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Organ: Ministry of Health/Brazilian National Health Surveillance Agency/Collegiate Board

RESOLUTION RDC No. 548, OF AUGUST 30th, 2021

It provides for clinical trials with medical devices in Brazil.

The Collegiate Board of the Brazilian National Health Surveillance Agency, exercising its powers granted to it by art. 15, III and IV, together with art. 7, III and IV of Law no. 9.782, dated January 26th, 1999, and art. 53, V, Paragraphs 1 and 3 of the Internal Regulation approved by Collegiate Board Resolution - RDC No. 255, dated December 10th, 2018, hereby resolves to adopt the following ANVISA Board Resolutions, as deliberated in a meeting held on August 30th, 2021, and I, Acting Managing Director, determine its publication.

CHAPTER I

INITIAL PROVISIONS

Section I

Objective

Art. 1 This Resolution aims to define the procedures and requirements for conducting clinical trials with medical devices in Brazil, introducing the concept of clinical investigation dossier of a medical device (DICD) and its procedures and requirements for approval by ANVISA.

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

Paragraph 1 Clinical trials with medical devices registered in Brazil with the objective of evaluating:

I - new indication of use;

II - new purpose proposed or use; and

III - relevant post-registration change.

Paragraph 2 This Resolution does not apply to tests for performance evaluation of diagnostic products for in vitro use.

Section II

Definitions

Art. 3. For purposes of this Resolution, the following definitions are adopted:

I - audit - systematic and independent analysis of the activities and documents related to the study to determine whether the evaluated activities were performed, and the data recorded, analyzed and accurately reported when complying with the protocol, the standard operational procedures defined by the sponsor, good clinical practices (GCP) and applicable regulatory requirements;

II - Good Clinical Practices (GCP) - standard for planning, conducting, performing, monitoring, auditing, recording, analyzing and reporting clinical trials that provides assurance 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 the Document of the Americas and the Good Clinical Practices Manual of the International Harmonisation Conference (Document E6(R2) and ISO14155;

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

IV - Good Laboratory Practice (GLP) - a quality system that covers the organizational process and the conditions in which non-clinical trials related to health and safety to the environment are planned, developed, monitored, registered, archived and reported;

V - investigator's brochure - compiled of clinical and non-clinical data on the medical device(s) under investigation, which have relevance to its study in humans;

VI - clinical trials site - public or private organization, legitimately constituted, duly registered in the National Registry of Health Establishments (CNES), in which clinical trials are conducted.

VII - independent ethics committee (IEC) - interdisciplinary and independent council with an advisory, deliberative, and educational role, created to defend the interests of individuals participating in studies, their integrity and dignity, therefore guaranteeing that the studies remain within ethical standards;

VIII - independent data monitoring committee - independent committee for monitoring data to assess at regular intervals the progress of a clinical trial, safety data and critical points to assess efficacy and to recommend to a sponsor whether a trial should be continued, modified or discontinued;

IX - comparator - medical device, therapy, placebo, simulation or absence of treatment used in the control group in a clinical trial;

X - special notice (CE) - an authorizing document, issued by ANVISA after analysis and approval of the DICD, which may be used in import or export requests for a clinical trial;

XI - specific special communication (CEE) - document issued by ANVISA, necessary for the import or export request for a clinical trial subject to the notification regime;

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

XIII - clinical trial start date in Brazil: corresponds to the date of inclusion of the first clinical trial participant in Brazil;

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

XV - end date of the clinical trial in Brazil: corresponds to the date of the last visit of the last clinical trial participant in Brazil or another definition of the sponsor, expressly determined in the specific dossier of the clinical trial;

XVI - clinical trial end date: corresponds to the date of the last visit of the last clinical trial participant in the world or another definition of the sponsor, expressly determined in the specific dossier of the clinical trial;

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

XVIII - medical device - it represents the health products defined below:

a) medical product: health product, such as equipment, apparatus, material, article or system for medical, dental, laboratory or aesthetic use or application, intended for prevention, diagnosis, treatment, rehabilitation or contraception and that does not use pharmacological means , immunological or metabolic to perform its main function in human beings, but may, however, be aided in its functions by such means;

b) diagnostic products for in vitro use: reagents, standards, calibrators, controls, materials, articles and instruments, together with instructions for their use, which contribute to carry out a qualitative, quantitative or semi-quantitative determination of a sample from the human body and which are not intended to fulfill any anatomical, physical or therapeutic function, which are not ingested, injected or inoculated into human beings and which are used solely to provide information on samples obtained from the human body;

XIX - medical device under investigation - medical device under test, object of DICD, to be used in the clinical trial, in order to obtain information for its registration or post-registration;

XX - import responsibility delegation document - document issued by the research sponsor, which contains the indication of the authorized importer, and the responsibilities related to the transport and clearance of the imported goods;

XXI- document for import of product(s) under investigation of the Clinical Investigation Dossier of Medical Device: document issued by ANVISA, necessary for the import or export request for a clinical trial, in cases of non-manifestation on the DICD;

