Inspection Guide on Good Clinical Practices (GCP) on clinical trials with drugs and biological products - Inspection in Sponsors and Clinical Research Organizations (CRO)

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Inspection Guide on Good Clinical Practices (GCP) on clinical trials with drugs and biological products - Inspection in Sponsors and Clinical Research Organizations (CROs)

EFFECTIVE AS OF 27/Jan/2022

This Guide expresses Anvisa's understanding of the best practices in relation to procedures, routines and methods considered adequate to comply with technical or administrative requirements required by the Agency's legislative and regulatory frameworks.[1]

It is a non-normative regulatory instrument, of a recommendatory and non-binding nature, therefore, it is possible to use alternative approaches to the propositions provided herein, as long as they are compatible with the requirements related to the specific case. Failure to comply with the content of this document does not characterize a health violation, nor does it constitute a reason for rejecting petitions, provided that the legislation requirements are met.

The recommendations contained in this Guide take effect from the date of their publication at Anvisa Portal.

[1]Ordinance No. 162, of March 12, 2021, which provides for guidelines and procedures for improving regulatory quality at the Brazilian Health Regulatory Agency (Anvisa).

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ABBREVIATIONS

ANVISA – Brazilian Health Regulatory Agency
GCP – Good Clinical Practices
CAPA – Corrective actions, preventive actions
CE – Special Notice
IEC – Independent Ethics Committee
CONEP – National Independent Ethics Committee
COPEC – Clinical Research Coordination for Drugs and Biological Products
CRF – Case Report Form
ICH – International Council for Harmonization
IN – Normative Instruction
IVRS - Interactive Voice Response System
IWRS – Interactive Web Response System
CRO – Clinical Research Organization
SOP – Standard Operating Procedure
RDC – Collegiate Board Resolution

1. SCOPE

This guide deals with the procedures for conducting an inspection in Good Clinical Practices (GCP) regarding clinical trials with drugs and biological products in sponsors and Clinical Research Organizations (CROs). The guide is intended for everyone who is involved in clinical trials, including sites, sponsors, Clinical Research Organization (CRO) and Anvisa inspectors.

2. INTRODUCTION

Good Clinical Practices (GCP) constitute an international standard of scientific and ethical quality for planning, conducting, performing, monitoring, recording, analyzing clinical trials reporting and auditing, which provides assurance that the data and results reported have credibility and accuracy, and that the rights, integrity and confidentiality of clinical trial subjects are protected, in accordance with the GCP guidelines set out in the Document of Americas and the International Council for Harmonisation - ICH Good Clinical Practices Guide (Document E6 (R2)).

The GCP inspections, which are foreseen in RDC No. 09, February 20, 2015, Chapter VIII, Article 71, have as main objectives to verify the rights protection of clinical trial subjects, the degree of compliance with current Brazilian legislation and compliance with GCP, and the quality of data generated in clinical trials. Inspections can be performed at any location where study activities are conducted, including clinical trial sites, sponsor, Clinical Research Organization (CRO), laboratories, and other institutions involved in the experimental drug development.

The Clinical Research Coordination for Drugs and Biological Products (COPEC) is the area responsible for conducting GCP inspections of clinical trials related to drugs and biological products and actions arising, according to point b, item I of Article 130-A of the Internal Rules of Anvisa (RDC No. 303, September 13, 2019).

This guide describes how Anvisa conducts GCP inspections in clinical trial sites, based on the Normative Instruction (IN) in force No. 20, October 2, 2017, in order to harmonize and guide all those involved in the inspection procedures, ensuring this forms a unified standard and the safety of all parties involved.

Throughout the text, the term "shall" is accompanied by the legal basis to which it refers (section 3 of this guide). E.g.: *The inspection shall*[3.5 (Art.5)] *take place within a maximum of five (5) business days.* In this case, item 3.5 is Normative Instruction 20/2017, therefore, the term refers to Article 5 of Normative Instruction 20/2017. For cases where there is no legal reference, the term "shall" can be interpreted as a recommendation.

3. LEGAL BASIS

3.1 Law No. 9,782, January 26, 1999, which defines the Brazilian National Health Surveillance System, creates the Brazilian Health Regulatory Agency, and provides other measures.

3.2 Law No. 6,437, August 20, 1977, which configures violations of federal health legislation, establishes the respective sanctions, and provides other measures.

3.3 Collegiate Board Resolution (RDC) No. 303, September 13, 2019, which approves and promulgates the Internal Rules of the Brazilian Health Regulatory Agency - Anvisa.

3.4 Collegiate Board Resolution (RDC) No. 9, February 20, 2015, which provides for the regulation for conducting clinical trials with drugs in Brazil.

3.5 Normative Instruction (IN) No. 20, October 2, 2017, which provides for inspection procedures in Good Clinical Practices for clinical trials with drugs.

3.6 Good Clinical Practices: ICH harmonised tripartite guidelines. Guideline for Good Clinical Practice E6 (R2). Current Step 4 version, 09 Nov 2016.

3.7 Good Clinical Practices: Document of Americas - IV Pan American Conference for the Harmonization of Pharmaceutical Regulations. March 2-4, 2005.

