

## **RESOLUTION -RDC No. 9, 20 FEBRUARY 2015**

**DOU 03/03/2015**

Regarding Regulation for realization of clinical trials of medication in Brazil.

The Board of the National Health Surveillance Agency, using the powers that are conferred on it in sections III and IV of art. 15 of Law No. 9,782, of January 26, 1999, item II and paragraphs 1 and 3 of art. 54 of the Bylaws approved under Annex I of Ordinance No. 354 of ANVISA, of August 11, 2006, and its updates, in view of the provisions of sections III, Art. 2, III and IV of art. 7 of Law No. 9782, 1999 in art. 35 of Decree no. 3.029 of 16 April 2009, and the Agency Process Improvement Regulations, established by Decree 422 of 16 April 2008, at a meeting held on 5 February 2015 adopts the following Resolution of the Board and I, Substitute President-Director, determine its publication:

### **Chapter I INITIAL PROVISIONS**

#### **Section 1**

#### **Objective**

Art. 1 This Resolution's objective is to define the procedures and requirements for conducting clinical trials for medications, including submission of the Drug Clinical Development Dossier (DDCM) to be approved by ANVISA.

#### Section II

#### Scope

Art. 2 This Resolution applies to all clinical trials with drugs that have all or part of their clinical development in Brazil in order to secure registration.

Sole paragraph. Clinical trials for medications registered in Brazil must follow all provisions of this Resolution when providing support for:

I- new therapeutic indication;

II- new method of administration;

III- new concentration;

IV- new pharmaceutical form;

V- expansion of use;

VI new dosage;

VII - new associations; or

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

Art. 3. Post-commercialization clinical trials (Phase IV) are not the primary object of this standard, subject only to Notification of Clinical Trial, being initiated only after obtaining ethical approvals, according to current legislation.

I- clinical trials phase is exempt from the provisions in the caput

IV involving vaccines and trials that aim to evaluate efficacy and safety to obtain registration or renewal, which are considered as phase 3 clinical trials;

II For Phase 4 clinical trials for a product that already has a Drug Clinical Development Dossier (DDCM) approved in ANVISA, the notification of petition must be linked to the DDCM;

III Phase 4 clinical trials and observational phase that are not part of a previously approved DDCM and involve import or export procedures, will be subject to Notification of Clinical Trial and issuing of a Specific Special Bulletin (SSB) within thirty (30) calendar days of receipt from the date of notification by ANVISA,

IV the Clinical Trial Notification must include the following documents:

a) duly filled out form for clinical trial presentation, available on the website of ANVISA;

b) proof of payment or exemption of the Health Surveillance fees as provided by the Tax Liability Form (GRU);

c) clinical trial protocol in accordance with GCP;

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

e) Substantiative opinion of the Ethics in Research Committee (ERC) issued for the first clinical trial center and forwarding the protocol for review by the ERC.

Art. 4 This Resolution shall not apply to studies of bioequivalence and relative bioavailability for clinical trials with cosmetics, with health products, with food, with gene therapy and stem cells, which must comply with specific regulations.

Art. 5 ANVISA may issue guidelines on the applicability of this resolution for cases not provided for clinical drug trials.

## **Section III**

### **Definitions**

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

I- Audit - systematic and independent review of activities and documents relating to the study to determine whether the evaluated activities were performed and data registered, analyzed and reported accurately to comply with the protocol and standard operational procedures defined by the sponsor, Good Clinical Practices (GCP) and the applicable regulatory requirements;

II- Good Clinical Practice (GCP) - Standard for planning, conducting, performing, monitoring, auditing, recording, analysis and reporting of clinical trials that provides the assurance that the data and reported results are credible and accurate, and that the rights, integrity and confidentiality of clinical trial participants are protected, according to

GCP guidelines established in the Document of the Americas and Manual of Good Clinical Practices of the International Conference on Harmonization (Document E6);

III-Good Manufacturing Practices (GMP) - part of the Quality Guarantee which ensures that products are consistently produced and controlled with appropriate quality standards for desired use and required by the record;

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

V- Investigator's Brochure - compiled clinical and non-clinical data on the product(s) found that have relevance the study in human beings;