XXII - Clinical Investigation Dossier of Medical Device (DICD) - compiled of documents to be submitted to ANVISA in order to assess the steps inherent in the clinical development of a medical device under investigation, in order to obtain information to support the registration or changes post-registration of said product;

XXIII - specific dossier for each clinical trial - compiled of documents to be submitted to ANVISA in order to obtain information regarding the clinical trials to be conducted in Brazil, which are part of the medical device development plan under investigation;

XXIV - amendment to the clinical trial protocol - any proposal for modification in an original clinical trial protocol, always presented with the justification that motivated it, and such amendment may be substantial or not;

XXV - clinical trial - research conducted on human beings with the objective of verifying the safety and/or efficacy of the medical device(s) under investigation;

XXVI - adverse event (AE) - any adverse medical occurrence in a patient or research participant that is not necessarily causally related to the treatment. As a result, an AE can be any unfavorable and unintended sign, symptom, or illness (including laboratory test results outside the normal range) associated with the use of an investigational medical device, whether related to it or not;

XXVII - serious adverse event - one that results in any adverse experience with drugs, biological products or medical devices, occurring at any dose and resulting in any of the following outcomes:

a) death;

b) potentially fatal adverse event (the one that, in the notifier's opinion, puts the individual at immediate risk of death due to the adverse event that occurred);

c) persistent or significant disability/inability;

d) requires hospitalization of the patient or prolongs hospitalization;

e) congenital anomaly or birth defect;

f) any suspected transmission of infectious agent by means of a medical device;

g) clinically significant event;

XXVIII - unexpected adverse event - event not described as adverse reaction in the brochure or instruction of use/manual of the operator of the medical device under investigation;

XXIX - proposed purpose - description of the expected results with the use of the device;

XXX - case report form: printed, optical or electronic document intended to record all information about each participant in the clinical trial that, according to the clinical trial protocol, must be reported to the sponsor;

XXXI - indication of use - comprises the indication of the disease or condition that the device is intended to diagnose, treat, prevent, mitigate or cure; parameters to be monitored or other indications of use associated with the device, including information on criteria for patient selection and target population of the device (e.g., adult, pediatric or newborn);

XXXII - inspection - the act by a regulatory authority to conduct an official review of documents, facilities, records and any other resources considered by the authority as relating to the clinical trial and which may be located where the trial is conducted, in the facilities of the sponsor and/or the clinical research organization (CRO), or other locations that the regulatory authority deems appropriate;

XXXIII - clinical investigation - any systematic investigation or study or in one or more humans, conducted to assess the safety and/or efficacy of a medical device;

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

XXXV - investigator-sponsor - individual 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, from national or international funding entities to research, from private entities and other non-profit entities;

XXXVI - monitoring - the act of continuously reviewing the process of a clinical trial and ensuring that it is conducted, recorded and reported in accordance with the protocol, standard operating procedures, good clinical practices and applicable regulatory requirements;

XXXVII - clinical research organization (CRO) - any company regularly installed in national territory hired by the sponsor or by the investigator/sponsor, which assumes, in part or in full, with ANVISA, the attributions of the clinical trial sponsor;

XXXVIII - sponsor: person, company, institution or organization responsible for initiating, administering, controlling and/or financing a clinical trial;

XXXIX - product under investigation - medical device under investigation, comparator or any other product to be used in the clinical trial;

XL - clinical trial protocol - document that describes the objectives, design, methodology, statistical considerations and organization of the study, as well as the context and rationale of the clinical trial;

XLI - annual report - document with annual periodicity containing specific information on the conduct of a specific clinical trial in centers in Brazil, in accordance with the clinical protocol and the GCP;

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

XLIII - proposed use - therapeutic, diagnostic or other function that is primarily conferred on the device, describing the procedure in which the device will be used (e.g., in vivo or in vitro diagnosis, treatment, monitoring, rehabilitation, contraception or disinfection);

XLIV - usability - feature of the user's medical device interface that establishes effectiveness, efficiency, ease of learning and user satisfaction;

XLV - clinical trial protocol violation: deviation from the clinical trial protocol that could affect the quality of the data, compromise the integrity of the study or that could affect the safety or rights of clinical trial participants.

Section III

General Provisions

Art. 4 Clinical trials involving medical devices under investigation that have the following characteristics are subject to the submission of a DICD:

I - risk class products III and IV;

II - devices intended for diagnostic use, regardless of risk class, that meet the criteria below:

a) the device under investigation is invasive;

b) the device under investigation is intended to supply energy to the clinical trial participant; or

c) the study uses the target device as the only diagnostic procedure, using other devices or diagnostic procedures, duly recognized and approved, to confirm the diagnosis;

Paragraph 1 Studies with the exclusive purpose of evaluating the usability/human factors in medical devices are outside the scope of this Resolution, except when clinical trials are conducted and include, among other outcomes, the evaluation of usability/human factors.