3.8 Collegiate Board Resolution (RDC) No. 449, December 15, 2020, which amends Collegiate Board Resolution - RDC No. 9, February 20, 2015, which approves the regulation for conducting clinical trials with drugs in Brazil.

3.9 Resolution of the National Health Council (CNS) No. 251, August 7, 1997, which approves the standards for research involving human beings for the thematic area of research with new drugs, medicines, vaccines and diagnostic tests.

3.10 Resolution of the National Health Council (CNS) No. 466 of December 12, 2012, which approves guidelines and regulatory standards for research involving human beings.

3.11 Operational Standard No. 001/2013 of the National Health Council (CNS), which provides for the organization and functioning of the IEC/CONEP System, and on the procedures for submission, evaluation and monitoring of research and development involving human beings in Brazil, in terms of item 5, Chapter XIII, of CNS Resolution No. 466, December 12, 2012.

4. SCOPE OF INSPECTION

Inspections in GCP may be performed before, during or after conducting the clinical trial and will be classified as routine inspection or complaint/suspected irregularity, as described in IN No. 20/2017.

5. INSPECTION TEAM AND DURATION

According to IN No. 20/2017, the GCP inspection will be performed by Anvisa's permanent staff, duly identified and qualified, respecting the attributions and competencies inherent to the said positions.

There will be at least 2 (two) inspectors, one being the lead inspector, who will be the focal point for communication with the inspected one.

The inspection shall[3.5 (Art.5)] take place within a maximum of five (5) business days. Exceptionally, this period may be altered with due justification.

Inspection can take place either in person or remotely[3.8 (Art. 71)].

6. SELECTION CRITERIA FOR THE CLINICAL TRIAL(S) AND THE LOCATION TO BE INSPECTED

The following are the most commonly used criteria for selecting the clinical trial and the sponsor/CRO to be inspected. However, this list is not exhaustive. Other selection criteria may be used by COPEC, as needed.

The selection of the site to be inspected is based mainly on the following criteria:

- Preference for national sponsors, since they are usually inspected only by Anvisa;
- CROs that work with many national sponsors;
- International sponsors and CROs, but which have not been inspected by other international agencies and institutions with recognized experience in the area of GCP inspections;
- Results of previous inspections;
- Demand from other areas of Anvisa;
- Report.

In sponsor/CRO inspection, more than one clinical trial may be selected, depending on the inspection objective. The selection of the trial(s) is based mainly on the following criteria:

- Studies not inspected internationally by other regulatory agencies;
- Studies with populations considered vulnerable, such as pediatric, elderly, Indians, people with disabilities;

- Studies evaluated as complex by COPEC (for example, studies with many procedures per visit, handling of experimental drug in an unusual way, etc.);
- Studies whose experimental drug is strategic for the country, such as for the treatment of diseases with an endemic profile or that have a socioeconomic impact;
- Studies initiated as provided for in Paragraph 1, Article 36 of RDC 09/2015;
- Results of previous inspections performed by Anvisa;
- Demand from other areas of Anvisa;
- Report.

7. INSPECTION STEPS

7.1. Before inspection

7.1.1. Inspection Notification

For each inspection, an administrative process (11407 - Health Investigation Dossier) will be instructed, which will contain all documentation related to the inspection. The inspection notification will be made by means of an Electronic Letter to the responsible sponsor or CRO.

Communications between Anvisa and sponsor/CRO or site about the inspection may also be made by inspection email inspecaobpc@anvisa.gov.br.

As described in Article 2 of IN No. 20/2017, if it is a routine inspection, the sponsor/CRO will be notified at least 15 (fifteen) calendar days in advance. In case of complaint or suspicion of irregularities, the inspection will take place without prior notice.

7.1.2. Request for prior documentation

In the inspection notification letter or email, the company is first asked for a list of all clinical trials conducted in Brazil in recent years. The number of years will depend on the inspection objective. In this notification, the company must[3.4 (Art.41)] fill in an electronic spreadsheet (according to the model in Annex 1a or 1b) containing the clinical trial details, such as the study title, number of CE issued by Anvisa, study phase, current study status, start and end date of the study (if applicable), number of sites in Brazil, total number of screened and randomized subjects in Brazil, name of the sponsor (in cases of inspection in CRO), name of CRO (in cases inspection on a sponsor who has hired an CRO) and activities delegated by the sponsor to the CRO, if applicable.

Upon receipt of the spreadsheet, inspectors select one or more clinical trials and send a new notification to the company, requesting some documents to assist in conducting the inspection. The following list is an example of what is usually requested. However, the list can be changed as needed.

General documents

I. General organization chart of the company, listing the department and name(s) of the person(s) responsible.
II. Detailed organization chart of activities related to clinical research, listing the department, brief summary and name(s) of the person(s) responsible. Include external contracted services in this organization chart (for example: statistical department, database, drug deposit, file)
III. List of Standard Operating Procedures (SOPs) of the company, related to the conduct of clinical trials. Inform the reference number, title, version and effective date.

