Resolution RDC No. 10, of February 20, 2015

BRAZILIAN OFFICIAL GAZETTE (DOU) 03/MAR/2015

Regulations for clinical trials with medical devices in Brazil.

The Collegial Board of the Brazilian Health Surveillance Agency, in exercise of the powers conferred on it by Sections III and IV of Article 15 of Law No. 9,782, of January 26, 1999, together with the provisions in Item I, Paragraph 1 of Article 6 of ANVISA Bylaws, approved in accordance with Annex I of Ordinance No. 650, of May 29, 2014, published in the DOU on June 2, 2014, in light of Item III of Article 2, III and IV, of Article 7 of Law No. 9,782, of 1999, Article 35 of Decree No. 3,029, of April 16, 1999, and the Program for Improvement of the Agency Regulatory Process, established by Ordinance No. 422, of April 16, 2008, adopts the following Collegial Board Resolution as deliberated at a meeting held on February 5, 2015, and I, Deputy Director-President, determine its publication:

Chapter I

INITIAL PROVISIONS

Section I

Objective

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

Section II

Scope

Art. 2. This Resolution applies to all clinical trials with medical devices that will be entirely or partly clinically developed in Brazil, for registration purposes.

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

I – new intended use,

II – new proposed purpose or use;

III – relevant post-registration change.

Paragraph 2. This resolution does not apply to performance evaluation trials of diagnostic products for *in-vitro* use.

Art. 3. Clinical trials involving investigational medical devices with the characteristics described in items I and II may be required to submit a MDCID:

I – products of risk class III and IV;

II – devices intended for diagnosis purposes, regardless of the risk class, that meet the following criteria:

a) the investigational device is invasive;

b) the investigational device is intended to supply power 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 sole purpose of evaluating the usability/human factors of medical devices are outside the scope of this Resolution, except when clinical trials are conducted and include, among other outcomes, a usability/human factors evaluation.

Paragraph 2. In cases where ANVISA approval of clinical trials is not required, these trials remain subject to other relevant regulatory approvals and ethics guidelines.

Art. 4. Clinical trials involving medical devices of risk classes I and II and observational and post-marketing clinical trials, regardless of the risk class, shall be subject to the notification procedure without the need for submission of a MDCID.

Paragraph 1. Clinical trial notification must be composed of the following documents:

a) duly completed clinical trial submission form, available at ANVISA website;

b) proof of payment, or exemption thereof, of the Sanitary Surveillance Inspection Fee (SSIF), with the Federal Payment Receipt (GRU)

c) clinical trial protocol in accordance with the GCP;

d) registration confirmation of the clinical trial at the International Clinical Trials Registration Platform/World Health Organization (ICTRP/WHO) database or other agencies acknowledged by the International Committee of Medical Journal Editors (ICMJE); and

e) Technical opinion letter of the Institutional Review Board (IRB) issued for the first clinical trial center and forwarding the protocol for review by the IRB.

Paragraph 2. Investigational medical devices 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 with a MDCID previously approved by ANVISA should file the Notification process, linking it to the corresponding MDCID.

Paragraph 4 A Specific Special Notice (SSN) shall be issued for clinical trials described in this article caput within thirty (30) calendar days from the date of receipt by ANVISA.

Art. 5. ANVISA may issue guidelines on the applicability of this Resolution to specific cases of clinical trials with medical devices.

Section III

Definitions

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

I – **Audit**: a systematic and independent review of the activities and documents related to the study aimed to determine whether the evaluated activities were accurately performed and the data was recorded, analyzed, and reported in compliance with the protocol, standard operating 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, reviewing, and reporting clinical trials ensuring the data and reported results are reliable and accurate, and that the rights, integrity, and confidentiality of clinical trial participants are protected, in accordance with GCP guidelines established in the Document of the Americas and Good Clinical Practices of the International Conference on Harmonization Manual (Document E6) and ISO14155;

III – **Good Manufacturing Practices (GMP):** part of the Quality Assurance which ensures that products are consistently produced and controlled to appropriate quality standards for its intended use and required by the registration;

IV – **Good Laboratory Practices (GLP):** quality system covering the organizational process and the conditions in which non-clinical studies related to health and environmental safety are planned, developed, monitored, recorded, files, and reported;

V – **Investigator's Brochure:** compiled clinical and non-clinical data on the investigational medical device(s), which are relevant for their study in humans;

VI – **Clinical Trial Center:** public or private organization, legally constituted, duly registered in the National Registry of Health Institution (CNES), where clinical trials are conducted;