Paragraph 2 In situations where there is no need for approval of the clinical trial(s) by ANVISA, these trials remain subject to other regulatory and ethical approvals.

Art. 5. Clinical trials involving medical devices of risk classes I and II, observational clinical trials and post-marketing independent of the risk class, without the need to submit a DICD, are subject to the notification regime.

Paragraph 1 The clinical trial notification must consist of the following documents:

I - duly completed clinical trial submission form, available on ANVISA's website;

II - proof of payment or exemption from the Sanitary Surveillance Inspection Fee (TFVS), through a Union Collection Guide (GRU);

III - clinical trial protocol according to GCP;

IV - proof that the clinical trial is registered in the International Clinical Trials Registration Platform/World Health Organization (ICTRP/WHO) clinical research registration database or others recognized by the International Committee of Medical Journals Editors (ICMJE); and,

V - Substantiated opinion of the Independent Ethics Committee (IEC) issued to the first clinical trial center to forward the protocol for analysis by the IEC.

Paragraph 2 The medical devices under investigation used in post-marketing and observational clinical trials must be duly registered with ANVISA.

Paragraph 3 Post-marketing and observational clinical trials investigating medical devices that have a DICD previously approved by ANVISA shall file the notification process by binding to the corresponding DICD.

Paragraph 4 For the clinical trials described in the caput, a Specific Special Press Release (CEE) will be issued within 30 (thirty) calendar days from the date of receipt by ANVISA.

Art. 6 ANVISA may issue guidelines on the applicability of this Resolution to specific cases of clinical trials with medical devices.

CHAPTER II

REQUIREMENTS FOR SUBMISSION OF THE CLINICAL INVESTIGATION DOSSIER OF MEDICAL DEVICE (DICD)

Art. 7 The documentation presented in the DICD shall ensure the safety and rights of clinical trial participants at all stages of clinical development, the quality of the medical device under investigation and the data obtained in the clinical stages of development so that they allow an assessment of the efficacy and safety of the medical device.

Art. 8 DICD may be submitted to ANVISA at any stage of the clinical development of the medical device for one or more phases of clinical trials.

Section I

General Requirements for the Request

Art. 9 The sponsor must submit a DICD to ANVISA only in the case where he intends to conduct clinical trials with medical devices in the national territory.

Sole paragraph. For the purpose of DICD analysis, at least one specific clinical trial dossier to be performed in Brazil must be filed.

Art. 10. A single Special Notice (CE) will be issued by DICD mentioning all clinical trials to be conducted in Brazil.

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

Art. 11. Upon receipt of the DICD, ANVISA will evaluate the DICD within 90 (ninety) calendar days.

Paragraph 1 If there is no manifestation of ANVISA within 90 (ninety) calendar days after receipt of the DICD, clinical development may be initiated after the relevant ethical approvals.

Paragraph 2 In cases of non-manifestation within the time limits described in the caput, ANVISA will issue a Document for importation of Product(s) under investigation of the Clinical Investigation Dossier of Medical Device (DICD) to be presented at the clearance site, for the importation of product(s) under investigation, necessary to conduct the clinical trial.

Art. 12. The DICD shall contain general information regarding the clinical investigation plan, investigative device and specific protocol(s) for the clinical trial(s), as described in Section II of this chapter.

Art. 13. DICD may be submitted by sponsor, sponsor investigator or CRO.

Paragraph 1 The person responsible for submission to ANVISA will also be responsible for all subsequent submissions related to DICD.

Paragraph 2 CRO submissions can only be made when the sponsor does not have a head office or branch in Brazil.

Paragraph 3 DICD submission of a sponsor investigator shall be performed by the primary sponsor.

Section II

Content and Format of the Request

Art. 14. The DICD should be submitted to ANVISA and will consist of the following documents:

I - petition form duly completed, according to model available on ANVISA's website;

II - proof of payment or exemption from the Sanitary Surveillance Inspection Fee (TFVS), through a Union Collection Guide (GRU);

III - clinical investigation plan of the medical device containing:

a) description of the medical device, its mechanism of operation/action and indications to be studied;

b) the general objectives and the planned duration for clinical development;

c) description for each planned clinical trial, containing information on phase, design, outcomes, comparators, objectives, population to be studied, hypotheses, estimated number of participants and statistical planning; and

d) information on phase, design, endpoints, 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 information from the experimental medical device in accordance with Annex I to this Resolution;

V - summary on safety aspects based on previous experience in humans with the medical device under investigation, as well as post-marketing experience in other countries, if applicable;

VI - dossier of the medical device under investigation in accordance with Annex II to this Resolution; and

VII - specific dossier of clinical trial to be performed in Brazil.

Paragraph 1 The provisions of item VII of the caput of this article shall be filed in the form of individual processes for each clinical trial.

Paragraph 2 Each process must be linked to the DICD and submitted by the sponsor, sponsor-investigator or by CRO.