VI- Center for Clinical Trials – private or public organization, legally constituted, duly registered in the National Register of Health Facilities (CNES) in which clinical trials are conducted;

VII- Ethics in Research Committee (ERC) - interdisciplinary and independent body, 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 in ethical standards;

VIII- Independent Committee of Security- independent monitoring committee, constituted to monitor specific safety data collected by one or more clinical trials in defined intervals. Recommends to the sponsor if the study should be continued, modified or discontinued;

IX -Special Bulletin (SB) - document of authoritative character issued by ANVISA, upon review and approval of DDCM and can be used in requests for import or export of clinical trial;

X- Specific Special Bulletin (SSB) - document issued by ANVISA, necessary for request of import or export of a clinical trial subject to the notification system for a clinical trial subject described in Chapter X (From Transitory Dispositions) of this norm;

XI –Cargo Knowledge - document issued on unloading date of product or product, by carrier or consolidator, consisting of international transport contract and proof of viability of good or product for import;

XII - Clinical Trial Start Date - corresponds to the inclusion dated the first clinical trial participant abroad;

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

XIV –Clinical Trial End Date - corresponds to appearance of the last clinical trial participant in a location abroad or another definition of sponsor explicitly provided by the specific protocol of the clinical trial;

XV Clinical Trial End Date in Brazil – corresponds to date of the last visit of the last clinical trial participant in Brazil or another definition of sponsor explicitly provided in the specific protocol of the clinical trial;

XVI Clinical Trial Protocol Violation - any non-compliance with procedures or requirements defined in the approved clinical trial version without major implications for testing integrity, data quality, rights of safety of trial participants;

XVII- Document of delegation of responsibility for importation-document issued by the sponsor of the research, which includes the appointment of the authorized importer and the responsibilities relating to the transport and clearance of imported merchandise;

XVIII Document for Importation of Product(s) under investigation by the Drug Clinical Development Dossier (DDCM): Document issued by ANVISA, with the goal of evaluating inherent steps in the development of an experimental medication for import or export to a clinical trial, necessary in cases of non-manifestation of the DDCM;

XIX Drug Clinical Development Dossier(DDCM) - compiled documents to be submitted to ANVISA for the purpose of evaluating the steps involved in the development of a experimental drug in order to obtain information to support registration or post-registration changes of the product;

XX- Specific Dossier for each Clinical Trial – compilation of documents to be submitted to ANVISA for the purpose of obtaining information relating to clinical trials, to be conducted in Brazil, which are part of the Experimental Medication Development Plan;

XXI Amendment to the clinical trial protocol – any modification proposal in an original clinical trial protocol, always presented with the rationale that motivate it; such modification may be substantial or not;

XII Clinical trial - research conducted on human beings in order to discover or verify the clinical effects and/or pharmacological effects and/or other pharmacodynamic effect of experimental medication and/or identify any adverse reaction to experimental medication and/or to study absorption, distribution, metabolism and excretion of the experimental drug to verify its safety and/or efficacy;

XXIII Adverse Event (AE) - 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 outside the range of normality) associated with the use of a medical device under investigation, whether it is related to it or not;

XXIV Grave Adverse Event-one that results in any adverse experience with drugs, biological products or devices, occurring at any dosage which results in any of the following outcomes:

- a) death;
- b) threat to life;
- c) disability/ persistent or significant disability;
- d) requirement of hospitalization or prolonged hospitalization;
- e) congenital anomaly or birth defect;
- f) infecting agent suspected of transmission by medication
- g) clinically significant event.

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

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

XXVII- Inspection – Act on the part of the regulatory authority to conduct an official review of documents, facilities, records and any other resources considered by the authority as relative to the trial and that may located where the trial is conducted, at the sponsor, CRO, or in other site locations that regulatory authority considers appropriate;

XXVIII- Active Pharmaceutical Ingredient (AFI) – any substance introduced in formulating of a pharmaceutical form which, when administered in a patient, acts as active ingredient. Such substances may exert direct pharmacological activity or other effect in the diagnosis, cure, treat or prevent an illness, may also affect the structure and function of the human organism;

XXIX- Researcher - responsible for the conduct of a clinical trial in the place where the trial is conducted. If the study is led by a group of people, the investigator is the leader of the group and will be called the principal investigator;