VII – **Institutional Review Board (IRB):** interdisciplinary and independent collegiate, of public relevance, consultative, deliberative and educational, created to defend the interests of research participants regarding integrity and dignity and to contribute to the development of research within ethical standards;

VIII – **Independent Data Monitoring Committee:** independent committee constituted to monitor data at regular intervals to assess the progress of a clinical trial, the safety data and the critical points, in order to evaluate the efficacy and to advise a sponsor if a trial should be continued, changed, or terminated;

IX – **Comparator:** medical device, therapy, placebo, simulation or absence of treatment used in the control group in a clinical trial;

X – **Special Notice (SN):** document of authoritative character issued by ANVISA upon review and approval by MDCID, which may be used in requests to import or export of clinical trial;

XI – **Specific Special Notice (SSN):** document issued by ANVISA necessary for requesting import or export of a clinical trial subject to the notification scheme;

XII - Bill of lading: document issued on the shipment date of the goods or product by the carrier or consolidator, establishing the international transport contract and proof of viability of good or product to the importer;

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

XIV – **Clinical Trial Start Date:** corresponds to date of the inclusion of the first clinical trial participant worldwide;

XV – **Clinical Trial End Date in Brazil**: corresponds to date of the last visit of the last participant of the clinical trial in Brazil or other definitions specified by the sponsor, explicitly provided by the specific clinical trial dossier;

XVI – **Clinical Trial End Date**: corresponds to date of the last visit of the last participant of the clinical trial worldwide or other definitions specified by the sponsor, explicitly stated in the specific dossier of the clinical trial;

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

XVIII – **Medical Device**: comprises health products defined below:

a. Medical Product: health-related product, such as equipment, device, material, article, or use system or medical, dental, laboratory, or aesthetics application, for the purpose of prevention, diagnosis, treatment, rehabilitation, or contraception, which does

not use pharmacological, immunological, or metabolic means to accomplish its main function in humans, although its function may be assisted by such means;

b. Diagnostic Products for *In Vitro* Use: reagents, standards, calibrators, controls, materials, articles, and tools, along with its instructions manual, which contribute to the 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 by humans and which are solely used for providing information on samples obtained from a human organism;

XIX – **Medical Investigational Device**: medical device, object of a MDCID, to be tested and used in the clinical trial for obtaining information for its registration or post-registration;

XX – **Document for Delegation of Importation Liability**: document issued by the research sponsor, which includes the appointment of the authorized importer and the responsibilities related to the transport and customs clearance of imported goods;

XXI – **Document for Importation of investigational medical product(s) in the Medical Device Clinical Investigation Dossier:** document issued by ANVISA, which is required to apply for import or export for a clinical trial, necessary in case of non-manifestation regarding the MDICD;

XXII – **Medical Device Clinical Investigation Dossier (MDCID):** compiled documents to be submitted to ANVISA for the purpose of evaluating the steps involved in the clinical development of a medical investigational device in order to obtain information to support the registration or post-registration changes to the mentioned product;

XXIII – **Specific Dossier for each Clinical Trial**: compiled documents to be submitted to ANVISA for the purpose of obtaining information related to clinical trials to be conducted in Brazil, which are part of the medical investigational device development plan;

XXIV – **Amendment to the Clinical Trial Protocol**: any proposal for changing an original clinical trial protocol, always presented with a rationale, regardless of whether or not the amendment is substantial;

XXV – **Clinical Trial:** research conducted in human beings in order to check the safety and/or effectiveness of the investigational medical device(s);

XXVI – **Adverse Event (AE):** any adverse medical occurrence in a patient or research participant, which does not necessarily have a causal relationship with the treatment. As a result, an AE can be any unfavorable and unintended sign, symptom or disease (including results of laboratory tests out of the reference range) associated with the use of an investigational medical device, whether or not it is related to it;

XXVII – **Serious Adverse Event:** that one resulting in any adverse experience with drugs, biological products or medical devices, occurring at any dose and which results in any of the following outcomes;

a) death;

b) life-threatening adverse event (one that, in the opinion of the notifying party, poses the individual to immediate danger of death due to the adverse event occurred);

c) persistent or significant disability/incapacity;

d) requires hospitalization of the patient or prolonged hospitalization;

e) congenital anomaly or birth defect;

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

g) clinically significant event;

XXVIII – **Unexpected Adverse Event**: an event not described as an adverse reaction in the instruction brochure or manual/operator's manual of the medical investigational device;

XXIX – **Intended Purpose**: description of the expected results with the use of the device;

XXX – **Case Report Form**: optical, electronic or printed document designed to record all the information of each clinical trial participant, in accordance with the clinical protocol, and must be reported to the sponsor;