Documents for each clinical trial selected for inspection

IV. List of all computerized systems used to conduct clinical trials (for example, database, CRF and IVRS/IWRS), even if *outsourced*.
V. List of study activities with the respective person in charge.
VI. List of study activities performed by third parties hired by the sponsor/CRO, if applicable, with the name of the company and those responsible for the activities.
VII. All the study protocol versions and amendments.
VIII. List of all study manuals provided by the sponsor or prepared by the CRO.
Example: manual of the central laboratory, of central radiology, of filling out the case report form (CRF), of IVRS (randomization system), etc.
IX. All versions of the investigator's brochure
X. All versions of the Informed Consent Form with the highlighted changes, including the specific versions of the site, if applicable.
XI. Responsibility delegation form for each site, if applicable.
XII. List of SOPs relevant to the study (title and version) provided by the sponsor/CRO.
XIII. Electronic spreadsheet with the number of subjects screened, screening failures, randomized, active, discontinued patients and patients who completed the study, for each Brazilian site and the study total, including justifications for the subjects considered as screening failure and discontinued. (Model of Annex 2)
XIV. Date of the first visit of the first screened subject and the last visit of the last randomized subject to all Brazilian sites. This information can be included in the spreadsheet described in item XIII. (Model of Annex 3)
XV. Electronic spreadsheet with all Serious Adverse Events that occurred in Brazil and worldwide, containing the subject's number, name of SAE, start and end date of the event, outcome (if applicable), relationship with the study drug, severity criterion (ex: death, hospitalization), action taken and if expected or not. (Model of Annex 4)
XVI. Contract between sponsor and CRO (financial aspects can be obliterated), if applicable.
XVII. Information about the CRF format (paper or electronic) and a blank model of CRF.
XVIII. All versions of the Monitoring Plan used in the study, with the changes highlighted

XIX. Monitoring reports from all sites, including the selection, initiation and closure visit, if applicable.
XX. Central laboratory information, if applicable: list of parameters analyzed, reference values and quality certificates
XXI. All submissions and ethical approvals from each site, list of IEC members and IEC registration at CONEP (or registration status, when registration renewal is not yet available). For submissions and approvals, a printscreen of Plataforma Brasil is sufficient.

The models included in Annexes 1 to 4 are optional and do not necessarily need to be used.

The electronic spreadsheets mentioned in items XIII and XV are control spreadsheets that can be prepared/generated by the sponsor/CRO. The objective of these spreadsheets is to facilitate the inspection preparation. When it is not possible to generate electronic spreadsheets, pdf reports with an active copy/paste function can be sent.

These documents shall[3.4 (Art.41)] be forwarded to Anvisa by Electronic Addition to the Health Investigation Dossier (informing the file number and date for the inspection email). The deadline for sending documents is usually 2 to 3 weeks, depending on the complexity of the requested documentation.

It should be noted that, before the inspection begins, Anvisa inspectors shall[6 (5.1.2)] have access to all the computerized systems used, or their data, if the systems are disabled due to the fact that the studies are closed.

7.1.3. Inspection preparatory meeting

Prior to the inspection, inspectors will be able to schedule a virtual meeting with the inspected party to align the inspection logistical details.

7.2. During the inspection

The inspection process is usually composed of the following steps:

- Opening meeting,
- Visit to facilities,
- Interview with the study team,
- Document analysis (including verification of computerized systems),
- Closure meeting.

7.2.1. Opening meeting

Inspection begins with the opening meeting and is conducted by the lead inspector. The meeting begins with the presentation of all those present.

The inspector informs the objectives, scope, planning (schedule) and the inspection main stages, in addition to the reasons for choosing the sponsor/CRO and the clinical trial(s) for the inspection, in the case of routine inspection. In the case of a complaint inspection, the inspected is informed that it is a complaint inspection, but the reason and the complainant are not disclosed.

The sponsor/CRO gives a brief description of the company and status of each clinical trial to be inspected.

During the meeting, inspectors sign a “Declaration on Absence of Interest Conflict and Confidentiality” before all subjects. This declaration is a model developed by Anvisa. If the sponsor/CRO also requires a declaration signed in its own model, inspectors may sign all the declaration models. The inspectors will keep a copy of any other declaration that is signed.

A member of the study team must be appointed to accompany the inspectors throughout the inspection process.

The attendance list prepared by Anvisa must be signed by all those present.

At the opening meeting end, the inspectors will deliver a document request form, which will be used as a tool to control the documents requested during the inspection, including the copies obtained to be taken by the inspectors to Anvisa.

During the inspection, inspectors must be in a separate room from the sponsor/CRO team and with internet access.

7.2.2 Visit to the facilities and document analysis

The visit to the facilities and the document analysis will be performed based on the items described in section 8 of this guide.

7.2.3. Interviews

Professionals involved in writing activities and developing the protocol and investigator's brochure, developing the statistical analysis plan, managing and monitoring clinical trials, quality system, reporting adverse events/pharmacovigilance, files, contracts, database management and other activities applicable to each company will be interviewed and questioned in relation to any

clarifications or doubts arising during the inspection. These interviews may be conducted remotely, as needed.

7.2.4. Closure meeting

At the inspection end, the team of inspectors will hold the closure meeting, in which the non-conformities found during the inspection will be informed. At this time, inspectors will not classify or discuss the findings. The findings classification will be informed in the inspection report.