XXX- Investigator-Sponsor – individual responsible for conducting and coordinating clinical trials, either alone or in a group, under their immediate direction and in an independent manner, developed with the researcher's own financial and material resources, that of national or international entities to encourage research, private entities and other non-profit entities;

XXXI- Experimental Medication – In a pharmaceutical trial, object of the DDCM, to be used in the clinical trial, for the purpose of obtaining information on its registration or post-registration;

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

XXXIII- Contract Clinical Research Organization (CRO) - every company regularly installed in national territory hired by the sponsor or by the researcher-sponsor, which partially or wholly assumes the responsibilities of the sponsor of the clinical trial with ANVISA;

XXXIV- Sponsor - individual, company, institution or organization responsible for starting, managing, controlling and/or financing of clinical study;

XXXV- Placebo - formulation without pharmacological effect, administered to participant in clinical trial for the purpose of acting as a masking and or comparator;

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

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

XXXVIII- 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;

XXXIX- Safety Update Report for development of the experimental drug - harmonized periodic report containing information on safety and development of experimental drug;

XL Final Report - document containing specific information about the conduct of a particular clinical trial at all study participants centers, according to the clinical protocol and GCP;

XLI- Active Substance - substance with pharmacological effect for intended therapeutic activity, used in the production of certain biological products;

XLII- Clinical Trial Protocol Deviation – deviation of clinical trial and protocol that can affect the quality of the data, which compromises the integrity of the study or may affect the safety and rights of trial participants;

Art. 7 The major responsibilities in this chapter include those set out in Good Clinical Practice, without prejudice to other legal and ethical accountabilities.

## Section I The Sponsor's Responsibilities

Art. 8. The sponsor is responsible for required information for the correct execution of DDCM throughout the range of researchers and skill centers, thus ensuring that the clinical trial is conducted according to the protocols and BPC.

Art. 9. The sponsor should utilize qualified professionals to supervise the overall conduct of clinical trials, to manage data, conduct statistical analysis and prepare reports.

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

Art. 11. The sponsor should maintain 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 in Brazil.

Sole paragraph. In case of discontinuation of clinical development or completion of application for registration is not achieved, the sponsor should maintain the clinical trial data in physical or digital file, for at least two (2) years after discontinuation of clinical development or formal conclusion of development.

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

Art. 13. The sponsor should ensure that the data obtained regarding safety and efficacy of the investigational medical product are sufficient to support human exposure by proposed means of administration, the chosen dosage, the duration of the proposed treatment and the population being studied.

Art. 14. The sponsor should ensure that the investigational product, modified comparator drug and placebo, when used, are manufactured according to GMP and are coded and labeled to protect blinding, if applicable, and characterized as products under clinical investigation.

Sole paragraph. In studies using active comparators, the sponsor must use those made in accordance with the GMP.

Art. 15. The sponsor is responsible for importing the necessary amount required to run the trial.

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

Art. 17. The sponsor is responsible for disposal of medications and products that have not been used in the clinical trial.

Art. 18. The sponsor should ensure the appropriate monitoring and auditing of clinical trials.

Art. 19. The sponsor shall immediately inform those involved in the trial if it is finished prematurely or suspended for any reason.

Art. 20. The sponsor may transfer its functions to a Clinical Research Organization CRO.

Paragraph 1. The transfer of what is contained in the caput does not remove the ultimate responsibility of the sponsor for the quality and integrity of clinical trial data.

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

## Section II

### The Investigator Responsibilities

Art. 21. The investigator shall conduct the trial according to the protocol agreed upon by the sponsor, with GCP, with regulatory and current and in force ethical requirements.

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

Art. 23. The investigator should allow for monitoring, audits and inspections.

Art. 24. The investigator must ensure appropriate medical care for trial participants regarding any adverse events related to the clinical trial, including clinically significant laboratory costs, without any onus on the participant.

Art. 25. The investigator should promptly inform the trial participants if the trial is finished prematurely or suspended for any reason, and ensure appropriate therapy and monitoring for participants.

Art. 26. The investigator is responsible for using the investigational product only in the clinical trial and should store them as specified by the sponsor and in accordance with applicable regulatory requirements.