XXXI – **Intended Use**: an indication of the disease or condition that the device is intended to diagnose, treat, prevent, mitigate, or heal; parameters to be monitored or other indications of use associated with the device. This includes information about criteria for patient selection and target population of the device (e.g. adult, pediatric, or neonate);

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 related to the clinical trial and that may be located where the trial is conducted, at the sponsor's facilities and/or the Contract Research Organization (CRO), or other site locations that the regulatory authority deems appropriate;

XXXIII – **Clinical Research**: any systematic investigation or study in one or more human beings, conducted to assess the safety and/or effectiveness of a medical device;

XXXIV – **Investigator:** person responsible for conducting a clinical trial at the site 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, either alone or in a group, performed under his/her independent direction developed with financial resources and the investigator's own materials, of national or international entities to support the research, private entities and other non-profit entities;

XXXVI – **Monitoring:** act of continuously reviewing the clinical trial process and ensuring that it is conducted, recorded, and reported in accordance with the protocol, standard operating procedures, Good Clinical Practices and the applicable regulatory requirements;

XXXVII – **Contract Research Organization (CRO):** any company regularly established in national territory contracted by the sponsor or by the investigator-sponsor, which partially or wholly assumes the responsibilities of the sponsor regarding the clinical trial with ANVISA;

XXXVIII **– Sponsor:** person, company, institution or organization responsible for starting, managing, controlling and/or financing a clinical study;

XXXIX – **Investigational Product**: investigational medical device, or any other product or comparator to be used in the clinical trial;

XL – **Clinical Trial Protocol**: document describing the objectives, design, methodology, statistical considerations and organization of a study. It also provides the context and background of the clinical trial;

XLI – **Annual report:** annual document containing specific information about the conduct of a particular clinical trial in centers in Brazil, according to the clinical protocol and GCP;

XLII – **Final report:** document containing specific information about the conduct of a particular clinical trial at all the centers participating in the study, according to the clinical protocol and GCP;

XLIII – **Proposed Use**: therapeutic, diagnostic or other function that is primarily conferred to 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**: medical device interface feature with a user establishing effectiveness, efficiency, ease of learning and user's satisfaction;

XLV – **Clinical Trial Protocol Violation**: a clinical trial protocol deviation that may affect the data quality compromising the integrity of the study or that may affect the safety or rights of participants in the clinical trial.

Chapter II

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

Art. 7. The documentation presented in the MDCID should ensure the rights and safety of clinical trial participants at all stages of clinical development, the quality of the medical investigational device and the data obtained in the phases of clinical development to allow an evaluation of the efficacy and safety of the medical device.

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

Section I

General Requirements for the Application

Art. 9. The sponsor must submit a MDCID to ANVISA only when it intends to conduct clinical trials with medical devices in the national territory.

Sole Paragraph. For MDCID analysis purposes, at least one specific dossier of a clinical trial to be held in Brazil must be filed.

Art. 10. A single Special Notice (SN) shall be issued through MDCID mentioning all clinical trials to be conducted in Brazil.

Sole Paragraph. Only clinical trials listed in the SN may be started in the country, respecting the other ethical approvals.

Art. 11. Upon receipt of MDCID, ANVISA shall evaluate MDCID within ninety (90) calendar days.

Paragraph 1. If ANVISA does not respond within ninety (90) calendar days after receiving MDCID, clinical development may be started after the relevant ethical approvals.

Paragraph 2. In cases of non-response within the time limits described in the caput, ANVISA shall issue an importation Document for the investigational medical product(s) in the Medical Device Clinical Investigation Dossier(MDCID) to be presented at the clearance location for the importation of investigational medical product(s), which are necessary to conduct the clinical trial.

Art. 12. MDCID should contain general information about the clinical research plan, medical investigational device and specific protocol(s) for the clinical trial(s), as described in Section II of this chapter.

Art. 13. MDCID may be submitted by the sponsor, investigator-sponsor or CRO.

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

Paragraph 2. Submissions by a CRO can only be performed when the sponsor does not have a headquarter office or affiliate in Brazil.