During the meeting, post-inspection procedures and deadlines will also be clarified. The meeting will be conducted by the lead inspector.

The attendance list must be signed by all those present.

7.3. After inspection

After the inspection, the team of inspectors will prepare the Inspection Report within 60 (sixty) calendar days, which will be sent to the Sponsor/CRO of the study via electronic letter and to PI, by email.

The findings found during the inspection will be listed in the report and will be classified, according to Article 12 of IN No. 20/2017, in observations:

- **Critical:** findings directly related to the safety of the research subject, which may result in death, risk of death or unsafe conditions; when related to the study data, may compromise its validity, such as studies conducted without authorization, tampering, lack of information or falsifications
- **Major:** findings that may result in a risk to the research subject health or data invalidation
- **Minor:** findings that do not fit critical or larger observations, but indicate deficiency and/or deviation; such findings shall be cited for the objective of implementing improvements in the conduct of studies
- **Informative:** descriptive and/or complementary findings

For each finding, appropriate references to the Document of Americas or International Council for Harmonisation (ICH E6 (R2)) and local legislation will be listed.

After receiving the inspection report, the Sponsor/CRO will have 120 calendar days to manifest, according to Article 8 of IN No. 20/2017.

The answer to each critical or major finding must be given by identifying the root cause and proposing corrective and preventive actions (CAPA) with the estimated deadlines and those responsible for each action. In addition, the impact and risk of the finding should be assessed for the

entire study and not just for the inspected site, as applicable. For minor findings, only corrective actions need to be sent to Anvisa.

The following is an example of an answer:

<table>
<tr><td colspan="3">Finding #XX</td></tr>
<tr><td colspan="3">Clarification</td></tr>
<tr><td colspan="3">Root cause</td></tr>
<tr><td colspan="3">Impact/risk of the finding for all company studies</td></tr>
<tr><td>Corrective action</td><td>Responsible</td><td>Deadline</td></tr>
<tr><td>Preventive action</td><td>Responsible</td><td>Deadline</td></tr>
</table>

To support each response given to the critical or major finding, the sponsor/CRO must attach the evidence justifying the response. For example, if the preventive action for the finding was the elaboration of a SOP, this SOP must be sent to Anvisa together with the response.

It is important to correct not only the items mentioned in the finding, but also to correct the deficiency of the identified root cause.

The response to the inspection report must be sent as an Electronic Addition to the Health Investigation Dossier to Anvisa. As soon as it is petitioned, the sponsor/CRO must inform the file number and the filing date to the email inspecaobpc@anvisa.gov.br.

After the Sponsor/CRO's manifestation, the inspectors' team will review the response and collectively decide on the GCP compliance in the study. New questions may be asked to the inspected. At the evaluation end, Anvisa will issue the Inspection's Final Opinion, which will be forwarded via letter (or email) to the sponsor/CRO. The deadline for sending the final opinion is up to 30 days, counted from the receipt date of the response to the inspection report. In exceptional cases, this period may be extended with appropriate justification.

The final opinion will contain the decision on compliance with the GCP, which may be:

- **Compliant with GCP:** Compliance with GCP does not mean that no findings have been found or no action has been required. However, the observations found were corrected or did not critically affect GCP, not leading to the determinations described in the following item.
- **Non-compliant with GCP:** Not being in compliance with the GCP means that, after evaluating the response to the findings identified in the inspection, Anvisa's conclusion is that the study was not conducted in accordance with the GCP. In case of non-compliance with the GCP, Anvisa may, according to Article 11 of IN No. 20/2017, determine:

I - the temporary interruption of the clinical trial;
II - the definitive cancellation of the clinical trial;
III - the definitive cancellation of the clinical trial in all sites in Brazil; or
IV - the data invalidation from the site concerned or the clinical trial.

Of note, systemic findings may have repercussions in clinical studies that were not evaluated during inspection.

A new inspection can be performed to evaluate the CAPA implementation, if necessary.

8. ITEMS TO BE CHECKED IN SPONSORS OR CROs

This section lists items that inspectors generally check during a sponsor/CRO inspection. However, depending on the inspection focus, not all items will be evaluated, or it may be necessary to check items that are not mentioned herein.

It is important to note that the sponsor is responsible for ensuring that clinical trials are in compliance with GCP and local regulations. According to items 5.2.1 and 5.2.2 of the ICH E6 (R2) guide, a sponsor can transfer any or all of the sponsor's tasks and functions related to the clinical trial to CRO, but the ultimate responsibility for the quality and integrity of the research data is of the sponsor. CRO must implement quality assurance and quality control. These procedures must be documented in writing before the study begins.

8.1. Organization and team

The objective of this item is to assess whether the company organization is able to guarantee the proper conduct of clinical trial activities and whether it has a sufficient number of qualified and trained employees in each area.

The following items can be checked, among others:

a. Organization chart of the company, containing all departments, functions and those responsible for each area in Brazil.
b. Organization chart and team assigned to each clinical trial inspected in Brazil.
c. Quality department, as an independent department.
d. Roles description, qualifications and training for each employee involved in any stage of the clinical trial.

e. List of employees participating in the clinical trial(s) selected for inspection, containing name, title, position in the study, date of entry and exit from the study (if applicable), signature and initial (manual or electronic).
f. Procedures for changing employees during a clinical trial.

