single paragraph. In case of changes to the products under investigation and their specifications informed in the CE, CEE or in the Document for Import of Product(s) under investigation of the Clinical Medicine Development Dossier (DDCM), this information must be notified to the competent technical area of Anvisa at its headquarters. The updated CE, CEE or Document for Import of Product(s) under investigation from the updated Drug Clinical Development Dossier (DDCM) must be presented at the customs clearance location.

Art. 77. The entry into the national territory of products under investigation not provided for in the CE, CEE or Document for Import of Product(s) under investigation of the Medicinal Clinical Development Dossier (DDCM) for the purposes of clinical trials regulated by this is prohibited. resolution.

Single paragraph. Changing the purpose of importing the goods and products covered by this resolution is prohibited.

CHAPTER X

TRANSITIONAL PROVISIONS

Art. 78. Clinical trial consent processes filed with Anvisa on a date prior to the publication of this Resolution and which are still awaiting technical analysis will be evaluated according to the Resolutions in force at the time of submission of the protocol.

§1 Petitions that are awaiting analysis and are within the scope of the 90 (ninety) day period as established by Article 36 of this Resolution, may begin clinical trials after the expiration of the period contained in the aforementioned article and after the pertinent ethical approvals.

§2º For the cases mentioned in §1º, a CEE will be issued for the purposes of import or export to be carried out in accordance with the resolution in force at the time of submission of the protocol to Anvisa.

§3° The deadline established in §3° of Art. 36 does not apply to the processes of consent awaiting technical analysis and which are found in the **caput** of this article.

Art. 79. When filing a DDCM, the holder must link all consent processes in clinical trials related to the experimental medicine that may have already been submitted for evaluation by Anvisa at some point.

Art. 80. Consent processes for clinical trials already approved by Anvisa must follow the Resolution in force at the time of their approval until the process is inserted into a DDCM, if applicable.

Chapter XI

FINAL PROVISIONS

Art. 81. Anvisa will publish specific guides and manuals to guide procedures related to this Resolution.

Art. 82. Failure to comply with the provisions of this Resolution implies a health infraction, with the offender being subject to the penalties provided for in Law No. 6,437 of August 20, 1977.

Art. 83 Omitted cases will be resolved in light of other national standards and international guidelines.

Art. 84. Resolution - RDC No. 39, of June 5, 2008, Resolution - RDC No. 36, of June 27, 2012 and items 1. and 1.1 are hereby revoked. of Section I of Chapter XXVI of Resolution - RDC No. 81, of November 5, 2008.

Art. 85. This Resolution comes into force on the date of its publication.

JAIME CÉSAR DE MOURA OLIVEIRA