MINISTRY OF HEALTH

NATIONAL HEALTH SURVEILLANCE AGENCY

BOARD

RESOLUTION - RDC NO. 837, OF DECEMBER 13, 2023

Provides for the conduct of clinical investigations with medical devices in Brazil.

THE COLLEGIATE BOARD OF DIRECTORS OF THE NATIONAL HEALTH SURVEILLANCE AGENCY, in the exercise of the powers conferred on it by articles 7, item III , and 15, items III and IV, of Law No. 9,782, of January 26, 1999 , and considering the provisions of article 187, item VI and §§ 1 and 3 , of the Internal Regulations, approved by the Resolution of the Collegiate Board of Directors - RDC No. 585, of December 10, 2021 , resolves to adopt the following Collegiate Board Resolution, as resolved at a meeting held on December 8, 2023, and I, Chief Executive Officer, determine its publication.

CHAPTER I

INITIAL PROVISIONS

Section I

Objective and scope

Art. 1 This Resolution aims to define the procedures and requirements for carrying out clinical investigations, the results of which may support the registration of class III and IV medical devices in Brazil, and to define the standards of Good Clinical Practices for clinical investigations that will support the registration of medical devices.

Art. 2 This Resolution applies to all clinical investigations with medical devices in the national territory intended to compose the clinical evaluation of the medical device for regulatory purposes.

Paragraph 1. This Resolution does not apply to:

I - clinical performance studies of medical devices for in vitro diagnosis; and

II - studies with the exclusive purpose of evaluating the usability/human factors in medical devices, except when clinical investigations are conducted and include, among other outcomes, the evaluation of usability/human factors;

III - clinical investigations with medical devices already registered in Brazil that are being researched for the same indications for use already approved by Anvisa;

IV - clinical investigations with medical devices of risk class I or II.

Paragraph 2. Although they are not part of the scope of submission to Anvisa, clinical investigations involving class I or II risk medical devices must also be conducted in accordance with good clinical practices.

Section II

Definitions

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

Audit: systematic review of activities and documents related to a clinical investigation carried out by one or more independent persons to determine whether these activities were conducted, and the data accurately recorded, analyzed, and reported in accordance with the clinical investigation plan, standardized operating procedures, good clinical practice, and applicable regulatory requirements;

II - Good Clinical Practice (GCP): standard for planning, conducting, conducting, monitoring, auditing, recording, analyzing, and reporting clinical investigations that provides assurance that the reported data and results are credible and accurate, and that the rights, integrity, and confidentiality of research participants are protected, in accordance with the BPC guidelines set forth in the Document of the Americas, and the ISO14155;

III – Good Manufacturing Practices (GMP): set of guidelines established to ensure the quality, safety and efficacy of medical devices during all stages necessary for their obtainment.

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

V - investigator's brochure: compiled from clinical and non-clinical data on the medical device(s) under investigation, which are relevant to clinical research;

VI – research center: public or private organization, legitimately constituted, duly registered with the CNES (National Registry of Health Establishments), in which clinical investigations are carried out;

VII - Independent Data Monitoring Committee: independent committee for data monitoring to evaluate at regular intervals the progress of a clinical investigation, safety data and critical points to evaluate efficacy and to recommend to a sponsor whether a clinical investigation should be continued, modified or stopped;

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

IX – 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;

X – date of Commencement of the clinical investigation in Brazil: corresponds to the date of inclusion of the first participant in the clinical investigation in Brazil;

XI - date of Commencement of Clinical Investigation: corresponds to the date of inclusion of the first participant in the clinical investigation in the world;

XII - date of end of the clinical investigation in Brazil: corresponds to the date of the last visit of the last participant of the clinical investigation in Brazil or another definition of the sponsor, expressly determined in the clinical investigation plan;

XIII - Clinical investigation end date: corresponds to the date of the last visit of the last clinical research participant in the world or another definition of the sponsor, expressly determined in the clinical investigation plan;

XIV – deviation from the clinical investigation plan: any non-compliance with the procedures or requirements defined in the version of the approved clinical investigation plan, without major implications for the integrity of the clinical investigation, the quality of the data or the rights and safety of the clinical investigation participants;

XV - medical device (medical product); Any instrument, apparatus, equipment, implant, in vitro diagnostic medical device, software, material or other article, intended by the manufacturer to be used, alone or in combination, in human beings, for any of the following specific medical purposes, and the principal intended action of which is not achieved by pharmacological, immunological or metabolic means in the human body, but which may be aided in its intended action by such means:

a) diagnosis, prevention, monitoring, treatment (or relief) of one; disease;

b) diagnosis, monitoring, treatment or repair of an injury or; disability;

c) investigation, replacement, alteration of anatomy or a process or; physiological or pathological status;

d) life support or maintenance;

e) control or support for conception; or

f) provision of information through in vitro examination of samples from the human body, including organ and tissue donations.