Paragraph 3 The dossier dealing with item VII of the caput of this article shall be composed of the following documents:

I - duly completed clinical trial submission form, available on ANVISA's website;

II - proof of payment or exemption from the Sanitary Surveillance Inspection Fee (TFVS), through a Union Collection Guide (GRU);

III - clinical protocol according to GCP;

IV - proof that the clinical trial is registered in the International Clinical Trials Registration Platform/World Health Organization (ICTRP/WHO) or other clinical research registration database recognized by the International Committee of Medical Journals Editors (ICMJE); and

V - Substantiated opinion of the Independent Ethics Committee.

Art. 15. Electronic protocoled documents should allow textual search.

Art. 16. Forms of the start and end of the clinical trial in Brazil should be filed as a petition secondary to the process of the corresponding clinical trial dossier, within 30 (thirty) calendar days after each start and end date.

Art. 17. ANVISA may, at any time, request other information it deems necessary for its evaluation and monitoring of clinical development.

CHAPTER III

SUBSTANTIAL MODIFICATIONS TO DICD

Art. 18. The substantial modifications of the DICD must be filed and await manifestation of ANVISA to implement it, according to the deadlines established in art. 11.

Sole paragraph. Modifications to the DICD must be submitted to ANVISA in the form of a secondary petition attached to the respective DICD process to which it is linked.

Art. 19. For the purposes of this Resolution, substantial changes consist on:

I - inclusion of clinical trial(s) protocol(s) not provided for in the initial clinical development plan of the medical device under investigation;

II - exclusion of clinical trial protocol(s); or

III - changes that potentially have an impact on the quality and safety of the medical device under investigation.

Art. 20. Modifications of the DICD arising from recommendations or alerts issued by health authorities should be notified before they are implemented and may be implemented regardless of the prior manifestation of ANVISA.

Art. 21. Modifications to the DICD not considered substantial should be submitted to ANVISA as part of the Annual Clinical Investigation Dossier of Medical Device.

CHAPTER IV

AMENDMENTS TO THE CLINICAL PROTOCOL

Art. 22. All amendments to a clinical trial protocol must be submitted to ANVISA, identifying the part of the protocol to be modified and its justifications.

Sole paragraph. All amendments should be implemented only after obtaining ethical approvals in accordance with current legislation.

Art. 23. Substantial amendments to clinical trial protocols should be filed and await manifestation of ANVISA before its implementation, respecting the deadlines established in Article 11.

Paragraph 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.

Paragraph 2 Except for the provisions of Paragraph 1 of Article 22 amendments aimed at eliminating immediate risks to the safety of clinical trial participants, which may be implemented and notified to ANVISA immediately.

Art. 24. For the purpose of this Resolution an amendment will be considered substantial when any of the following criteria are met:

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

II - Change in the scientific value of the clinical protocol.

Art. 25. Amendments to the clinical trial protocol not considered substantial should be submitted to ANVISA as part of the annual clinical trial protocol follow-up report.

CHAPTER V

SUSPENSIONS AND CANCELLATIONS

Article 26. The sponsor may cancel or suspend DICD or clinical trial at any time, provided that proper technical-scientific justifications are sent, as well as a follow-up plan for the participants of the clinical trial(s) that have already started.

Paragraph 1 Once a DICD has been cancelled, no clinical trial related to it may be continued.

Paragraph 2 Where a DICD or clinical trial is cancelled for safety reasons, the sponsor shall technically and scientifically justify the reasons for the cancellation and present measures for risk minimization/mitigation to the participants of the clinical trial(s).

Paragraph 3 Suspensions and cancellations of clinical trial protocol or DICD shall be submitted to ANVISA in the form of a secondary application attached to the respective file.

Art. 27. The sponsor shall notify ANVISA of the decision to suspend or cancel a clinical trial protocol.

Sole paragraph. After a decision to suspend or cancel the sponsor must notify ANVISA within a maximum of 15 (fifteen) calendar days.

Art. 28. In cases of temporary suspension of the clinical trial as an immediate safety measure, the sponsor shall notify ANVISA within seven (7) calendar days of the date of suspension of the clinical trial, justifying the reasons.

Sole paragraph. The reasons, coverage, interruption of treatment and suspension of recruitment of participants should be clearly explained in the notification of temporary suspension.

Art. 29. Requests for reactivation of suspended clinical trials should be forwarded to ANVISA accompanied by the appropriate justifications for the study to be restarted.

Sole paragraph. The study will only be restarted after approval by ANVISA.

Art. 30. ANVISA may, at any time, cancel or suspend dicd or any linked clinical trial if it deems that the approval conditions have not been met, or there are safety/efficacy reports that significantly affect research participants, or the scientific validity of data obtained in clinical trials.

CHAPTER VI

RESPONSIBILITIES

Art. 31. Art. 7. The responsibilities listed in this chapter include those defined in the Good Clinical Practices, without prejudice to other ethical and legal responsibilities.