8.2. Infrastructure

The objective of this item is to identify and assess whether the company's infrastructure is suitable for conducting clinical trials.

The following items can be checked, among others:

a. File room, where the company's documentation and clinical trials are stored. The following will be evaluated, among others:
   1. Identification and organization of file folders
   2. Adequate structure for document storage
   3. Controlled file access
   4. Procedure for archiving and withdrawing documents
   5. Action plan/contingency plan in cases of fire, flood and pests
   6. Archiving after clinical trials are completed

b. Location where the experimental drug and clinical trial supplies are stored. The following will be evaluated, among others:
   1. Controlled access
   2. Temperature and humidity control
   3. Contingency plan in the event of a power outage
   4. Segregated and duly identified location for the investigational products of each study to enable the products to be stored in a logical manner, allowing for prompt, agile location and without the possibility of errors in separation and dispensing.
   5. Segregated location for quarantined products, returned, expired or separated for destruction

c. Computerized systems. The following will be evaluated, among others:
   1. Purpose of using the system
   2. Procedures for creating, modifying, deleting, maintaining or transmitting electronic records
   3. Presence of an audit trail to identify any data entry and changes in the system
   4. Presence of *backup*, data recovery or contingency plan to avoid data loss (including in cases of software updates)
   5. Procedures for handling the electronic record after closing the study
   6. System validation, based on references such as PIC/S Guidance PI 011-3: Good Practices for Computerized Systems in Regulated GXP Environments, 2007.
   7. Access to system
   8. Manuals and training on how to use the system

8.3. Operating procedures

During the inspection, it will be assessed whether the company's procedures ensure proper conduct of clinical trials and in accordance with GCP and local regulations.

Adherence to the procedures will be verified, by sampling, through the clinical trials selected for inspection.

8.3.1. Implementation and finalization of clinical trials

The objective of this item is to evaluate the procedures established for the implementation and completion of a clinical study.

The following items can be checked, among others:

a. Document preparation: protocol format, content and distribution, protocol amendments, documents related to informed consent, investigator's brochure, CRF and any other document related to the clinical trial.
b. Document approval procedure.
c. Procedure for ensuring compliance with regulatory requirements, such as obtaining ethical approval by IEC/CONEP and regulatory approval by Anvisa.
d. Selection, training and monitoring of investigators.
e. Selection, training, and monitoring of the sponsor/CRO team, including managers and monitors.
f. Comparison of critical dates: approval by IEC/CONEP, approval by Anvisa, study start, start date of each site, recruitment period, closure of sites, end of the study.
g. Applicable contracts signed.
h. Procedures for closing the study.

8.3.2. Clinical trial management

The objective of this item is to evaluate the system established for the clinical trials management.

The following items can be checked, among others:

a. Management/supervision of all activities related to conducting clinical trials.
b. Handling major problems, deviations and violations of protocol, GCP and local regulations (including root cause investigation).
c. Sponsor/CRO control procedure to ensure that all applicable ICFs were obtained by study subjects.
d. Procedure to ensure that all ethical/regulatory approvals were obtained throughout the study (e.g., amendments, new versions of ICFs, serious adverse events).
e. Systems used to control and manage the studies, including an appropriate system for recording violation/protocol deviations and problems/pending issues raised during the study (including the corrective and preventive measures adopted).

8.3.3. Monitoring

The objective of this item is to evaluate the system established for monitoring clinical trials.

The following items can be checked, among others:

a. Procedure for planning, frequency, extent and nature of monitoring activities.
b. Procedure for content, processing and monitoring of follow-up reports.
c. Monitoring plans used for the inspected clinical trials.
d. Corrective actions from monitoring visits.
e. Communication flow between monitor and superior staff for the treatment of critical findings.

8.3.4. Experimental drug

The objective of this item is to verify that the sponsor/CRO procedures for the different stages of the experimental drug life cycle are in accordance with the GCP.

The following items can be checked, among others:

a. Procedure to ensure the integrity of the experimental drug from manufacture to receipt at clinical trial sites.
    1. Evaluation of batch analysis certificates
    2. Evaluation of storage and transport conditions
    3. Procedure for the experimental drug release, after receipt by the sites
    4. Evaluation of packaging and labeling
    5. Comparison of labels used x labels approved by Anvisa
    6. Recall and re-labeling procedure
b. Experimental drug accounting, including shipping, return and destruction information.
    1. Evaluation of the experimental drug inventory
    2. Comparison between physical stock vs. accounting records
c. Procedures for randomization, blinding and unblinding.

8.3.5. Sample management

The procedures established for managing samples obtained from clinical trials can be verified, including transportation, receipt, storage, processing, analysis, reporting of results and final disposal of the samples.

8.3.6. Safety report and adverse events

The objective of this item is to verify procedures for reviewing and reporting findings that may adversely affect the safety of subjects, and to verify procedures for reporting serious adverse events to regulatory agencies, investigators and IECs.