XVI – investigational medical device: medical device being evaluated for its clinical performance, efficacy or safety in a clinical investigation;

XVII - import responsibility delegation document:

document issued by the sponsor of the clinical investigation, which includes the indication of the authorized importer and the responsibilities related to the transport and clearance of the imported goods;

XIII – document for importation of product(s) under investigation of the Dossier of Clinical Investigation of Medical Device: document issued by ANVISA, published in a resolution in the Official Gazette of the Union, necessary for the request for import or export for a clinical investigation, in cases of non-manifestation on the DICD within the deadlines defined by this Resolution;

XIX – medical device clinical investigation dossier (DICD): compiled from documents to be submitted to ANVISA for the purpose of evaluating the steps inherent to the design of a medical device under investigation and the clinical investigation plan aimed at obtaining information to support the clinical evaluation of the medical device;

XX – amendment to the clinical investigation plan: any proposal for modification to an original clinical investigation plan, always presented with the justification that motivated it, and such amendment may or may not be substantial;

XXI - Adverse Event (AE): any adverse medical occurrence in a participant in the clinical investigation and that does not necessarily have a causal relationship with the treatment, which may be any unfavorable and unintended sign, symptom, or disease (including laboratory test results outside the normal range), associated with the use of an investigational medical device, whether related to it or not;

XXII - serious adverse event: event that results in any of the following outcomes:

a) death;

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

c) persistent or significant disability/disability;

d) hospitalization of the patient or prolongation of hospitalization;

e) congenital anomaly or birth defect;

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

g) clinically significant event.

XXIII - unexpected adverse event: event not described as an adverse reaction in the brochure or instruction for use/operator's manual of the medical device under investigation;

XXIV – case report form: printed document, optical or electronic, intended to record all the information about each participant in the clinical investigation that, according to the clinical investigation plan, must be reported to the sponsor;

XXV – indication of use: comprises the indication of the disease or condition that the medical device is intended to diagnose, treat, prevent, mitigate or cure;

parameters to be monitored or other indications for use associated with the device, including information on criteria for patient selection and target population of the device (e.g., adult, pediatric, or newborn);

Inspection: the act by a regulatory authority to conduct an official review of the documents, facilities, records and any other resources deemed by the authority to be related to the clinical investigation and which may be located at the site where the clinical investigation is conducted, at the premises of the sponsor and/or the representative clinical research organization (ORPC), or in other locations that the regulatory authority deems appropriate;

XXVII – clinical investigation: any investigation or systematic study in one or more human beings, carried out to evaluate the safety, clinical performance and/or efficacy of a medical device;

XXVIII - Pivotal clinical investigation: confirmatory clinical investigation designed to collect data on the clinical performance, efficacy or safety of a medical device for a specific indication for use in a statistically justified number of research participants;

XXIX - investigator: individual member of the research site team designated and supervised by the principal investigator at the research site to carry out procedures related to the investigation or make important decisions related to clinical research and medical treatment, and may also be called "sub-investigator" or "co-investigator";

XXX - principal investigator: leader of the investigation conducted by a group of people;

XXXI – sponsoring investigator: an individual responsible for conducting and coordinating clinical investigations, alone or in a group, carried out under his or her immediate direction independently, developed with the investigator's own financial and material resources, national or international research funding entities, private entities and other non-profit entities;

XXXII - monitoring: the act of continuously reviewing the process of a clinical investigation and making sure that it is conducted, recorded and reported in accordance with the clinical investigation plan, standard operating procedures, good clinical practices and applicable regulatory requirements;

XXXIII – representative organization of clinical research (ORPC): any company regularly installed in the national territory contracted by the sponsor or by the sponsor-investigator, which partially or totally assumes, together with ANVISA, the duties of the sponsor of the clinical investigation;

XXXIV – sponsor: person, company, institution or organization responsible for initiating, administering, controlling and/or financing a clinical investigation;

XXXV - primary sponsor: the institution to which the sponsoring researcher is linked;

XXXVI – investigational product: investigational medical device, comparator or any other product to be used in clinical investigation;

XXXVII – Clinical Investigation Plan (PIC): document that describes the justification, objectives, design, rationale, methodology, organization, monitoring, conduct and record-keeping of the clinical investigation;

XXXVIII – annual report: annual document containing specific information on the conduct of a given clinical investigation in centers in Brazil, in accordance with the clinical investigation plan and the GCP;

XXXIX – final report: document describing the design, execution, statistical analysis and results of a clinical investigation;

XL – usability: a feature of the user interface that facilitates use and thus establishes effectiveness, efficiency and user satisfaction in the intended use environment;

XLI - violation of the clinical investigation plan: deviation from the clinical investigation plan that may affect the quality of the data, that compromises the integrity of the study or that may affect the safety or rights of the participants in the clinical investigation.