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

Section II

Application Content and Format

Art. 14. MDCID must be submitted to ANVISA and will be composed of the following documents:

I – Duly completed application form in accordance with model available at ANVISA website;

II – proof of payment, or exemption, of the Health Surveillance Inspection Fee (SSIF), and the respective Federal Payment Receipt (GRU); and

III – medical device clinical research plan containing:

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

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

c. description of each clinical trial planned, containing information about phase, design, outcomes, comparators, objectives, target population, hypothesis, estimated sample size and statistical planning; and

d. information about phase, design, outcomes, comparators, objectives, target population, hypothesis, estimated sample size and statistical planning for each clinical trial planned;

IV – the investigator's brochure, containing information about the experimental medical device as shown in the Annex I;

V – summary of the safety aspects based on prior experience in humans of the medical investigational device, as well as post-marketing experiences in other countries, if applicable;

VI – dossier of the medical investigational device in accordance with Annex II of this standard;

VII – specific dossier of the clinical trial to be held in Brazil. Such dossiers shall be filed as individual processes for each clinical trial. Each process must be linked to the MDCID and submitted by the sponsor, investigator-sponsor, or CRO. The dossier must consist of the following documents:

a. duly completed clinical trial submission form, available at ANVISA website;

b. proof of payment, or exemption, of the Health Surveillance Inspection Fee (SSIF), as the Federal Payment Receipt (GRU);

c. clinical protocol in accordance with the GCP;

d. proof that the clinical trial is registered in the International Clinical Trials Registration Platform/World Health Organization (ICTRP/WHO) or other agencies recognized by the International Committee of Medical Journal Editors (ICMJE); and

e. Technical opinion letter of the Institutional Review Board (IRB).

Art. 15. All physically filed documentation, including proof of compliance with the requirement(s), must be accompanied by a copy in an electronic media (pdf or Word file).

Paragraph 1. The electronic files shall allow text search.

Paragraph 2. The submission of electronic media applies to the adoption of Information Technology tools that allow the electronic submission of documents requested.

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

Art. 17. ANVISA may, at any time, request other information deemed necessary for the assessment and monitoring of the clinical development.

Chapter III

SUBSTANTIAL AMENDMENTS TO THE MDCID

Art. 18. Substantial amendments to MDCID should be filed and await ANVISA response before being implemented, in accordance with the deadlines described in Art. 11.

Sole Paragraph. Amendments to MDCID must be submitted to ANVISA in the form of a secondary petition attached to the respective MDCID process to which it is linked.

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

I – inclusion of clinical trial protocol(s) that were not foreseen in the original development plan of the medical investigational device;

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

III – changes that may impact the quality and safety of the medical investigational device.

Art. 20. Changes to MDCID arising from recommendations or warnings issued by health authorities should be notified before they are implemented, and may be implemented regardless of prior ANVISA approval.

Art. 21. Changes to MDCID not considered to be substantial must be presented to ANVISA as part of the medical device's Annual Clinical Development Report.

Chapter IV

AMENDMENTS TO THE CLINICAL PROTOCOL

Art. 22. All amendments to a clinical trial protocol should be presented to ANVISA, identifying the part of the protocol to be changed and their rationales.

Sole Paragraph. Amendments should only be implemented after obtaining ethical approval in accordance with current legislation.

Art. 23. Substantial amendments to clinical trial protocols should be filed and wait ANVISA response before being implemented, respecting the deadlines described in Article 11.

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

Paragraph 2. Amendments aiming to eliminate immediate risks to the safety of the clinical trial participants are exempt from the aforementioned requirements. These can be implemented and immediately reported to ANVISA.

Art. 24. For the purposes of this Resolution, amendments will be considered substantial when any of the following criteria are met:

I – Amendments to the clinical trial protocol which affects the safety or physical or mental integrity of the participants; or

II – Amendments to the scientific value of the clinical trial protocol.

Art. 25. Amendments to the clinical trial protocol not considered substantial must be presented to ANVISA as part of the annual clinical trial protocol monitoring report.

Chapter V

SUSPENSIONS AND CANCELLATIONS

Art. 26. The sponsor may cancel or suspend a MDCID or clinical trial at any time, provided that appropriate scientific and technical rationales are disclosed, as well as a follow-up plan for participants in a clinical trials already started.

Paragraph 1. Once a MDCID is cancelled, no clinical trial related to it may be continued.

Paragraph 2. If a MDCID or clinical trial is cancelled for safety reasons, the sponsor must technically and scientifically justify the reasons for cancelling and introduce measures for minimization/mitigation of risk to clinical trial participants.

Paragraph 3. Suspensions and cancellations of a clinical trial protocol or MDCID must be submitted to ANVISA in the form of a secondary petition attached to the respective process.

Art. 27. The sponsor must notify ANVISA about the decision to suspend or cancel a clinical trial protocol. After deciding to suspend or cancel, the sponsor must notify ANVISA within fifteen (15) calendar days.