The following items can be checked, among others:

a. Identification and monitoring by the investigator or sponsor/CRO of an adverse event, serious adverse event, or unexpected and serious adverse drug reaction.
b. Procedure for assessing the causality between the adverse event and the investigational product.
c. Immediate notification to Anvisa of serious and unexpected adverse events, possibly/probably/definitely related to the investigational product that occurred in the national territory and notification of adverse drug reactions to investigators.
d. Comparison between the events reported in the study x events notified to Anvisa, according to RDC 39/2008 or RDC 09/2015.
e. Notification of serious adverse events by investigators to the IEC and the sponsor.
f. Management of serious adverse events reported by investigators, including sponsor/CRO procedures for receiving, evaluating, and monitoring events.
g. Safety updates (including update of the investigator's brochure) and periodic safety reports, including verification of the need to update the ICF.
h. Communication of safety updates to investigators, IECs (through investigators) and Anvisa.
i. Procedures for interrupting the development or withdrawal of the experimental drug from any country on the market, for reasons of safety or lack of efficacy.
j. Full availability (24 hours, 7 days a week) of the team responsible for the safety aspects of the experimental drug in the clinical trial.

8.3.7. Data collection and treatment

The objective of this item is to assess the system established by the sponsor/CRO for collecting and processing data obtained during clinical trials and their reporting in the clinical trial report, if applicable.

In the Case Report Form (CRF), the following items may be evaluated, among others:

a. CRF design
b. Elaboration and validation of database
c. Data entry and cleaning
d. Closure of database
e. Data reconciliation
f. Access profile

For each study inspected, a sample of the CRF pages will be selected to assess:

g. Protocol adherence
h. If the data is complete, legible and filled in the expected time
i. CRF corrections and audit trails
j. Comparison of dates of the first and the last subject included with the start and end dates of the study as well as with the sending of the experimental drug

For data processing, the following items may be checked, among others:

k. Procedure to ensure the integrity of data collected from clinical trial sites
    1. Evaluation of data processing, data analysis and control procedures
    2. Audit trails (for both paper and electronic systems)
l. Procedures for preparing the clinical trial report
m. Data management
n. Statistical analysis (as established in the protocol)
o. Content of the clinical trial report and review process
p. Quality control applied to data processing

8.3.8. Quality Assurance

The objective of this item is to verify that the sponsor/CRO has a system that manages quality at all stages of a clinical trial.

The following items can be checked, among others:

a. Audits for critical clinical trial processes, including monitoring activities, data management, safety reporting, preparation of the clinical trial report, archiving and validation of computerized systems.
b. Audit in contracted/subcontracted services.
c. Communication process and addressing audit findings, including format and distribution of audit reports.
d. Procedures to deal with GCP adherence problems that are serious or recurring.
e. Procedures for preparing and implementing audit programs/plans.
f. Audit reports, if applicable.
g. Qualification of auditors.

In addition, the operation of the company's quality system in relation to the management of SOPs will be verified. The following items will be checked, among others:

h. Preparation of SOPs
i. Maintenance of SOPs, including periodic review
j. Master list of SOPs
k. List of applicable SOPs for each inspected clinical trial

8.3.9. Delegation of activities

The objective is to verify the procedures related to contracted/subcontracted services related to clinical trials.

The following procedures can be verified, among others:

a. Prior selection and continuous evaluation of contracted/subcontracted services.
b. Documentation on the service delegation, including the contract/agreement signed.
c. Treatment of amendments to the contract.
d. Review of contracts (both specific contracts and the draft model of the contract).
e. Communication between involved parties.

8.3.10. File

The objective of this item is to verify that the system established by the sponsor/CRO ensures that the general documentation that must be filed with the sponsor/CRO (according to the GCP) is available, complete and maintained in good conditions for the expected period.

The following items can be checked, among others:

a. Preparation, review and approval of documents.
b. Update of documents.
c. Document version control.
d. Form of filing.
e. Archiving of essential documents, according to GCP.
f. Retention of documentation as required by GCP and local regulations.

9. GLOSSARY

Critical findings: findings directly related to the safety of the research subject, which may result in death, risk of death or unsafe conditions; when related to the study data, may compromise its validity, such as studies conducted without authorization, tampering, lack of information or falsifications. [Reference: IN 20/2017]

Major findings: findings that may result in a risk to the research subject health or data invalidation. [Reference: IN 20/2017]

Minor findings: findings that do not fit critical or larger observations, but indicate deficiency and/or deviation; such findings shall be cited for the objective of implementing improvements in the conduct of studies. [Reference: IN 20/2017]

Informative Findings: descriptive and/or complementary findings. [Reference: IN 20/2017]

GCP (Good Clinical Practices): standard for planning, conducting, performing, monitoring, auditing, recording, analyzing and reporting clinical trials that provides assurance that the data and results reported have credibility and accuracy, and that the rights, integrity and confidentiality of clinical trial

subjects are protected, in accordance with the GCP guidelines set out in the Document of Americas and the Good Clinical Practices Manual of the International Harmonisation Conference (Document E6(R2)). [Reference: RDC 09/2015]