Sole Paragraph. For the purposes of this Resolution, "clinical investigation" is synonymous with "clinical trial" or "clinical research", and "protocol" is synonymous with "clinical investigation plan (PIC)".

Section III

General provisions

Art. 4 Clinical investigations involving class III or IV high-risk medical devices that are not yet registered in Brazil are subject to the submission of a DICD.

Paragraph 1 - If the clinical investigation involves a medical device that is already registered in Brazil, but has an indication for use different from that contained in the sanitary registration, this investigation must be submitted in the form of a DICD in accordance with this Resolution.

Paragraph 2 - In order to issue a final decision by Anvisa on the information submitted in the DICD and clinical investigations described in the caput, a resolution will be published in the Federal Official Gazette.

Art. 5 Anvisa may issue guidelines on the applicability of this Resolution for specific cases of clinical investigations with medical devices.

CHAPTER II

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

Art. 6 - The documentation presented in the DICD must guarantee the safety and rights of the participants in the clinical investigation, the quality of the medical device under investigation and the data obtained to support the clinical evaluation of the medical device.

Article 7. The DICD must be submitted to Anvisa prior to conducting a clinical investigation involving a medical device of risk classes III or IV.

Section I

General Requirements for the Request

Article 8. Upon receipt of the DICD, Anvisa will evaluate it and issue a statement within ninety (90) calendar days.

Paragraph 1 - If there is no statement from Anvisa within ninety (90) calendar days after receipt of the DICD, the clinical investigation may be initiated after the pertinent ethical approvals.

Paragraph 2 - In cases of non-manifestation within the period described in the caput of this article, Anvisa will issue a Document for the importation of Product(s) under investigation from the Medical Device Clinical Investigation Dossier (DICD) to be published in a resolution in the Official Gazette for the importation of product(s) under investigation, necessary for the conduct of the clinical investigation.

Article 9 - The DICD shall contain general information regarding the provision under investigation, as described in Section II of this chapter.

Art. 10. The DICD may be submitted by the sponsor, sponsoring researcher or ORPC.

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

Paragraph 2 - Submissions by ORPC may be made only when the sponsor does not have a headquarters or branch in Brazil.

§3 The submission of the DICD of an investigator-sponsor must be carried out by the primary sponsor.

Section II

Content and Format of the Request

Article 11. The DICD must be filed with Anvisa and will consist of the following documents:

I - DICD petition form, according to the model available on ANVISA's website;

II - proof of payment, or exemption, of the sanitary surveillance inspection fee, by means of the Federal Government Collection Guide (GRU);

III - the investigator's brochure, containing the information of the medical device under investigation, according to Annex I of this Resolution, or, if this documentation has already been offered and is identical to another DICD already filed with Anvisa, a statement contained in Annex III of this Resolution;

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

V - dossier of the medical device under investigation, according to Annex II of this Resolution, or, if this documentation has already been offered and is identical to another DICD already filed with Anvisa, a statement contained in Annex IV of this Resolution;

VI - plano de investigação clínica de acordo com as BPC;

VII - comprovante de que a investigação clínica está registrada na base de dados de registro de pesquisas clínicas da International Clinical Trials Registration Plataform / World Health Organization (ICTRP/WHO) ou outras reconhecidas pelo International Commitee of Medical Journals Editors (ICMJE).

Parágrafo único. Se o documento descrito no inciso VII do caput deste artigo não estiver disponível no momento da protocolização, este deverá ser submetido na protocolização da notificação de início da investigação clínica.

Art. 12. Toda documentação deve ser protocolizada digitalmente, incluindo cumprimento de exigência(s), os documentos eletrônicos deverão permitir busca textual.

Art. 13. Formulários de data de início e término da investigação clínica no Brasil deverão ser protocolizados na forma de petição secundária em até 30 (trinta) dias corridos após cada data de início e término.

Art. 14. As alterações relativas às informações contidas exclusivamente no formulário de petição do DICD tais como relação de centros de pesquisa e produtos destinados a importação devem ser protocolizadas utilizando assunto específico para esta finalidade.

Art. 15. A Anvisa poderá, a qualquer momento, solicitar outras informações que julgar necessárias para sua avaliação e monitoramento da investigação clínica.