Section I

Sponsor's Responsibilities

Art. 32. The sponsor is responsible for the information necessary for the correct execution of the DICD, the selection of qualified investigators and research centers, ensuring that clinical trials are conducted in accordance with protocols and Good Clinical Practices.

Art. 33. The sponsor must use qualified professionals to supervise the general conduct of clinical trials, manage data, conduct statistical analysis and prepare reports.

Art. 34. The sponsor shall ensure that quality assurance and quality control are implemented in all areas of the institutions involved in the clinical development of the medical device under investigation.

Art. 35. The sponsor must keep the clinical trial data on file, physical or digital, for a period of 5(five) years after the last approval of a registration application in Brazil.

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

Art. 36. The sponsor is responsible for all expenses related to procedures and examinations, especially those of diagnosis, treatment and hospitalization of the clinical trial participant, and other actions necessary for the resolution of adverse events related to the clinical trial.

Art. 37. The sponsor shall ensure that the data obtained on the safety and efficacy of the medical device under investigation are sufficient to support human exposure to the medical device.

Art. 38. The sponsor shall ensure that the medical device under investigation, placebo and the simulated device, when used, are manufactured in accordance with GMP and are coded and labelled in such a way as to protect masking, if applicable, and characterize them as products under investigation.

Sole paragraph. In studies using other medical devices(s) as a comparator, the sponsor should use those manufactured according to GMP.

Art. 39. The sponsor is responsible for importing the amount necessary to perform the clinical trial.

Art. 40. 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 Independent Ethics Committees.

Sole paragraph. The sponsor is responsible for the final destination of the products under investigation that were not used in the clinical trial.

Art. 41. The sponsor shall ensure adequate monitoring and auditing of clinical trials.

Art. 42. The sponsor must promptly inform those involved in the clinical trial when it is prematurely terminated or suspended for any reason.

Art. 43. The sponsor can transfer its functions to a CRO.

Paragraph 1 The transfer of the caput of this article does not depart from the definitive responsibility of the sponsor for the quality and integrity of the research data.

Paragraph 2 Any functions related to the clinical trial that are transferred to and assumed by a CRO shall be specified in writing in a document signed by the sponsor and CRO.

Section II

Investigator's Responsibilities

Art. 44. The investigator shall 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. 45. The investigator should personally supervise the clinical trial and may only delegate tasks, but not responsibilities.

Art. 46. The investigator shall allow monitoring, audits and inspections.

Art. 47. The investigator shall ensure adequate medical assistance to clinical trial participants for any adverse events relating to the clinical trial, including clinically significant laboratory values, at no charge to the participant.

Art. 48. The investigator shall promptly inform the participants of the clinical trial when it is prematurely terminated or suspended for any reason, in addition to ensuring appropriate therapy and follow-up to the participants.

Art. 49. The investigator is responsible for using the products under investigation only within the clinical trial and storing according to the sponsor's specification and in line with applicable regulatory requirements.

Section III

Investigator-Sponsor Responsibilities

Art. 50. In the case of a clinical trial developed by a sponsor investigator, the institution with which it has a link will be the primary sponsor.

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

Paragraph 2 In case of delegation of responsibilities and activities, a written document shall be signed between the parties.

Paragraph 3 The primary sponsor may not delegate quality assurance activities, audits and clinical trial monitoring to the sponsor investigator, but may delegate them to a CRO.

Paragraph 4 The primary sponsor shall 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.

Paragraph 5 The institution referred to in the caput shall be the institution in which the clinical trial will be conducted.

Paragraph 6 The responsibilities listed in this article do not exclude the provisions of the chapter on sponsor and investigator responsibilities.

Art. 51. In the case of donation of medical devices under investigation already registered in Brazil, for clinical trial, the donor will be the sponsor if there is an agreement to transfer or ownership of the data obtained in the research to the said donor.

Art. 52. In the case of donation of medical devices under investigation not registered in Brazil for clinical trial, the donor shares the responsibilities of sponsor.

Section IV

Clinical Trial Site Structure

Art. 53. The clinical trial site shall have facilities suitable for the conduct of the protocol, with regard to physical structure, equipment/instruments and human resources, and suitable for the study population, such as the elderly, children, and persons with special needs, among others.

Art. 54. The direction of the institution shall be notified of the conduct of the clinical trial.

CHAPTER VII

SAFETY MONITORING AND ALERTS

Section I

Adverse Event Monitoring

Art. 55. The sponsor should monitor all adverse events, including non-serious adverse events, during the development of the medical device under investigation.

Art. 56. The sponsor or the Independent Data Monitoring Committee shall systematically collect and evaluate aggregated data of adverse events that occurred in the clinical trial, submitting to ANVISA in the annual reports.

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

Subsection I

Immediate Measures

Art. 58. In the event of a serious adverse event while conducting the clinical trial at any stage of clinical development of the medical device, the sponsor and the investigator shall take immediate safety measures to protect clinical trial participants from any imminent risk.