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

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

Art. 29. Requests for reactivation of suspended clinical trials must be forwarded to ANVISA accompanied by proper rationales, in order for the study to be restarted. The study will only be restarted after approval by ANVISA.

Art. 30. ANVISA may, at any time, cancel or suspend MDCID or any linked clinical trial if it deems that the conditions for approval were not met, or safety/efficacy reports exist indicating that the research participants or scientific validity of data obtained in clinical trials are significantly affected.

CHAPTER VI

RESPONSIBILITIES

Art. 31. The responsibilities listed in this chapter cover 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 MDCID, the selection of qualified investigators and research centers, thus ensuring that clinical trials are conducted in accordance with the protocols and Good Clinical Practices.

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

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

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

Sole Paragraph. In the event of clinical development discontinuation or completion not followed by a registration application, the sponsor must keep clinical trial data in a physical or digital file for a minimum of two (2) years after clinical development discontinuation or formal development completion.

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

Art. 37. The sponsor must ensure that the data obtained about safety and effectiveness of the medical investigational device is sufficient to support human exposure to such medical device.

Art. 38. The sponsor must ensure that the medical investigational device, placebo and simulated, when used, are manufactured in accordance with the GMP and are coded and labeled in such a way as to protect the masking, if applicable, and denotes them as investigational products.

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

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

Art. 40. The sponsor is responsible for only distributing the investigational medical product(s) to institutions mentioned in the Clinical Trial submission form contained in the Specific Dossier for each Clinical Trial and authorized by Institutional Review Boards.

Sole Paragraph. The sponsor is responsible for the final destination of the investigational products that have not been used in the clinical trial.

Art. 41. The sponsor must ensure the appropriate audit and monitoring of clinical trials.

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

Art. 43. The sponsor may transfer its duties to a CRO.

Paragraph 1. The transfer referred to in the caput of this article does not eradicate the sponsor's final responsibility for the quality and integrity of research data.

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

Section II

Investigator's Responsibilities

Art. 44. The investigator must conduct the clinical trial according to the protocol agreed with the sponsor, GCP, regulatory and ethical applicable requirements in force.

Art. 45. The investigator must personally oversee the clinical trial, and may only delegate tasks, not responsibilities.

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

Art. 47. The investigator must ensure that appropriate medical assistance is given to clinical trial participants for any clinical trial-related adverse events, including clinically significant laboratory values, at no cost to the participant.

Art. 48. The investigator must promptly inform the clinical trial participants when the clinical trial is prematurely terminated or suspended for any reason, as well as ensure appropriate therapy and participant's follow-up.

Art. 49. The investigator is responsible for using the investigational products only in the context of the clinical trial and for storing them in accordance with the sponsor's specification and with applicable regulatory requirements.

Section III

Investigator-Sponsor's Responsibilities

Art. 50. In case a clinical trial is developed by an investigator-sponsor, the institution to which he/she is linked 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 such case, the investigator-sponsor will be the secondary sponsor.

Paragraph 2. In case of delegation of responsibilities and activities, a written authorization should be signed between the parts.

Paragraph 3. The primary sponsor cannot delegate activities relating to quality assurance, audits and monitoring of clinical trials to the investigator-sponsor, but may delegate them to a CRO.

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

I – management of adverse events;

II – project management;

III – data management;

IV – training;

V – information technology;

VI – quality assurance;

VII – monitoring.

Paragraph 5. The institution referred to in the caput must be the one where the trial will be held.

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

Art. 51. In case of donation of investigational medical devices previously registered in Brazil, for conducting clinical trials, the donor will be the sponsor if there is an agreement of transfer or ownership of the data obtained in the research to the mentioned donor.

Art. 52. In case of donation of investigational medical devices not registered in Brazil for conducting clinical trials, the donor will share the responsibility with the sponsor.

Section IV

Structure of the Clinical Trial Center

Art. 53. The clinical trial center must have appropriate facilities to conduct the protocol, regarding the physical structure, equipment/tools and human resources, and appropriated to the sample population, for example the elderly, children, people with special needs, but not limited to.

Art. 54. The institution's management must be notified on the conduct of the clinical trial.

CHAPTER VII

SAFETY MONITORING AND ALERTS

Section I

Adverse Events Monitoring

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

Art. 56. The sponsor or the Independent Data Monitoring Committee must systematically collect and evaluate aggregated data on adverse events that occurring in the clinical trial, and this information should be included in the annual reports submitted to ANVISA.

Art. 57. The sponsor must 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 occurring during the clinical trial at any stage of clinical development of the medical device, the sponsor and the investigator must take immediate safety measures to protect the clinical trial participants from any imminent risk.