CAPÍTULO III

DAS MODIFICAÇÕES SUBSTANCIAIS DO DICD

Art. 16. As modificações substanciais relacionadas ao DICD devem ser protocolizadas e aguardar manifestação da Anvisa em até 90 (noventa) dias corridos para efetivar sua implementação.

Parágrafo único. As modificações substanciais do DICD devem ser submetidas à Anvisa na forma de petição secundária anexada ao respectivo processo de DICD.

Art. 17. Para efeito desta Resolução as modificações substanciais do DICD consistem em alterações nas informações contidas na brochura do investigador e dossiê do dispositivo médico que potencialmente geram impacto na qualidade e segurança do dispositivo médico em investigação.

Art. 18. As modificações do projeto do dispositivo médico oriundas de recomendações ou alertas emitidos por outras autoridades sanitárias deverão ser notificadas à ANVISA antes de serem implementadas, e poderão ser executadas independente da manifestação prévia da Anvisa.

Art. 19. As modificações do DICD consideradas não substanciais devem ser apresentadas à ANVISA como parte do relatório final do plano de investigação clínica.

CAPÍTULO IV

DAS EMENDAS AO PLANO DE INVESTIGAÇÃO CLÍNICA

Art. 20. Todas as emendas a um plano de investigação clínica devem ser apresentadas à Anvisa, identificando a(s) alteração(ões) e suas justificativas.

Article 21. Substantial amendments to clinical investigation plans must be filed and await Anvisa's statement within ninety (90) calendar days to implement them.

Paragraph 1 - Substantial amendments must be submitted to Anvisa in the form of a secondary petition attached to the DICD process.

Paragraph 2 - Amendments aimed at eliminating immediate risks to the safety of clinical investigation participants are excepted from the provisions of the caput and paragraph 1 of this article, which may be implemented and notified to Anvisa immediately.

Article 22. For the purposes of this Resolution, an amendment shall be considered substantial when any of the following criteria are met:

I - alteration in the clinical investigation plan that interferes with the safety or physical or mental integrity of the research participants and/or members of the research team; or

II - change in the scientific value of the clinical investigation plan.

Article 23. Amendments to the clinical investigation plan considered insubstantial must be submitted to ANVISA as part of the annual monitoring report of the clinical investigation plan.

CHAPTER V

SUSPENSIONS AND CANCELLATIONS

Article 24. The sponsor may cancel or suspend the clinical investigation at any time, provided that the appropriate technical-scientific justifications are submitted, as well as a follow-up plan for the participants of the clinical investigation already started.

Paragraph 1 - For the purposes of this resolution, the cancellation or suspension of the clinical investigation implies the cancellation or suspension of the DICD.

Paragraph 2 - After the decision to suspend or cancel the clinical investigation, the sponsor must notify Anvisa within a maximum period of fifteen (15) calendar days.

Paragraph 3 - Suspensions and cancellations of clinical investigations must be filed with Anvisa in the form of a secondary petition attached to the respective DCD process.

Article 25. In cases of cancellation of the clinical investigation for safety reasons, the sponsor must technically and scientifically justify the reasons for the cancellation and present the measures for minimization/mitigation of risk to the participants of the clinical investigation(s).

Article 26. In cases of temporary suspension of the clinical investigation as an immediate safety measure, the sponsor must notify ANVISA within 7 (seven) calendar days from the date of suspension of the clinical investigation, justifying the reasons.

Sole Paragraph. The reasons, the scope, the interruption of treatment, the measures to minimize/mitigate the risk to the participants and the suspension of the recruitment of participants must be clearly explained in the notification of temporary suspension described in the caput of this article.

Article 27. The request for reactivation of the suspended clinical investigation must be filed with Anvisa as a secondary petition to the respective DICD process, accompanied by the appropriate justifications for the clinical investigation to be restarted.

Sole Paragraph. The clinical investigation can only be restarted after approval by Anvisa to be published in the official gazette of the union.

Article 28. Anvisa may, at any time, cancel or suspend the clinical investigation if it deems that the conditions for approval have not been met, or there are reports of safety/efficacy that significantly affect the research participants or the scientific validity of the data obtained in the clinical investigations.

CHAPTER VI

RESPONSIBILITIES

Article 29. The responsibilities listed in this chapter include those defined in Good Clinical Practices, without prejudice to other ethical and legal responsibilities.

Section I

Sponsor's Responsibilities

Article 30. The sponsor is responsible for the information necessary for the correct execution of the clinical investigation plan, for the selection of qualified investigators and research sites, ensuring that clinical investigations are conducted in accordance with the clinical investigation plan and Good Clinical Practice.

Article 31. The sponsor must use qualified professionals to supervise the overall conduct of clinical investigations, manage data, conduct statistical analysis, and prepare reports.