Sole paragraph. In the event of a serious adverse event to be notified, it will be necessary to inform which measures were adopted, the action plan in the occurrence of new events of the same nature, data from the place where the service took place, along with other data requested in the notification form, especially those that allow the traceability of the event and the affected participant.

Art. 59. Notification of unexpected serious adverse events, the causality of which is possible, probable or defined, is independent of the submission of the investigator's brochure, amendments, reports or early termination of the clinical trial.

Art. 60. The sponsor shall consider establishing a data monitoring committee before starting a clinical trial, the decision of which should be guided by risk analysis, taking into account both the risks associated with the use of the medical device under investigation and the risks associated with the subject's participation in the clinical trial.

Paragraph 1 The development of pivotal and phase III clinical trials should be monitored by the data monitoring committee and its recommendations should be reported to ANVISA by the sponsor.

Paragraph 2 The main functions of the data monitoring committee should be described in the protocol and the responsibilities of the data monitoring committee will be detailed in separate written procedures to establish the frequency and documentation of meetings and the management of emergency situations, cases where there is no constitution of a data monitoring committee should be justified.

Subsection II

Communication of Adverse Events by the Investigator

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

Sole paragraph. Adverse events or abnormalities in laboratory test results affecting the safety of participants should be reported to the sponsor in accordance with the GCP and protocol.

Art. 62. All adverse events should be treated and affected participants monitored by the principal investigator and his/her team until resolution or stabilization.

Subsection III

Notification of Adverse Events by Sponsor

Art. 63. The sponsor must notify ANVISA, by means of 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.

Paragraph 1 The sponsor shall keep all detailed records of adverse events reported by the investigators.

Paragraph 2 ANVISA may request such records at any time.

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

Subsection IV

Deadlines

Art. 65. The investigator must inform the sponsor of serious adverse events or death 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, by means of an electronic form, within a maximum of 7 (seven) calendar days from the date of knowledge of the case by the sponsor.

Sole paragraph. Additional information on the follow-up of adverse events mentioned in the caput of this article should be included in the form within 8 (eight) calendar days after its notification.

Art. 67. All other adverse events that are unexpected and serious, the causality of which is possible, probable or defined in relation to the products under investigation must be notified to ANVISA within 15 (fifteen) calendar days of knowledge of the case by the sponsor.

Section II

Monitoring Reports

Subsection I

Clinical Trial Protocols Monitoring Reports

Article 68. The sponsor shall send ANVISA annual follow-up reports containing the following information, exclusively from Brazilian centers, in a tabulated manner, for each clinical trial protocol:

I - title of the clinical trial;

II - protocol code;

III - recruitment status of clinical trial participants;

IV - discrimination in the number of participants recruited per center;

V - number and description of deviations and violations of protocol by center; and

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

Paragraph 1 The annual report of follow-up of clinical trial protocol shall be submitted to ANVISA in the form of a secondary petition attached to the process of the respective protocol to which it is linked.

Paragraph 2 The annual report must be filed within a maximum period of 60 (sixty) calendar days having as annuity reference the date of notification of the start of the clinical trial in Brazil.

Art. 69. After completing, for any reasons, the activities of a clinical trial protocol, the sponsor shall submit to ANVISA a final report containing minimally the following information:

I - title of the clinical trial with the protocol code, end date of the clinical trial;

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

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

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

V - statistical analysis;

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

VII - relationship of all adverse events and laboratory abnormalities with causality assessment occurred per participant;

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

IX - rational for the premature termination of clinical trial or development in Brazil or worldwide, when applicable.

Paragraph 1 The final clinical trial protocol report 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.

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

Paragraph 3 Clinical trials submitted under the notification scheme shall file only the final report to ANVISA.

Art. 70. Failure to submit and non-compliance with the deadlines set out in Articles 65 and 66 may lead to the cancellation of the clinical trial or DICD.

Subsection II

Clinical Investigation Dossier of Medical Device

Art. 71. The sponsor must send annually to ANVISA:

I - clinical development reports of the medical device under investigation;

II - information relating to changes in the design of the medical device when it occurs, containing:

a) information on the status of product development in the world;

b) security alerts (where applicable); and

c) information regarding the available results of clinical studies in progress worldwide.

Paragraph 1 If design changes occur, the report must include:

I - analysis of the impact on ongoing clinical investigation due to the alteration(s) performed in the medical device when it occurred; and

II - non-clinical study report that supports the changes, where relevant.

Paragraph 2 The annual reports of clinical development of the medical device must be filed within a maximum period of 60 (sixty) calendar days, having as reference of annuity the date of approval of the DICD by ANVISA or date determined by the sponsor in the development of the medical device.

CHAPTER VIII

INSPECTIONS

Section I

Inspections to Verify Compliance with Good Clinical Practices

Art. 72. In order to ensure 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 GCP at the testing centers clinicians, sponsor, CRO, laboratories and other institutions involved in the development of the medical device under investigation to verify the degree of adherence to current Brazilian legislation and compliance with the GCP, in addition to ensuring the rights and duties that concern the scientific community and the State.