Clinical Trials Site: public or private organization, legitimately constituted, duly registered in the National Registry of Health Establishments (CNES), in which clinical trials are conducted. [Reference: RDC 09/2015]

Independent Ethics Committee (IEC): interdisciplinary and independent council with an advisory, deliberative, and educational role, created to defend the interests of individuals participating in studies, their integrity and dignity, therefore guaranteeing that the studies remain within ethical standards. [Reference: RDC 09/2015]

Special Notice (CE): authorizing document, issued by Anvisa, after DDCM analysis and approval, which can be used in import or export requests for a clinical trial. [Reference: RDC 09/2015]

Informed Consent: A process by which a research subject voluntarily confirms his/her willingness to participate in a given study, after being informed of all aspects relevant to his/her decision to participate. Informed consent is documented through an informed consent form, in writing, signed and dated. [Reference: Document of the Americas and E6(R2)]

Deviation from clinical trial protocol: any non-compliance with the procedures or requirements defined in the approved version of the clinical trial protocol, with no major implications for the trial integrity, the data quality or the rights and safety of the trial subjects. [Reference: RDC 09/2015]

Essential Documents: Documents that individually or collectively allow to evaluate the conduct of the study and the quality of the data produced. [Reference: Document of the Americas and E6(R2)]

Clinical Trial: research conducted in human beings with the objective of discovering or confirming the clinical and/or pharmacological effects and/or any other pharmacodynamic effect of the experimental drug and/or identifying any adverse reaction to the experimental drug and/or studying absorption, distribution, metabolism and excretion of the experimental drug to verify its safety and/or efficacy; [Reference: RDC 09/2015]

Adverse Event (AE): Any untoward medical occurrence in a patient, consumer, subject of the clinical trial who administered a pharmaceutical product, which does not necessarily have to have a causal relationship with the treatment. As a result, an AE can be any untoward and unintended sign, symptom, or disease (including results outside the reference range), associated with the use of an investigational product, whether related to it or not. [Reference: RDC 09/2015]

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

a) death;

b) threat to life;

c) persistent or significant disability/inability;

d) requires hospitalization or prolongs hospitalization;

e) congenital anomaly or birth defect;

f) any suspicion of transmission of an infectious agent by means of a drug or;

g) clinically significant event.

[Reference: RDC 09/2015]

Case Report Form (CRF): printed, optical or electronic document designed to record all information about each clinical trial subject that, according to the clinical trial protocol, must be reported to the sponsor. [Reference: RDC 09/2015]

Inspection: The act on the part of a regulatory authority to conduct an official review of documents, facilities, records and any other resources considered by the authority to be related to the clinical trial and which may be located where the trial is conducted, at the sponsor's premises, Clinical Research Organization (CRO) or other places that the regulatory authority deems appropriate. [Reference: RDC 09/2015]

Investigator: person responsible for conducting a clinical trial at the site where the study is conducted. If the study is conducted by a group of people, the investigator is the leader of the group and will be called the principal investigator. [Reference: RDC 09/2015]

Experimental drug: pharmaceutical product under test, subject of DDCM, to be used in the clinical trial, in order to obtain information for its registration or post-registration. [Reference: RDC 09/2015]

Monitoring: act of continually reviewing the clinical trial process and making sure that it is conducted, recorded and reported in accordance with the protocol, standard operating procedures, GCP and applicable regulatory requirements. [Reference: RDC 09/2015]

Clinical Research Organization (CRO): every company regularly installed in national territory contracted by the sponsor or sponsor-investigator, which partially or fully, with Anvisa, assume the sponsor's attributions. [Reference: RDC 09/2015]

Sponsor: person, company, institution or organization responsible for initiating, administering, controlling and/or funding a clinical trial. [Reference: RDC 09/2015]

Monitoring plan: document that describes the strategy, methods, responsibilities and requirements for monitoring a study. [Reference: E6(R2)]

Standard Operating Procedure: Detailed written instructions for achieving uniformity of performance for a specific function. [Reference: E6(R2)]

Investigational product: experimental drug, placebo, active comparator or any other product to be used in the clinical trial. [Reference: RDC 09/2015]

Computerized systems validation: a process that establishes and documents that specific requirements for a computerized system can be consistently met from design up to system deactivation or transition to a new system. The validation approach should be based on a risk assessment that takes into account the intended use of the system and the potential of the system to affect the protection of subjects and the reliability of the study results. [Reference: E6(R2)]

Violation of clinical trial protocol: deviation from clinical trial protocol that may affect the data quality, compromise the study integrity, or that may affect the safety or rights of the clinical trial subjects. [Reference: RDC 09/2015]