## Section III

### The Investigator-Sponsor Responsibilities

Art. 27. In the case of a clinical trial developed by sponsor-investigator, the institution with which the individual is linked to is the primary sponsor.

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

Paragraph2 In the case of delegation of responsibilities and activities, a written authorization must be signed by the parties.

Paragraph3 The primary sponsor may not delegate quality assurance activities, audits and monitoring of clinical trials to investigator-sponsor, but can delegate them to a CRO.

Paragraph4 The primary sponsor shall submit its own or outsourced structure with at least the following units:

I - management of adverse events;

II - project management;

III - data management;

IV - training;

V - information technology;

VI - quality assurance and;

VII - monitoring.

Paragraph5 The institution referred to in the caput should be the one at which the trial will be held.

Paragraph 6. The major responsibilities in this article do not exclude the provisions of Sections I and II of this chapter on the sponsor and investigator responsibilities.

Art. 28. In the case of donation of medication already registered in Brazil for clinical testing, the donor will be the sponsor, if there is any agreement for transfer of ownership or ownership of the data obtained in donor research.

Art. 29. In the case of donation of medication not registered in Brazil for clinical testing, the donor shares the responsibilities of the sponsor.

## Section IV

### Structure of the Clinical Trial Center

Art. 30. The clinical trial center must have adequate facilities to conduct the protocol with regard to the physical structure, equipment, instruments and human resources, and also be consistent with the clinical trial population, for example, the elderly, children, persons with special needs, among others.



Art. 31. The management of the institution must be notified that the trial will be conducted.

### **Chapter III Requirements for submission of clinical medication development dossier (DDCM)**

Art. 32. The documentation in the DDCM should assure safety and rights of participants in all phases of clinical development, the quality of the investigational medicinal product and the data obtained in the clinical phases of development so that it may allow for evaluation of the efficacy and safety of the drug.

Art. 33. The DDCM may be presented to ANVISA at any stage of clinical development of the drug for one or more phases of clinical trials.

#### **Section I General Requirements for the Request**

Art. 34. The sponsor must submit a DDCM to ANVISA only if it intends to conduct clinical trials of medication in Brazil.

Sole paragraph. For analysis of the DDCM, at least one specific dossier must be filed for a clinical trial to be held in Brazil.

Art. 35. A Special Bulletin (SB) will be emitted through the DDCM mentioning all clinical trials to be conducted in Brazil.

Sole paragraph. Only clinical trials listed in the SB can be initiated in the country, respecting the other ethical approvals.

Art. 36. Upon receipt of the DDCM, ANVISA has ninety (90) days to evaluate.

Paragraph 1. If there is no response from ANVISA in ninety (90) calendar days after receipt of DDCM by ANVISA, clinical development can be started after the relevant ethical approvals.

Paragraph 2. In cases of non-manifestation, ANVISA will issue a document for Importation of Product(s) under investigation by the DDCM, will be presented at the location of unloading for import or export of product(s) under investigation, needed to conduct the clinical trial.

Paragraph 3 Not applying to the provisions of the caput and in Paragraph1 are clinical development submissions that fall into at least one of the following: national development, clinical development of biological products - including vaccines - and clinical development Phase I or Phase II. For these cases, the technical area will evaluate the DDCM within 180 (one hundred and eighty) days after receipt of DDCM by ANVISA and the clinical trial may be initiated only after approval by ANVISA.

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

Paragraph1 The party responsible for submitting the DDCM to ANVISA must be the same for all subsequent submissions related to this.

Paragraph2 Submissions by a CRO can only be made when the sponsor has no headquarters or subsidiary in Brazil.

Paragraph3 The DDCM of a sponsor-investigator should be done through the primary sponsor.

#### **Section II**

##### **Content and Request Format**

Art. 38. The DDCM submitted to ANVISA must include the following documents:

I - Application form duly completed, according to the model available on the ANVISA website;

II - proof of payment or exemption of payment of the Health Surveillance Inspection Fee by the Tax Liability Payment Form (GRU);

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

a) IFA or active substance;

b) category of medication (synthetic, organic, herbal or radiopharmaceutical);



- c) therapeutic class;
- d) means of administration;
- e) mechanism of action;
- f) indications to be studied;
- g) general objectives and the planned duration of clinical development; and
- h) information about phases, designs, outcomes, comparators, objectives, population to be studied, hypothesis/hypotheses, estimated number of participants and statistical design for each clinical trial planned.