Sole Paragraph. In the event a serious adverse event is notified, the following information must be notified: measures that have been adopted, the plan of action in the event of new events of a similar nature, information regarding the location where healthcare was provided to participants, along with other data required in the notification form, especially those allowing the traceability of the event and of the affected participant.

Art. 59. Notification of unexpected serious adverse events, where causality is possible, probable or defined, does not depend on the submission of the investigator's brochure, amendments, reports or early termination of the clinical trial.

Art. 60. The sponsor must consider the establishment of a data monitoring committee before starting a clinical trial, whose decision must be guided by risk analysis, taking into account both the risks associated with use of the medical investigational device and the risks associated with the subject's participation in the clinical trial. The development of pivotal and phase III clinical trials must be monitored by the data

monitoring committee and their recommendations must be reported to ANVISA by the sponsor.

Sole Paragraph. The main functions of the data monitoring committee must be described in the protocol and the responsibilities of the data monitoring committee shall be detailed in separate written procedures to establish the frequency and documentation of meetings and the management of emergency situations; cases that have no data monitoring committee must be justified.

Subsection II

Communication of Adverse Events by the Investigator

Art. 61. The investigator must report the occurrence of any adverse events to the sponsor, providing any information requested and expressing his/her opinion regarding the causal relationship between the adverse event and the investigational product.

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

Art. 62. All adverse events must be treated and affected participants followed-up by the principal investigator and his/her team until their resolution or stabilization.

Subsection III

Notification of Adverse Events by Sponsor

Art. 63. The sponsor must notify ANVISA, through specific electronic form, of unexpected serious adverse events that occurring in national territory, where causality is possible, probable or defined in relation to the investigational product.

Sole Paragraph. The sponsor must keep detailed records of all adverse events reported by investigators. ANVISA may request such records at any time.

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

Subsection IV

Deadlines

Art. 65. The investigator must inform the sponsor of serious adverse events or death within twenty four (24) hours from the date the event is acknowledged.

Art. 66. The sponsor must ensure that all relevant information about adverse events cited in Art. 63 that are fatal or life-threatening are documented and reported to ANVISA, through the electronic form, in no more than seven (7) calendar days from the date the case is acknowledged by the sponsor.

Sole Paragraph. Additional information on the monitoring of adverse events mentioned in the caput must be included in the form in no more than eight (8) calendar days from the date of their notification.

Art. 67. All other unexpected serious adverse events where causality is possible, probable or defined in relation to the investigational products must be notified to ANVISA within fifteen (15) calendar days from the date the case is acknowledged by the sponsor.

Section II

Follow-up Reports

Subsection I

Follow-up Reports for Clinical Trial Protocol

Art. 68. The sponsor must submit annual follow-up reports to ANVISA containing the following information, exclusively from Brazilian centers, in tabulated form, for each clinical trial protocol:

I – title of the clinical trial;

II – protocol code;

III – status of the clinical trial participants' recruitment;

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

V – number and description of protocol deviations and violations per center; and

VI – description of all adverse events occurring at each center during this period evaluated, identifying the clinical trial participants with the codes used in the Case Report Form in the clinical trial protocol.

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

Paragraph 2. The annual report must be filed within sixty (60) calendar days, having as reference for the annual nature, the clinical trial start date in Brazil.

Art. 69. Upon completion of the activities of a clinical trial protocol for any reasons, the sponsor must submit a final report to ANVISA, containing at least the following information:

I –clinical trial title with the protocol code and end date of the clinical trial;

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

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

IV – demographic description of participants recruited for the clinical trial;

V – statistical analysis;

VI – number and description of protocol deviations and violations;

VII – list of all adverse events and laboratory abnormalities with assessment of causality that occurred per participant;

VIII – the results obtained in outcome measurements for each participant of the clinical trial;

IX – rationale for the clinical trial early termination or development in Brazil and abroad, where applicable.

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

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

Paragraph 3. Clinical trials submitted in the notification regime should only protocol the final report to ANVISA.

Art. 70. The lack of submission and non-compliance with the deadlines set out in articles 65 and 66 may result in the cancellation of the clinical trial or MDCID.

Subsection II

Medical Device Clinical Development Report

Art. 71. The sponsor must annually submit clinical development reports of the medical investigational device to ANVISA, as well as information related to design changes, if any, containing information on the status of product development in the world, safety alerts (where applicable) and information relating to available results of clinical studies in progress worldwide, if any changes are made to the project report, the report

must include an analysis of the impact such changes will have on clinical research in progress relating to changes made to the medical device and a non-clinical study report that supports these changes, where appropriate.