Article 32. The sponsor must ensure that quality assurance and control are implemented in all areas of the institutions involved in the clinical investigation.

Article 33. The sponsor must keep the clinical trial data on file, physical or digital, for a period of five (5) years after the last approval of a request for registration/notification of the investigational medical device in Brazil.

Sole Paragraph. In case of discontinuation of the clinical investigation or its conclusion not followed by a request for registration/notification, the sponsor must keep the clinical trial data in a physical or digital file for a minimum of two (2) years after the discontinuation of the clinical investigation or its formal conclusion.

Article 34. The sponsor is responsible for all expenses related to procedures and tests, especially those related to diagnosis, treatment and hospitalization of the clinical research participant, and other actions necessary for the resolution of adverse events related to the clinical investigation.

Article 35. The sponsor shall ensure that the data obtained on the safety and efficacy of the investigational medical device are sufficient to support human exposure to the investigational medical device.

Article 36. The sponsor shall ensure that the investigational medical device, placebo and sham, when used, are manufactured in accordance with Good Manufacturing Practice (GMP) and are coded and labelled in a manner that protects masking, if applicable, and characterises them as products of clinical investigation.

Sole Paragraph. In clinical investigations using other medical device(s) as a comparator, the sponsor must use those manufactured in accordance with GMP.

Article 37. The sponsor is responsible for importing only the amount necessary to carry out the clinical investigation.

Article 38. The sponsor is responsible for distributing the clinical investigation product(s) only to the institutions informed in the DICD form and authorized by the Research Ethics Committees.

Sole Paragraph. The sponsor is responsible for the final disposal of the clinical research products that were not used in the study.

Article 39. The sponsor must ensure adequate monitoring and auditing of clinical investigations.

Article 40. The sponsor must immediately inform those involved in the clinical investigation when the clinical investigation is terminated prematurely or suspended for any reason.

Article 41. The sponsor may transfer its functions to an ORPC.

Paragraph 1 - The transfer referred to in the caput of this article does not remove the sponsor's definitive responsibility for the quality and integrity of the clinical investigation data.

§2 Any functions related to clinical research 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

Responsibilities of the investigator

Article 42. The investigator must conduct the clinical investigation in accordance with the clinical investigation plan agreed with the sponsor, good clinical practice, and applicable and current regulatory and ethical requirements.

Article 43. The investigator must personally supervise the clinical investigation, and may only delegate tasks, but not responsibilities.

Article 44. The investigator must allow monitoring, audits and inspections to be carried out.

Article 45. The investigator should ensure adequate medical care to clinical trial participants for any adverse events related to the clinical investigation, including clinically significant laboratory findings, at no cost to the participant.

Article 46. The investigator should promptly inform participants of the clinical investigation when the investigation is terminated prematurely or suspended for any reason, and ensure appropriate therapy and follow-up for participants.

Article 47. The investigator is responsible for using the investigational products only in connection with this investigation and storing as specified by the sponsor and in accordance with applicable regulatory requirements.

Section III

Responsibilities of the Researcher-Sponsor

Article 48. In clinical investigations carried out by an investigator-sponsor, the institution with which he or she has a link will be qualified as the primary sponsor.

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

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

Paragraph 3 - The primary sponsor may not delegate quality assurance, audits and monitoring of clinical investigations to the investigator-sponsor, but may delegate them to an ORPC.

Paragraph 4 - The primary sponsor must present its own or outsourced structure with, at least, the following processes:

I - management of adverse events;

II - project management;

III - data management;

IV - training;

V - information technology;

VI - quality assurance;

VII - monitoring.

Paragraph 5 - The institution referred to in the caput of this article must be the one in which the clinical investigation will be carried out.

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

Article 49. In the case of donation of investigational medical devices already registered in Brazil, to carry out clinical investigation, the donor will be the sponsor if there is an agreement to transfer or own the data obtained in the research to said donor.

Article 50. In the case of donation of investigational medical devices not registered in Brazil for clinical investigation, the donor shares the responsibilities of sponsor.

Sole Paragraph. This article applies to donations of class III or IV medical devices already registered in Brazil that are being studied for indications of use not approved by Anvisa.

Section IV

Structure of the Research Center

Article 51. The research center must have adequate facilities to conduct the clinical investigation plan, with regard to the physical structure, equipment/instruments and human resources, and appropriate to the population of this clinical investigation, such as the elderly, children, people with special needs, among others.

Sole Paragraph. The list of research centers must be informed to Anvisa using the DICD petition form and changes related to this list must be filed using the subject of the petition related to the amendment of this form.

Article 52. The management of the research site must be notified of the conduct of the clinical investigation.