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

- a) experimental drug;
- b) formulation;
- c) pharmacological and toxicological effects of the experimental drug in animals and in humans, where applicable;
- d) information on safety and efficacy in humans obtained from clinical trials that have already been carried out; and
- e) possible risks and adverse events related to experimental medications, based on past experience, as well as precautions or special procedures to be followed during development.

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

VI- information regarding the discontinuation of development or withdrawal of the experimental drug market of any country, for security reasons or lack of efficacy, if applicable. Those countries with discontinuation of access should be identified, as well as the reasons for interruption/withdrawal of the product;

VII - Experimental Drug dossier containing the following documents:

- a) description of the AFI or active substance, including:
  1. Physical and chemical characteristics, organoleptic and biological;
  2. name and address of the manufacturer;
  3. general method of obtaining;
  4. validated analytical methodology and acceptable ranges to assure identity, quality and purity; and
  5. Results of stability studies.
- b) description of the experimental drug, including:
  1. list of all active and inactive components with their respective functions, including those not present in the finished product;
  2. quantitative composition;
  3. General description of the manufacturing process and packaging with information about the capacity of the equipment;
  4. the analytical methodology and the acceptable limits as to ensure the identity; and
  5. Results of stability studies showing that the use of the investigational product in planned clinical trials.

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

1. composition;
2. organoleptic characteristics;
3. manufacturing process; and
4. analytical controls.

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

e) documentation referring to the transmissibility of the Transmissible Spongiform Encephalopathies (TSE), in accordance with current health conditions or justifications for the absence of this document;

- f) model(s) for label of product(s) under investigation;
  - g) critical analysis of non-clinical pharmacological and toxicological studies to ensure safety in performance of the proposed clinical development and information about location conducting these studies, as well as where records are available for inspection, including a statement that each study was conducted according to GLP compliance or justification for the absence. Description of the risks known about the experimental drug based on toxicological studies in animal models or in vitro tests, already conducted, or studied therapeutic class; risk/benefit related to the development plan;
  - h) critical analysis of already realized clinical trials, if applicable, including the basis for efficacy and safety. Description of already known risks about the experimental drug based on clinical trials already carried out or studied therapeutic class, evaluation of risk/benefit related to the development plan;
  - i) in the case of the experimental drug already on record in Brazil, only the information that supports the post-registration proposed changes must be submitted in the DDCM;
  - j) in the cases for in which the investigator-sponsor wishes to conduct a clinical trial with a drug that already has a DDCM approved by ANVISA, it may use the information already submitted by the holder of the initial DDCM, if agreed, without the need to resubmit all documentation. When authorization of the original holder is not presented, the investigator-sponsor shall submit to ANVISA all information through updated and indexed literature that supports the rational of the proposed development;
- VIII - Specific dossier for each clinical trial to be held in Brazil. These files must be filed as individual processes for each clinical trial. Each process should be linked to DDCM and submitted by the sponsor or CRO. The file should consist of the following documents:
- a) clinical trial application form duly completed, available on the website of ANVISA;
  - b) proof of payment or exemption, the Health Surveillance Inspection Fee by the Tax Liability Payment Form (GRU);
  - c) clinical trial protocol in accordance with GCP;
  - d) registration confirmation of the clinical trial in the data base of the International Clinical Trials Registration Platform/World Health Organization (ICTRP/WHO) or other recognized by the International Committee of Medical Journal Editors (ICMJE); and
  - e) Consubstantiated opinion of the Ethics in Research Committee (ERC) issued for the first clinical trial center to forward the protocol for analysis by the ERC

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

Paragraph1 Electronic documents should allow for text search.

Paragraph 2. The submission of electronic media applies to the adoption by ANVISA of information technology tools that allow the electronic submission of the requested documents.

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

Art. 41. ANVISA may at any time request other information it judges necessary for evaluation and monitoring of clinical development.

## **Chapter IV**

### **MODIFICATIONS TO THE DDCM**

Art. 42. Substantial modifications to the DDCM should be filed and shall await manifestation of ANVISA prior to implementation, according to the timetable set out in Art. 36.