Paragraph 1 The GCP inspections will follow the harmonized guidelines in the Document of the Americas, Manual of Good Clinical Practice of the International Conference on Harmonization (Document E6), ISO 14155 and in specific GCP inspection guides published by ANVISA.

Paragraph 2 Depending on the outcome of the GCP inspection, ANVISA may determine:

I - temporary discontinuation of the clinical trial;

II - the definitive cancellation of the clinical trial, in the site concerned;

III - the definitive cancellation of the clinical trial in all sites 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. 73. ANVISA may perform GMP inspections of the medical device under investigation or product under investigation produced or modified by the sponsor in order to verify the technical, production and quality control information reported in the DICD, and whether the device under investigation is sufficiently safe to allow use in clinical trial participants.

CHAPTER XI

IMPORT

Art. 74. The import of products under investigation for exclusive use in clinical trial should be subject to inspection by the health authority in office at the clearance site.

Art. 75. The following documents shall be submitted after the arrival of the products under investigation in the national territory:

I - copy of the Special Notice (CE) for the clinical investigation dossier of medical device (DICD), Specific Special Press Release (CEE) or the Document for importation of Product(s) under investigation issued by the competent technical area of ANVISA at its head office;

II - in cases of imports made by imports other than the holder of the DICD, the import liability delegation document signed by both parties shall be submitted;

III - term of responsibility for importation for clinical research provided for in health regulations;

IV - copy of the knowledge of embarked cargo - Airborne cargo, Water embedded cargo or Land embedded cargo; and

V - copy of commercial invoice.

Art. 76. The competent health authority in office at the place of clearance of the product under investigation shall verify compliance with the indications for packaging, transport and storage, in accordance with specific information in the CE, CEE, or Document for Product(s) under investigation import of the Clinical Investigation Dossier of Medical Device (DICD) subsidiary to those provided by the manufacturer or sponsor.

Paragraph 1 In the external or transport packaging used for the movement of the products of which this chapter is treated shall include:

I - CE, CEE number or Product Import Document(s) under investigation of the Clinical Investigation Dossier of Medical Device (DICD) to which the product under investigation is submitted;

II - quantity of imported material;

III - information on special care for storage, such as temperature, humidity, luminosity;

IV - information on physical form regarding the presentation of the product(s);

V - information on shelf life; and

VI - batch number or serial number.

Art. 77. Qualitative information and specifications of the products under investigation to be used in the clinical trial shall be provided in the Special Press Release (CE), Specific Special Communication (CEE) or in the Document for the Importation of Product(s) under investigation by the DICD.

Paragraph 1 In case of alteration of the products under investigation and their specifications reported in the CE, the CEE or the Document for the importation of Products(s) under investigation by the DICD, this information shall be notified to the competent technical area of ANVISA at its head office.

Paragraph 2 The CE, CEE or document for import of product(s) under investigation by the updated DICD shall be presented at the clearance site.

Art. 78. The agreement of the Substitute Import Licensing by the competent health authority, at the place of clearance, will take place from a fiscal context, if conclusive and satisfactory, linked to the import licensing that preceded it, provided that the change has been informed in the previous import permit, and does not present itself in disagreement with the inspection and/or conclusion of the previous sanitary inspection.

Art. 79. The entry into the national territory of products under investigation not provided for in the CE, CEE or the Document for the importation of Product(s) under investigation by the DICD, is closed for use in clinical trials regulated by this Resolution.

Sole paragraph. It is prohibited to change the purpose of importing the goods and products covered by this Resolution.

CHAPTER X

FINAL PROVISIONS

Art. 80. When filing a DICD, the holder must link all the evaluation processes in a clinical trial related to the medical device under investigation that may have already undergone an ANVISA evaluation at some point.

Art. 81. Considering the great technological diversity of the sector and the scope of reasonably foreseeable risks for a given technology, additional information that supports the proof of the minimum safety of a particular medical device may be required for approval of a DICD by ANVISA.

Art. 82. Failure to comply with the provisions of this Resolution implies a health violation, and the infringer is subject to the penalties provided for in Law 6,437 of 1977.

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

Art. 84. The Collegiate Board Resolution - RDC No. 10 of February 20th, 2015, published in the Official Gazette no. 41 of March 3rd, 2015, Section 1, p. 1, is repealed. 73.

Art. 85. This Resolution enters into force on October 1st, 2021.

ANTONIO
BARRA TORRES

ANNEX I

Investigator's Brochure – IB

1) Identification:

a) Name of the device under investigation;

b) Title(s) of the clinical trial(s) and protocol code(s);

c) Version or issue date of the investigator's brochure;

d) Declaration of Confidentiality, if appropriate;

e) Review history summary in case of changes, if applicable; and

f) Each page of the IB must contain the version number or date of issue, according to the identification adopted, with the page number and the total number of pages of the IB.

2) Sponsor/manufacturer:

a) Name and address of the sponsor; and

b) Name and address of the manufacturer of the medical device under investigation.