CHAPTER VII

SECURITY MONITORING AND ALERTS

Section I

Monitoring of adverse events

Article 53. The sponsor must monitor all adverse events during the development of the investigational medical device.

Article 54. The sponsor or the Independent Data Monitoring Committee must systematically collect and evaluate aggregate data on adverse events that occur in the clinical investigation, submitting them to Anvisa in the annual reports.

Subsection I

Immediate Measures Involving the Safety of the Clinical Investigation Participant

Article 55. In the event of a serious adverse event during the conduct of the clinical investigation, the sponsor and the investigator must take immediate safety measures to protect the clinical investigation participants against any imminent risk.

Sole Paragraph. In the event of a serious adverse event to be notified, it will be necessary to inform what measures have been 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 enable the traceability of the event and the affected participant.

Article 56. Reporting of unexpected serious adverse events, the causality of which is possible, probable, or defined, should occur regardless of the investigator's brochure submission, amendments, reports, or early termination of the clinical investigation.

Article 57. The sponsor should consider establishing a data monitoring committee before initiating a clinical investigation, whose decision should be guided by risk analysis, taking into account both the risks associated with the use of the investigational medical device and the risks associated with the subject's participation in the clinical investigation.

Paragraph 1 - The design of pivotal clinical investigations for high-risk medical devices (classes III and IV) must establish the constitution of a data monitoring committee and its recommendations must be reported to ANVISA by the sponsor, filing an amendment to the DICD within 30 calendar days after receipt of the recommendations by the sponsor.

The main functions of the data monitoring committee shall be described in the clinical investigation plan and the responsibilities of this committee shall be detailed in separate written procedures to establish the frequency, documentation of meetings and the management of emergency situations, justifying cases in which there is no constitution of a data monitoring committee.

Subsection II

Reporting of Adverse Events by the Investigator

Article 58. The investigator must report the occurrence of all adverse events to the sponsor, and must provide any requested information and express his/her opinion regarding the causality between the adverse event and the products/interventions used in the clinical investigation.

Sole Paragraph. Adverse events or abnormalities in laboratory test results that affect the safety of participants must be reported to the sponsor in accordance with good clinical practice and the clinical investigation plan.

Art. 59. All adverse events must be treated and affected participants must be monitored by the principal investigator and his team until their resolution or stabilization.

Subsection III

Reporting of Adverse Events by the Sponsor

Art. 60. The sponsor must notify Anvisa, by means of a specific electronic form, of unexpected serious adverse events occurring in the national territory, whose causality is possible, probable or defined in relation to the product under investigation.

The sponsor must keep all detailed records of adverse events reported by the investigators.

Paragraph 2 - Anvisa may request the registrations referred to in paragraph 1 of this article at any time

Art. 61. The sponsor must inform the investigators involved in the clinical investigation about unexpected serious adverse events, the causality of which is possible, probable or defined, and adopt the procedures for updating the investigator's brochure, in addition to reassessing the risks and benefits for the participants.

Subsection IV

Deadlines for security notifications

Art. 62. The investigator must inform the sponsor about serious adverse events or death within 24 (twenty-four) hours from the date of knowledge of the event.

Art. 63. The sponsor must ensure that all relevant information on unexpected serious adverse events occurring in the national territory, whose causality is possible, probable or defined in relation to the product under investigation and which are fatal or life-threatening, are documented and notified to Anvisa, by means of an electronic form, within a maximum of seven (7) calendar days from the date of knowledge of the case by the sponsor.

Sole Paragraph. Complementary information on the follow-up of adverse events mentioned in the caput must be included in the form within eight (8) calendar days after its notification.

Art. 64. All other adverse events that are serious, unexpected, whose causality is possible, probable or defined in relation to the products under investigation must be notified to Anvisa within 15 calendar days from the sponsor's knowledge.

Sole Paragraph. The notification referred to in the caput of this article shall be made through an electronic form to be disclosed by Anvisa.

Section II

Clinical Investigation Plan Monitoring Report

Art. 65. The sponsor must send Anvisa annual follow-up reports containing the following information, exclusively from Brazilian centers, in tabulated form, for each clinical investigation plan:

I - title of the Clinical Investigation;

II- reference number identifying the specific clinical investigation, if any;

III - recruitment status of clinical investigation participants;

IV- summary of the revision history in the case of amendments;

V- breakdown of the number of participants recruited by research center;

VI- number and description of deviations and violations of the clinical investigation plan by center; and

VII - Description of all adverse events that occurred by center in the period evaluated, identifying the participants of the clinical investigation with the codes used in the Case Report Form adopted in the clinical investigation plan.