Sole Paragraph. The annual clinical development reports of the medical device must be filed within a maximum period of sixty (60) calendar days with reference to the date of MDCID approval by ANVISA or date specified by the sponsor in the medical device development.

Chapter VIII

INSPECTIONS

Section I

Inspections to Verify the Compliance with the Good Clinical Practices

Art. 72. In order to ensure 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 to the health registration, ANVISA may perform GCP inspections at clinical trial centers, sponsor, CRO, laboratories, and other institutions involved in the development of the medical investigational device to verify the level of compliance with current Brazilian legislation and compliance with the GCP, in addition to ensure the rights and duties concerning the scientific community and to the State.

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

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

I – the temporary interruption of the clinical trial;

II – the definitive cancellation of the clinical trial at the concerned center;

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

IV – invalidation of data from centers and clinical trials which are not in compliance with the GCP.

Section II

Inspections to Verify Compliance with Good Manufacturing Practices of Investigational products

Art. 73. ANVISA may conduct GMP inspections of the medical investigational device or investigational product produced or changed by the sponsor in order to verify technical, production and quality control information provided in MDCID, and if the investigational device is sufficiently safe to allow the use in the clinical trial participants.

Chapter IX

IMPORTS

Art. 74. Import of investigational products for exclusive use in the clinical trial must undergo inspection by the health authority operating on the clearance site.

Art. 75. The following documents must be presented after the arrival of the investigational products in national territory:

I – copy of the Medical Device Clinical Investigation Dossier's (MDCID) Special Notice (SN), Specific Special Notice (SSN) or import Document for Investigational medical product(s) issued by the relevant technical ANVISA department;

II – in case of imports executed by entities other than MDCID holder, the delegation of import responsibilities document signed by both parties must be presented;

III – health regulation liability waiver to import for the purpose clinical research;

IV – copy of the shipment bill– air Cargo, shipped Cargo or overland Cargo; and

V – copy of the commercial invoice.

Art. 76. The competent health authority operating in the clearance site of the investigational medical product(s) shall verify compliance to packaging, transport and storage guidelines, in accordance with specific information in the SN, SSN or Import Document for the investigational medical product(s) in addition to those supplied by the manufacturer or sponsor.

Paragraph 1. The external or shipping packages, used for the shipping of products discussed in this chapter, the following information should be included:

a) number of SN, SSN or Import Document for the investigational medical product(s) of the clinical investigation of the medical device dossier (MDCID) to which the investigational product is submitted;

b) amount of imported material;

c) information on special storage conditions, such as temperature, humidity and light;

d) information about physical form related to pharmaceutical form of the product(s);

e) information about shelf-life; and

f) lot number or serial number.

Art. 77. The qualitative information and specifications of the investigational products to be used in the clinical trial will be informed in the Special Notice (SN), Specific Special Notice (SSN) or Import Document of Investigational Medical Product(s) in MDCID.

Sole Paragraph. In the event of a change to the investigational products and their specifications informed in the SN, SSN or MDCID import Document of investigational medical product(s), that information must be notified to the competent technical area of ANVISA in its headquarters. The updated SN, SSN and Import Document should be presented at the clearance site.

Art. 78. The Substitutive Import Licensing authorization by the competent health authority will occur from a fiscal context at the clearance site. If conclusive and satisfactory, it shall be linked to the import licensing that preceded it, provided that the amendment has been informed in the previous import License, and is not at odds with the control and/or previously concluded health control.

Art. 79. Entry to national territory of investigational products not foreseen in the SN, SSN or Import Document for Investigational Medical Product(s) of MDCID for use in clinical trials is strictly forbidden by this Resolution.

Sole Paragraph. Changes to the import purpose of goods and products referred to in this Resolution are strictly forbidden.

Chapter X

TRANSIENT PROVISIONS

Art. 80. Upon filing a MDCID, the holder must bind all clinical trial consent processes related to the medical investigational device that may have already been submitted to assessment by ANVISA at any time.

Art. 81. The clinical trial authorization processes previously approved by ANVISA should comply with the resolution in force at the time of its adoption until the process is included in a MDCID, if applicable.

Chapter XI

FINAL PROVISIONS

Art. 82. Considering the great technological diversity of the sector and the scope of the reasonably foreseeable risks for a given technology, additional information supporting the minimum-safety assurance of a particular medical device may be required for approval of a MDCID by ANVISA.

Art. 83. Failure to comply with the provisions of this Resolution implies a health infraction; the offender may be subject to the penalties provided for in Law 6,427/77.