Sole paragraph. Modifications to the DDCM must be submitted to ANVISA in the form of secondary petition attached to the DDCM protocol to which it is linked.

Art. 43. For purposes of this Resolution, substantial changes are:

I – inclusion of clinical study protocol(s) not previously established in the initial development plan,

II – exclusion of clinical study protocol(s)

III - alterations that potentially impact quality or safety of the investigational product, active comparator or placebo.

Art. 44. Modifications to the DDCM arising from recommendations or warnings issued by health authorities should be reported before they are implemented and may be executed, regardless of prior approval of ANVISA.

Art. 45. Modifications to DDCM not considered substantial must be submitted to ANVISA as part of the Safety Update Report of the development of the experimental drug.

## **Chapter V**

### **AMENDMENTS TO THE CLINICAL TRIAL PROTOCOL**

Art. 46. All amendments to a clinical trial protocol must be submitted to ANVISA, identifying the part of the protocol to be modified and their justifications.

Sole paragraph. Any amendment should be implemented only after obtaining ethical approval in accordance with current legislation.

Art. 47. Substantial amendments to clinical trial protocols must be filed and must await manifestation of ANVISA prior to implementation, according to the timetable set out in Art. 36.

Paragraph1 Substantial amendments shall be submitted to ANVISA in the form of secondary petition attached to the method of its clinical trial protocol to which it is linked.

Paragraph2 The petition of substantial amendments should contain the new protocol and the Opinion of the Ethics in Research Committee (ERC) issued for the first clinical trial center to forward the protocol for analysis by the ERC.

Paragraph3 Exceptions to the provisions in the caput of the amendments are those designed to eliminate immediate hazards to the safety of trial participants. These can be implemented and reported to ANVISA immediately.

Art. 48. For purposes of this Resolution, an amendment shall be sufficient if at least one of the following criteria is met:

I- change in the clinical trial protocol which affects the safety or physical or mental integrity of the participants;

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

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

## **Chapter VI**

### **SUSPENSION AND CANCELLATIONS**

Art. 50. The sponsor may cancel or suspend the DDCM or clinical trial at any time, provided that the appropriate technical and scientific justification is sent, as well as a follow-up plan for clinical trial participants.

Paragraph1 After canceling a specific DDCM, no clinical trials related to it can be continued in the country (Brazil).

Paragraph2 If a DDCM or clinical trial is canceled for safety reasons, the sponsor must technically and scientifically justify the reasons for the cancellation and outline measures to minimize/mitigate risk to clinical trial participants.

Paragraph3 The suspensions and clinical trial cancellations or of the DDCM must be submitted to ANVISA in the form of secondary petition attached to the respective file.

Art. 51. The sponsor shall notify the ANVISA regarding the decision to suspend or terminate a clinical trial of DDCM. After decision for suspension or cancellation, the sponsor must notify ANVISA within fifteen (15) calendar days.

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

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

Art. 53. Requests for reactivation of clinical trials protocols or suspended DDCMs should be sent to ANVISA, accompanied by justifications for trials to be restarted.

Sole paragraph. The clinical trial(s) and DDCM(s) will be restated only after approval by ANVISA.

Art. 54. ANVISA may, at any time, cancel or suspend the DDCM or any related clinical trial if it considers that the approval conditions are not met or if any safety or efficacy reports show significant effects on the trial participants or on the scientific validity of data, informing the sponsor of the reasons.

## **Chapter VII**

### **SECURITY AND ALERTS MONITORING**

#### Section I

##### The Adverse Event Monitoring

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

Art. 56. The sponsor or Independent Safety Monitoring Committee should systematically collect and evaluate aggregated data on adverse events occurring in the clinical trial, submitting the results of this assessment to ANVISA in the security update report in development of the experimental drug.

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

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

#### Subsection I

##### The Immediate Measures

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

Sole paragraph. In case of serious adverse event to be notified, the following must be stated: which measures have been taken, the action plan on new events of the same

nature, location data where treatment was, together with other data requested in the report form, especially those that allow the traceability of the event and the affected participant.

Art. 59. The notification of unexpected grave adverse events, whose causality is possible, probable or definite, independent of the Investigator's Brochure submission, amendments, or early end of the trial.