Paragraph 1 - The annual report on the follow-up of the clinical investigation must be submitted to Anvisa in the form of a petition secondary to the process of the respective DICD.

Paragraph 2 - The annual report must be filed within a maximum period of sixty (60) calendar days, with the date of notification of the beginning of the clinical investigation in Brazil as an annual reference.

Article 66. After the conclusion, for any reason, of the activities of a clinical investigation, the sponsor must submit to Anvisa a final report containing, at least, the following information:

I - title of the clinical investigation with the code and date of end of the clinical investigation;

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

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 investigation;

V- statistical analysis;

VI- number and description of deviations and violations of the clinical investigation plan;

VII- list of all adverse events and laboratory abnormalities with causality assessment occurred by participant;

VIII – the results obtained in the measurement of outcomes for each participant in the clinical investigation;

IX - rationale for the premature termination of the clinical investigation;

X - summary of the design changes (if any) that occurred and their impact on clinical research.

Paragraph 1 - The final report of the clinical investigation plan must be submitted to Anvisa in the form of a secondary petition to the respective DIPD process.

Paragraph 2 - The final report must be filed within twelve (12) months of the date of completion of the clinical investigation.

Article 67. Failure to submit and failure to comply with the deadlines established in articles 65 and 66 may result in the cancellation of the clinical investigation.

CHAPTER VIII

INSPECTIONS

Section I

Inspections to Verify Compliance with Good Clinical Practice

Article 68. In order to ensure the protection of the rights, safety and well-being of the participants in the clinical investigation, 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 research centers, sponsors, ORPC, 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 BPC, in addition to ensuring the rights and duties that concern the scientific community and the State.

Sole Paragraph. The GMP inspections will follow the harmonized guidelines in the Document of the Americas, ISO 14155 and specific GMP inspection guides published by ANVISA.

Section II

Inspections to Verify Compliance with Good Manufacturing Practices for Products under Investigation

Article 69. ANVISA may carry out GMP inspections at the manufacturing unit of the investigational medical device in order to verify the technical, production and quality control information informed in the DICD, and whether the investigational device is sufficiently safe to allow use in clinical research participants.

CHAPTER IX

IMPORT

Art. 70. The importation of medical devices for exclusive use in clinical investigation is subject to sanitary inspection and must be submitted to analysis and approval by the sanitary authority, upon presentation of a Petition for Sanitary Inspection and Release, through the SISCOMEX modality.

Sole Paragraph. The importer must inform the number of the D.O.U. resolution regarding the approval of the DICD in the description of the product for import purposes.

Article 71. The following are mandatory documents for the instruction of the import process referred to in this Chapter:

I - bill of lading shipped;

II - commercial invoice;

III - in the case of imports made by others than the holder of the DICD, the document of delegation of import responsibilities signed by both parties must be presented.

Article 72. It will be up to the competent health authority, at its discretion, to verify compliance with the indications expressed on the packaging and conditions of transport and storage, in accordance with specific information in the D.O.U. resolution regarding the DICD in a subsidiary manner to that provided by the manufacturer or sponsor.

Sole Paragraph. The external or transport packaging used for the movement of the products referred to in this chapter must contain:

I- number of the D.O.U. resolution related to the DICD to which the product under investigation is subjected;

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

III - lot number or identification code or serial number that allows the traceability of the imported product.

Article 73. The qualitative information and specifications of the investigational products to be used in the clinical investigation will be informed in the D.O.U. resolution regarding the approval of the DICD.

Paragraph 1 - In case of changes to the products under investigation and their specifications informed in the D.O.U. resolution regarding the approval of the DICD, this information must be notified to the competent technical area of ANVISA at its headquarters.

Paragraph 2 - The updated D.O.U. resolution regarding the granted DICD must be presented in the procedural instruction of the import under analysis.

Article 74. The entry into the national territory of products under investigation not provided for in the D.O.U. resolution regarding the approval of the DICD or in quantities not provided for to meet the exclusive needs of clinical research regulated by this resolution is prohibited.

Article 75. The commercialization of the products referred to in this Chapter is prohibited, as well as the change in the purpose for which the import is intended.

CHAPTER X

TRANSITIONAL PROVISIONS

Article 76. Clinical trial consent processes already approved by ANVISA must follow the resolution in force at the time of its approval.

CHAPTER XI

FINAL PROVISIONS

Article 77. Anvisa may, at any time, request additional information that supports the proof of the minimum safety of a given medical device, for the purposes of approval and monitoring of a DICD.

Article 78. Omissions will be resolved in the light of other national standards and international guidelines.

