Inspection Guide in Good Clinical Practices (GCP) regarding clinical trials with drugs and biological products - Inspection of Sponsors and Representative Organizations of Clinical Research (ORPC)

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

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This Guide expresses Anvisa's understanding of 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, and, therefore, it is possible to use alternative approaches to the propositions set out here, 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 sanitary infraction, nor does it constitute a reason for rejecting petitions, provided that the requirements required by law are met.

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

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

SUMMARY

ACRONYMS

ANVISA - National Health Surveillance Agency
BPC - Good Clinical Practices
COVER – *Corrective actions, preventive actions (Corrective actions, Preventive actions)*
EC - Special Notice
CEP - Research Ethics Committee
CONEP - National Research Ethics Commission
COPEC – Coordination of Clinical Research in Medicines 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 (Interactive Web Response System)*
ORPC - Representative Clinical Research Organization
SOP - Standard Operating Procedure
RDC - Resolution of the Collegiate Board of Directors

1. SCOPE

This guide deals with the procedures for conducting a Good Clinical Practice (GCP) inspection regarding clinical trials with drugs and biological products at sponsors and Representative Clinical Research Organizations (ORPCs). The guide is intended for everyone involved with clinical trials, including centers, sponsors, the Clinical Research Representative Organization (ORPC) and Anvisa inspectors.

2. INTRODUCTION

Good Clinical Practice (GCP) is an international standard of scientific and ethical quality for planning, conducting, carrying out, monitoring, recording, analyzing, reporting clinical trials and auditing, which provides assurance that data and reported results are credible and accurate, and that the rights, integrity, and confidentiality of clinical trial participants are protected, in accordance with the GCP guidelines set forth in the Americas Document and the International Council's Good Clinical Practice Manual for Harmonization/ *International Council for Harmonization - ICH* (Document E6 (R2)).

Inspections in BPC, which are provided for in RDC No. 09, of February 20, 2015, Chapter VIII, Art. 71, have as main objectives to verify the protection of the rights of clinical trial participants, the degree of adherence to current Brazilian legislation and GCP compliance, and the quality of data generated in clinical trials. Inspections can be performed at any location where study activities are conducted, including clinical trial centers, sponsor, Representative Clinical Research Organization (ORPC), laboratories and other institutions involved in the development of the investigational drug.

The Coordination of Clinical Research on Medicines and Biological Products (COPEC) is the area responsible for carrying out inspections in BPC of clinical trials related to medicines and biological products and actions arising, according to item b, item I of Art. 130-A of the Rules of Procedure Anvisa Internal (RDC No. 303 of September 13, 2019).

This guide describes how Anvisa conducts GCP inspections in clinical trial centers, based on the current Normative Instruction (IN) No. 20 of October 2, 2017, with the objective of harmonizing and guiding all those involved in the inspection procedures, ensuring that forms a unified standard and security for all parties involved.

Throughout the text, the term “shall” is accompanied by the legal basis to which it refers (section 3 of this guide). For example: *The inspection must3.5 (Art.5) take place within a maximum period of 5 (five) working days.* In this case, item 3.5 is Normative Instruction No. 20/2017, therefore, the term refers to Art. 5 of Normative Instruction No. 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, of January 26, 1999, which defines the National Health Surveillance System, creates the National Health Surveillance Agency, and makes other provisions.

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

3.3. Resolution of the Collegiate Board of Directors (RDC) No. 303 of September 13, 2019, which approves and promulgates the Internal Regulation of the National Health Surveillance Agency – Anvisa.

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

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

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

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

3.8. Collegiate Board Resolution (RDC) No. 449 of December 15, 2020, which amends Collegiate Board Resolution - RDC No. 9, of 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, of August 7, 1997, which approves the norms 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 Norm nº 001/2013 of the National Health Council (CNS), which provides for the organization and functioning of the CEP/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, of Chapter XIII, of CNS Resolution No. 466 of 12 December 2012.

4. SCOPE OF INSPECTION

Inspections in BPC may be carried out before, during or after the conduction of 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 inspection in BPC will be carried out by employees of Anvisa's effective staff, duly identified and qualified, respecting the duties and competences inherent to 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 party.

The inspection must 3.5 (Art.5) occur within a maximum period of 5 (five) business days. Exceptionally, this period may be changed with due justification.

The inspection can take place both in person and remotely3.8(Art.71) .

6. SELECTION CRITERIA OF THE CLINICAL TEST(S) AND THE PLACE TO BE INSPECTED

Listed below are the most commonly used criteria for selecting the clinical trial and 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 mainly based on the following criteria:

- Preference for national sponsors, since they are generally inspected only by Anvisa;
- CROs working with many national sponsors;
- Sponsors and international CROs, but which have not been inspected by other international agencies and institutions with recognized experience in the area of inspections in BPC;
- Results of previous inspections;
- Demand from other areas of Anvisa;
- Complaint.