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

Sole paragraph. In cases where there is no constitution of Independent Safety Monitoring Committees there must be justification presented.

## Subsection II

### Communication of Adverse Events by Investigator

Art. 61. The investigator shall report the occurrence of any adverse events to the sponsor and must provide any requested information and must express their opinion regarding the causal link between the adverse event and the product under investigation.

Sole paragraph. Adverse events or abnormalities in laboratory test results that affect the safety of participants must be reported to the sponsor according to GCP and protocol.

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

## Subsection III

### Adverse Events Reporting by Sponsor

Art. 63. The sponsor shall notify ANVISA, through a specific electronic form, of unexpected serious adverse events occurring in the country, in which causality is possible, probable or defined for the product under investigation.

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

Art. 64. The sponsor should inform the researchers involved in the clinical trial about serious unexpected adverse events, in which causality is possible, probable or definite, and adopt procedures for updating of the investigator's brochure, in addition to re-evaluating the risks and benefits to participants.

## Subsection IV

### Deadlines

Art. 65. The investigator shall inform the sponsor of serious adverse events within 24 (twenty four) hours of the event being discovered.

Art. 66. The sponsor should ensure that all relevant information on adverse events referred to in Art. 63 that are fatal or life-threatening are documented and reported to ANVISA, through electronic form in no more than seven (7) days starting from the date of knowledge of the case by the sponsor.

Sole paragraph. The additional information on the monitoring of adverse events mentioned in the caput should be included in the application up to eight (8) calendar days from the date of notification.

Art. 67. All other adverse events that are unexpected, serious, whose causality is possible, probable or definite for the products under investigation should be reported to ANVISA within 15 (fifteen) calendar days from the date of knowledge of the case by the sponsor.

## Section II

### Accompanying Reports

#### Subsection I

##### Reports on Monitoring Clinical Trials Protocols

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

I- title of the clinical trial;

II- protocol code;

III- status of participants recruited for clinical trial;

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

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

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



Paragraph 1 The Annual clinical trial protocol monitoring report should be submitted to ANVISA in the form of secondary petition attached to the respective protocol process to which it is linked.

Paragraph 2. The annual report shall be filed within sixty (60) calendar days, from the beginning of the trial date in Brazil.

Art. 69. Upon completion of the activities of a clinical trial in all participating countries, for whatever reason, the sponsor shall submit a final report to ANVISA, containing least the following information:

I- title of the clinical trial;

II protocol code;

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

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

V- demographic description of participants recruited for clinical trial;

VI-statistical analysis;

VII- number and description of protocol deviations and violations;

VIII relating of all adverse events and laboratory abnormalities with causality assessment, occurring in participants;

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

X-rationale for the early termination of development in Brazil or elsewhere in the world, where applicable.

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

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

## Subsection II

Security Update Report for development of the investigated product

Art. 70. The sponsor must submit to ANVISA annual safety update reports on the development of the experimental drug.

Sole paragraph. The annual report must be filed within a maximum of sixty (60) calendar days starting from the DDCM approval date by ANVISA or determined date in international development.

## **Chapter VIII**

### **INSPECTIONS**

#### Section I

##### Inspections to verify Good Clinical Practice compliance

Art. 71. In order to ensure the protection of the rights, safety and wellbeing of participants in addition to ensuring accuracy and reliability of the data to be obtained or submitted for health registration, ANVISA may carry out GCP inspections in clinical trials centers, sponsors, CRO, laboratories and other institutions involved in the development of the experimental drug to verify level of compliance of current Brazilian legislation and compliance with GCP, and to ensure the rights and duties concerning the scientific community and the State.

Paragraph1 Inspections in GCP will follow the harmonized guidelines in the Document of the Americas, Manual of Good Clinical Practices of the International Conference on Harmonization (Document E6) and specific GCP inspection standards published by ANVISA.

Paragraph2 Depending on the outcome of the GCP review, ANVISA can determine:

I- temporary interruption of the clinical trial;

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

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

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

#### Section II

##### Inspections to verify compliance of Good Practice Manufacture of Products under Investigation

Art. 72. ANVISA may carry out inspections in BMP of the experimental drug or product under investigation produced or modified by the sponsor in order to verify the chemical information, production and quality control in DDCM and to report if the drug is safe enough to administer to trial participants.