Article 79. Depending on the result of the inspection in GCP or verification of non-conformities in relation to the provisions of this resolution, ANVISA may determine:

I- The temporary interruption of clinical research;

II- The definitive cancellation of the clinical investigation in a specific research center;

III- The definitive cancellation of clinical investigation in all research centers in Brazil; or

IV- The invalidation of data from clinical centers and investigations that do not comply with BPC.

Article 80. The Collegiate Board Resolution - RDC No. 548, of August 30, 2021 , published in the Federal Official Gazette No. 165, of August 31, 2021, Section 1, page 133, is hereby revoked.

Article 81. This Resolution enters into force on the date of its publication.

ANTONIO BARRA TORRES
Chief Executive Officer

ANNEX I

Investigator's Brochure - BI

1) Identification:

a) Name of the device under investigation;

b) Title(s) of the clinical investigation(s) and code(s) of the clinical investigation plan(s);

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

d) Declaration of Confidentiality, if applicable;

e) Summary of the revision history in case of changes, if applicable; and

f) Each page of the BI 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 BI.

2) Sponsor/Manufacturer:

a) Name and address of the sponsor; and

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

Note: if the medical device has part of its manufacturing process outsourced, this information must also be indicated, informing the name and address of the outsourced executor of the production.

3) Information on the device under investigation:

(a) summary of relevant prior clinical experience with the investigational medical device and with medical devices that have similar characteristics, including those that relate to other indications for use of the investigational medical device and analysis of adverse effects of the product and any history of modification or recall.

b) Regulatory classification of the medical device under investigation;

(c) general description of the investigational medical device and its components, including materials, accessories used.

Note: in the case of software such as medical devices, include development data, which is the development methodology, chosen technology, system architecture, user experience design, data storage and management, auxiliary communication equipment, interoperability, security and reliability;

d) Summary of manufacturing processes and related relevant 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 investigational medical device, 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 safety or performance assessment, and the 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 the non-clinical tests that have been performed on the investigational medical device, together with an assessment 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 tests;

c) Mechanical and electrical tests;

d) Reliability tests;

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

f) All performance tests;

g) Ex vivo tests; and

h) Biological safety assessment.

5) Clinical data available:

(a) summary of relevant previous clinical experience with the investigational medical device and with other medical devices that have similar characteristics, including those that relate to other indications for use for the investigational medical device; and

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

6)Risk management:

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

(b) the outcome of the risk assessment; and

c) Foreseeable 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 the relevant national regulations; and

c) List of relevant technical-scientific references.

ANNEX II

INVESTIGATIONAL MEDICAL DEVICE DOSSIER

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

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

3) Intended use environment and use settings;

4) Contraindications for use;

5) Description of the packaging of the investigational medical device;

6) Development history of the investigational medical device;

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

8) Global incident reporting and recall, when the medical device under investigation is already commercialized in the international market;

9) NON-CLINICAL TRIAL REPORT (the trial reports described below must be submitted according to the relevance related to the technology associated with the investigational medical device):

a. Check-list of compliance with the Essential Safety and Efficacy Requirements;

b. List of technical standards complied with in full 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 / Firmware Description: version, hazard analysis, specification of software requirements, traceability analysis, description of the process associated with the software life cycle, verification and validation of the software, 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;

or. Stability studies and validation of the packaging;

p. If the investigational medical device 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 for 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 the current regulations on good manufacturing practices for medical devices within the scope of ANVISA, accompanied by the documents that are part of the Historical Record of the Project of the medical device under investigation, containing at least:

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 the information, the presentation of specific reports and protocols may be requested);

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

d. Record of the transfer from design to production, for devices that are already in the production phase;

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

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

g. In cases where an investigator-sponsor wishes to carry out a clinical investigation with an investigational medical device that already has a DICD approved by ANVISA, he may use the information already sent by the holder of the initial DICD if he authorizes it, without the need to resubmit all the documentation. When an authorization from the initial holder is not presented, the sponsoring investigator must submit to ANVISA all the information available in updated and indexed literature that supports the proposed clinical development rationale; and

h. In the event that the medical device under investigation is already registered in Brazil, only the information that supports the proposed post-registration changes must be submitted to the DICD.

ANNEX III

STATEMENT

I declare that the INVESTIGATOR's BROCHURE has already been submitted to Anvisa in process 25351.xxxxxxxx and remains unchanged at the time of this submission.

Signature of the Sponsor, sponsoring investigator or ORPC

ANNEX IV

STATEMENT

I declare that the documentation related to the DOSSIER OF THE MEDICAL DEVICE UNDER INVESTIGATION has already been submitted to Anvisa in process 25351.xxxxxxxx and remains unchanged at the time of this submission.

Signature of the Sponsor, sponsoring investigator or ORPC

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