Art. 84. Unforeseen cases shall be subject to other international and national standard guidelines.

Art. 85. The BRAZILIAN COLLEGIAL BOARD OF GOVERNORS' RESOLUTION– RDC No. 39, OF JUNE 5, 2008, and RESOLUTION RDC No. 36, OF JUNE 27, 2012, and ITEMS 1 and 1.1 of SECTION I, and ITEMS 2, 2.1 and 2.1.1 of SECTION II of CHAPTER XXVI of RESOLUTION RDC No. 81, OF NOVEMBER 5, 2008 are hereby revoked.

Art. 86. This Resolution shall enter in force on the date of its publication.

JAIME CÉSAR DE MOURA OLIVEIRA

ANNEX I

Investigator's Brochure – IB

1) Identification:

a) Name of the investigational device;

b) Clinical Trial Title(s) and protocol code(s);

c) Issue date or version of the investigator's brochure;

d) Confidentiality Statement, if applicable;

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

f) Each page of the IB must contain the version number or issue date, depending on the identification method 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 investigational device.

Note: If the medical device's manufacturing process is partly outsourced, this information must also be indicated, stating the name and address of the third-party production enforcer.

3) Information of the investigational device:

a) Literature summary and follow-up evaluation with the rationale behind the project and intended use of the medical investigational device;

b) Regulatory classification of the medical investigational device;

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

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

e) Description of the action mechanism of the medical investigational device, along with the scientific basis in the literature;

f) Manufacturer's instructions for installation and use of the medical investigational device, including any need and requirements for storage and handling, preparation for use and re-use (for example, sterilization), any pre-use evaluation of safety or performance and the precautions to be taken after use (e.g. elimination), if relevant; and

g) Description of the intended clinical performance.

4) Non-Clinical Trials:

Summary of non-clinical tests which were conducted with the medical investigational device along with an evaluation of the results of such tests to justify its use in humans.

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

a) Design calculations;

b) *In vitro* assays;

c) Mechanical and electrical assays;

d) Reliability assays;

e) Validation of the software related to the function of the device;

f) All performance assays;

g) *Ex vivo* assays; and

h) Biological safety evaluation.

5) Clinical Data Available:

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

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

6) Risk Management:

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

b) Outcome of the risk assessment; and

c) Foreseeable risks, contraindications and warnings for the investigational device.

7) Regulation and Other References:

a) List of existing technical standards, met in full or in part;

b) Declaration of compliance with the relevant national regulations; and

c) List of relevant scientific-technical references.

ANNEX II

DOSSIER OF THE MEDICAL INVESTIGATIONAL DEVICE

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

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

3) Environment of intended use and usage settings;

4) Contraindications for use;

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

6) Development history of the medical investigational device;

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

8) Global incidents and recall report, when the medical investigational device is already sold on the international market;

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

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

b. List of technical standards fulfilled 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. Radiation safety;

g. Description of the Software/Firmware: version, risk analysis, software requirements specification, 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. Animal model trials;

o. Packaging stability and validation studies;

p. If the medical investigational device needs to be cleaned or reprocessed between successive uses, the description and validation of cleaning process/re-process must be indicated; and

q. Existing bibliographical review about the medical investigational device or other similar technology devices with the same intended use, when these exist.

10. Description of the manufacture stages of the experimental device; and

11. Good Manufacturing Practices - present procedures of the Design and Development of the medical investigational device, in accordance with the current regulations on good manufacturing practices of medical devices by ANVISA accompanied by the documents included in the Project History Registration of the medical investigational device, including at least the following:

a. Project development plan;

b. Traceability matrix correlating: input data, output data, reference to protocols and verification and validation reports (NOTE: during the information analysis, reports and specific protocols may be requested);

c. Record of project revisions in accordance with the plan set for the project, up to the date of the MDCID submission;

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

e. Initial transfer plan from project to production, for devices that are still at the stage of project development;

f. If the medical investigational device is not a conventional production unit, present rationale of the validity of the data obtained with clinical research for products originating in conventional production.

g. In cases where an investigator-sponsor wishes to conduct a clinical trial with a medical investigational device that already has a MDCID previously approved by ANVISA, he/she may use the information already submitted by the holder of the initial MDCID if appropriate authorization is obtained, without the need for re-submission of all documentation. When an initial holder's authorization is not submitted, the investigator-sponsor must submit all information available in the updated and indexed literature that supports the rationale behind the clinical development proposed to ANVISA; and

h. If the medical investigational device has been previously registered in Brazil, only information relating to post-registration change proposals should be submitted in MDCID.