Note: If the medical device is part of its outsourced manufacturing process, this information should also be indicated, informing the name and address of the third-party executor of the production.

3) Information of the device under investigation:

a) Summary of the literature and evaluation of follow-up with the justification for the design and intended use of the medical device under investigation;

b) Regulatory classification of the medical device under investigation;

c) General description of the medical device under investigation and its components, including materials and accessories used;

d) Summary of relevant manufacturing processes and related validation processes;

e) Description of the mechanism of action of the medical device under investigation, together with the scientific basis in the literature;

f) The manufacturer's instructions for the installation and use of the medical device under investigation, including any storage and handling needs and requirements, preparation for use and any re-use (e.g., sterilization) for which it is intended, any pre-use evaluation of safety or performance and precautions to be taken after use (e.g., disposal), if relevant; and

g) Description of the intended clinical performance.

4) Non-clinical trials:

Summary of non-clinical tests that have been performed on the medical device under investigation, together with an evaluation of the results of such tests that justify their use in humans.

The summary shall include, where applicable, the results of:

a) Design calculations;

b) In vitro trials;

c) Mechanical and electrical trials;

d) Reliability tests;

e) The validation of software related to the function of the device;

f) All Performance trials;

g) Ex vivo trials; and

h) Biosafety assessment.

5) Available Clinical Data:

a) Summary of relevant prior clinical experience with the medical device under investigation and with other medical devices that have similar characteristics, including those that relate to other indications for use for the medical device under investigation; and

b) Review of device adverse events and any history of modification or recall.

6) Risk management:

a) Summary of the risk analysis, including identification of residual risks;

b) Result of the risk assessment; and

c) Predictable risks, contraindications and warnings for the device under investigation.

7) Regulations and other references:

a) List of existing technical standards, fully or partially complied with;

b) Declaration of compliance with relevant national regulations; and

c) List of relevant technical-scientific references.

ANNEX II

DOSSIER OF THE MEDICAL DEVICE UNDER INVESTIGATION

1) Full description of the medical device under investigation and its principle of operation;

2) Intended use, purpose of use, intended user and indication of use;

3) Intended use environment and usage settings;

4) Contraindications for use;

5) Description of the packaging of the medical device under investigation;

6) History of development of the medical device under investigation;

7) References and comparison with similar devices or previous generations of the medical device under investigation;

8) Report of global incidents and recall, when the medical device under investigation is already marketed in the international market;

9) NON-CLINICAL TRIAL REPORT (the following trial reports shall be submitted in accordance with the relevance related to the technology associated with the medical device under investigation):

a. Check-list of compliance with essential safety and efficacy requirements;

b. List of technical standards complied with in whole or in part;

c. Physical and Mechanical Characterization;

d. Chemical/Material Characterization;

e. Electrical Systems: electrical, mechanical and environmental protection safety, and electromagnetic compatibility;

f. Radiological safety;

g. Software Description/Firmware: version, hazard analysis, specification of software requirements, traceability analysis, description of the process associated with the software lifecycle, software verification and validation, unresolved anomalies (errors or defects).

h. Biocompatibility and toxicological evaluation;

i. Pyrogenicity not mediated by the material;

j. Safety of materials of biological origin;

l. Validation of the sterilization process;

m. Residual toxicity;

n. Tests on animal models;

o. Stability studies and packaging validation;

p. If the medical device under investigation needs to be cleaned or reprocessed between successive uses, description and validation of the indicated cleaning/reprocessing process; and

q. Existing literature review on the medical device under investigation or other devices of similar technology, with the same indication of use, when existing.

10. Description of the manufacturing steps of the experimental device; and

11. Good Manufacturing Practices - present procedures for the Design and Development of the medical device under investigation, in accordance with current regulations on good manufacturing practices for medical devices within the scope of ANVISA, accompanied by the documents included in the Historical Register of the Project of the medical device under investigation, minimally containing:

a. Project development plan;

b. Traceability matrix correlating: input data, output data, reference to protocols and Verification and Validation reports (Note: during the analysis of information, it can be requested the presentation of specific reports and protocols);

c. Record of performing project reviews in accordance with the plan defined for the project, up to the date of submission of the DICD;

d. Registration of the transfer of the project to production, for the devices that are already in the production phase;

e. Initial project-to-production transfer plan for devices that are still in the project development phase;

f. If the medical device under investigation is not a conventional production unit, provide justification for the validity of the data obtained with clinical investigation for products originating from conventional production.

g. In cases where a sponsor investigator wishes to conduct a clinical trial with a medical device under investigation that already has an ANVISA-approved DICD, an ANVISA may use the information already sent by the holder of the initial DICD if they authorize it, without the need for resubmission of all documentation. When an authorization from the initial holder is not submitted, the sponsor investigator shall submit to ANVISA all information available in updated and indexed literature that supports the proposed clinical development rationale; and

h. In case the medical device under investigation already has registration in Brazil, only the information that supports the proposed post-registration changes should be submitted to the DICD.