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11. EDITION HISTORY

VERSION	DATE	CHANGE	JUSTIFICATION
1	11/Sep/2020	Initial issue	Not applicable
2	26/Jan/2022	Changes made based on contributions received during the Public Consultation period (14/Sep/20 to 11/Mar/21):	
		The acronyms CAPA, CRF, ICH, IVRS, IWRS have been updated with the English nomenclature.	As the acronyms originate from English, the meaning of the acronym in English has been included for clarification.
		Section 3 (Legal Basis): References 3.8 to 3.11 have been included	Update of regulations and inclusion of ethical regulations, which were not in the first version.
		Section 5 (Team and Duration of Inspection): Remote inspection forecast has been included.	RDC 449/2020 clarifies that remote inspections can be conducted in certain cases. The

			section has been updated to have this prediction.
		Section 6 (Criteria for selecting the clinical trial(s) and the site to be inspected), the part in bold has been included: • Studies with populations considered vulnerable, such as pediatrics, the elderly, **pregnant women**, indigenous people, people with disabilities;	Another example of a vulnerable population was included, according to the contribution received. It should be noted that this list is not exhaustive.
		Section 7.1.2 (Request for prior documentation): General Documents – items I and II. The part in bold has been included in the text. I. General organization chart of the company **in Brazil**, listing the department and name(s) of the person in charge.	To clarify that it refers to the organization chart of the Brazil team.
		II. Detailed organization chart of activities related to clinical research **in Brazil**, listing the department, brief summary and name(s) of the person in charge. Include in this organizational chart contracted external services (for example: statistics department, database, drug warehouse, archive)	
		Section 7.1.2 (Request for prior documentation): The following item has been moved from "General Documents" to "Documents relating to each clinical trial selected for inspection": - List of all computerized systems used to conduct clinical trials (e.g. database, CRF and IVRS/IWRS), even if outsourced.	So that the list of computerized systems is only the systems used in the clinical trial selected for inspection.
		Section 7.1.2 (Request for prior documentation): item X – the part in bold has been included: X. All versions of the Informed Consent Form **applicable to Brazil** with the changes highlighted, including the specific versions of the site, if applicable.	To clarify which versions are applicable for Brazil.
		Section 7.1.2 (Request for prior	To clarify that in case the

		documentation): In the last paragraph of this section, the part in bold was added and the strikethrough part was deleted: It is noteworthy that, before the inspection start, Anvisa inspectors must have access to all the computerized systems used **or their data**, ~~including in cases~~ the **systems are deactivated due to the fact that the studies** are closed.	computerized systems are no longer active due to the study end, their data must be available.
		Section 7.1.3 (Preparatory meeting for inspection) was included	A pre-inspection virtual meeting will make it easier to align with the inspected party the inspection logistical details.
		Section 7.2.1 (Opening Meeting): on the attendance list, the part in bold was included - The attendance list **prepared by Anvisa** must be signed by all those present.	To clarify that the attendance list is prepared by Anvisa.
		Section 7.2.3 (Interviews): At the end of the paragraph, the following sentence was included: **These interviews may be conducted remotely, as needed.**	To provide for cases where the person in charge is not present at the inspection (e.g. activities carried out by employees located in another country).
		Section 7.3 (After inspection): The part in bold has been included: The deadline for sending the final opinion is up to 30 days from the receipt date of the response to the inspection report. In exceptional cases, this period may be extended and the **inspected party will be informed** with due justification.	To clarify that the new deadline will be informed to the inspected party, with the reason for the deadline extension.
		Section 8.1 (Organization and Team): the part in bold was added: a. Organizational chart of the company **in Brazil**, containing all departments, functions and responsible for each area. b. Organizational chart and team assigned **in Brazil** for each clinical trial inspected.	To clarify that the organizational charts refer to the Brazil team.
		Section 8.1 (Organization and Team): the part in bold was added: e. List of employees participating in the clinical trial**(s) selected for inspection**, including name, title, role in the study, date of entry and exit	To clarify that the list to be evaluated is of employees participating in the clinical trial selected for inspection and to clarify that the signature/initial can be either manual or

		from the study (if applicable), signature and initials **(manual or electronics).**	electronic.
		Section 8.2 (Infrastructure): the part in bold was added: c. Computerized systems. Among others, the following will be evaluated: 6. System validation, **based on references such as *PIC/S Guidance PI 011-3: Good Practices for Computerized Systems in Regulated GXP Environments, 2007*.**	A reference suggestion for validation of computerized systems has been included.
		Section 8.3.6 (Safety and adverse event reporting) - the part in bold was added and the strikethrough part deleted:	To comply with Brazilian regulations (RDC 09/2015) and clarify the types of adverse events that must be immediately reported for each instance.
		c. Immediate notification **to Anvisa** of **serious and unexpected adverse events, possibly/probably/definitely related to the investigational product that occurred in the national territory** ~~to Anvisa~~ **and notification of** adverse drug reactions to ~~regulatory agencies~~, investigators and IECs.	
		Section 10 (Bibliographic References): inclusion of the following reference: **PHARMACEUTICAL INSPECTION CO-OPERATION SCHEME (PIC/S): PIC/S Guidance: Good Practices for Computerised systems in regulated GXP environments. PI 011-3 de 25 de setembro de 2007.**	To update the reference used after reviewing the guide.

12. ANNEXES

- **Annex 1** Model list of all clinical trials conducted in Brazil
  - Annex 1a: model for sponsor
  - Annex 1b: model for CRO
- **Annex 2:** Spreadsheet model with the number of subjects screened in the study
- **Annex 3** Document model with the first visit date of the first screened subject and the last visit of the last randomized subject in Brazil
- **Annex 4:** Spreadsheet model with all serious adverse events in the study