## **Chapter IX**

### **IMPORTATION**

Art. 73. The importation of the products under investigation for exclusive use in a clinical trial should be subject only to inspection/regulation by the sanitary authority in the location of unloading.

Sole paragraph. Exceptions are investigated products subject to special control that have, in addition to monitoring in the location of unloading, must have prior authorization of shipment by the responsible technical area at ANVISA.

Art. 74. The following documents must be submitted after the arrival of the product under investigation in the country (Brazil):

I - copy of the Special Bulletin (SB), Special Specific Communication (SSB) or Document for Importing of Product (s) under investigation by DDCM issued by the competent technical area of ANVISA in its headquarters;

II - in the case of imports made by a body other than the holder of DDCM, a copy of the document of delegation of responsibilities for importation must be submitted;

III – term of responsibility for imports intended for clinical research provisions in health regulation of goods and imported products;

IV - embedded copy cargo knowledge; and

V – copy of commercial invoice.

Art. 75. The competent health authority for the product under investigation being unloaded will verify compliance with the packaging instructions, transport and storage, according to specific information in the SB, SSB, or Document for Importing Product(s) under the DDCM, subsidiary alternative to those provided by the manufacturer or sponsor.

Sole paragraph. The external or shipping containers used for shipping the products referred to in this Chapter shall include:

a) SB number, SSB number or Document for Importing Product (s) under investigation by the Drug Clinical Development Dossier (DDCM) to which the investigational product is subject;

b) amount of imported material;

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

d) information on physical form or pharmaceutical form referring to the presentation of the product;

e) information on the validity of the product and, where applicable, the medical device; and

f) lot number or serial number.

Art. 76. The qualitative information and specifications of the products under investigation for use in clinical trials will be reported in the Special Bulletin (SB), the Specific Special Bulletin (SSB) and in the Document for Importing Product (s) under investigation in the DDCM.

Sole paragraph. In case of change of purpose of products investigated and its specifications informed the SB, SSB or in the Document for Importing Product(s) under investigation by the Drug Clinical Development Dossier (DDCM), this must be reported to the competent technical area of ANVISA at its headquarters. SB, SSB or Document for Importing Product (s) under investigation in the DDCM date must be presented at clearance site.

Art. 77. The entry of a products into the country for products under investigation that are not in accordance with the SB, SSB or Document for Importing Product (s) under investigation by the DDCM for the purpose of clinical trials regulated by this resolution is strictly prohibited.

Sole paragraph. Any change in purpose of imported goods and products mentioned in this resolution is strictly prohibited.

## **Chapter X**

### **TRANSITORY PROVISIONS**

Art. 78. The approval processes for clinical trials protocolled/filed at ANVISA that predate the publication of this resolution and are still awaiting technical analysis will be assessed in accordance with the resolutions in force at the time of protocol submission.

Paragraph1 Petitions that are awaiting analysis and are within the scope of 90 (ninety) days as provided by Art. 36 of this Resolution, may commence clinical trials after the deadline contained in that referred to article and after the relevant ethical approvals.

Paragraph2 For the cases referred to in Paragraph1, will be issued a SSB will be issued for the purposes of import or export, according to the current resolution at the time of the submission protocol at ANVISA.

Paragraph3 The time frame established by Paragraph 3 of Art. 36 does not apply to consent for those awaiting technical analysis and is found in the caput of this article.

Art. 79. In filing a DDCM, the holder shall link all approval processes for consent in clinical trials related to experimental drug trials they have already been submitted for assessment by ANVISA at some moment.

Art. 80. The approval processes for clinical trials already approved by ANVISA must comply with the current resolution at the time of its approval, so that the process is inserted in a DDCM, if applicable.

## **Chapter XI**

## **FINAL PROVISIONS**

Art. 81 ANVISA publishes guides and manuals to assist in the following specific procedures related to this Resolution.

Art. 82. Failure to comply with the provisions of this Resolution is considered a health violation, with the offender subject to penalty as provided by Law No. 6437 of August 20, 1977.

Art. 83 Omissions will be resolved in consideration of other national and international guideline standards.

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

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

JAIME CÉSAR DE MOURA OLIVEIRA