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

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

- Studies evaluated as complex by COPEC (eg, 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 started as provided for in §1 of Art. 36 of RDC 09/2015;
- Results of previous inspections carried out by Anvisa;
- Demand from other areas of Anvisa;
- Complaint.

7. INSPECTION STEPS

7.1. before inspection

7.1.1. Inspection Notification

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

Communications between Anvisa and the sponsor/CRO or center about the inspection also can be made by the inspection e-mail inspecaobpc@anvisa.gov.br.

As described in Art. 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 denunciation 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 e-mail, the company is first asked to provide a list of all clinical trials conducted in Brazil in recent years. The number of years will depend on the purpose of the inspection. In this notification, the company must3.4(Art.41) complete an electronic spreadsheet (according to the model in Annex 1a or 1b) containing details of the clinical trial, such as study title, EC number issued by Anvisa, study phase, current status of the study, start and end date of the study (if applicable), number of centers in Brazil, total number of screened and randomized participants in Brazil, name of sponsor (in cases of inspection in CRO), name of CRO (in cases of inspection at a sponsor that has contracted a 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 often requested. However, the list can be changed as needed.

general documents

I. General organization chart of the company in Brazil, listing the department and name(s) of the company(s) responsible(s).

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(s). Include in this organizational chart contracted external services (for example: statistics department, database, medication warehouse, archive)

III. List of company's Standard Operating Procedures (SOPs) related to conduct of clinical trials. Inform the reference number, title, version and effective date.

Documents referring to each clinical trial selected for inspection

IV. List of all computerized systems used to conduct clinical trials (eg, database, CRF and IVRS/IWRS), even if outsourced .

V. List of study activities with their respective guardians.

SAW. List of study activities performed by third parties contracted by the sponsor/CRO, if applicable, with the name of the company and those responsible for the activities.

VII. All versions of the study protocol and its amendments.

VIII. List of all study manuals provided by the sponsor or prepared by the ORPC. Example: central laboratory manual, central radiology manual, filling out a case report form (CRF), IVRS (randomization system), etc.

IX. All versions of the investigator's brochure

X. All versions of the Free and Informed Consent Form applicable for Brazil with the changes highlighted, including the specific versions of the center, if applicable.

XI. Delegation of responsibilities form for each center, 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 screened participants, screening failure, randomized, active, discontinued and who completed the study, for each Brazilian center and the total of the study, including justifications for participants considered screening failure and discontinued. (Model in Annex 2)

XIV. Date of the first visit of the first participant screened and of the last visit of the last participant randomized to all Brazilian centers. This information can be included in the worksheet described in item XIII. (Model in Annex 3)

XV. Electronic spreadsheet with all Serious Adverse Events that occurred in Brazil and worldwide, containing participant number, EAG name, start and end date of the event, outcome (if applicable), relationship with the study drug, severity criteria (eg : death, hospitalization), action taken and whether expected or not. (Model in Annex 4)

XVI. Contract between sponsor and ORPC (financial aspects may be obliterated), if applicable.

XVII. Information about the CRF format (paper or electronic) and a blank CRF template

XVIII. All versions of the Monitoring Plan used in the study, with the changes highlighted

XIX. Monitoring reports from all centres, including the selection visit, initiation and closing, if applicable.

XX. Information on the central laboratory, if applicable: list of analyzed parameters, reference values and quality certificates

XXI. All ethical submissions and approvals from each center, CEP membership list, and CEP registration with CONEP (or registration status, when registration renewal is not yet available). For submissions and approvals, the screen capture *(printscreen)* of Plataforma Brasil is sufficient.

The templates included in Appendices 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 purpose of these worksheets is to facilitate inspection preparation. When it is not possible to generate electronic spreadsheets, pdf reports with an active copy/ paste function can be forwarded.

These documents must3.4(Art.41) be forwarded to Anvisa by Electronic Addendum to the Sanitary Investigation Dossier (informing the file number and date for the inspection e-mail). The deadline for sending documents is usually 2 to 3 weeks, depending on the complexity of the requested documentation.

It is noteworthy that, before the start of the inspection, Anvisa inspectors must3.6(5.1.2) have access to all computerized systems used or to their data, in case the systems are deactivated 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 objective of aligning logistical details of the inspection.

7.2. during inspection

The inspection process generally consists of the following steps:

- Opening meeting,
- Visit to the facilities,
- Interview with the study team,
- Document review (including verification of computer systems),
- Closing meeting.

7.2.1. Opening meeting

The inspection starts with the opening meeting and is conducted by the lead inspector. The meeting if starts with the presentation of all the gifts.

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

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

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

A member of the study team must be designated who will accompany the inspectors throughout the inspection process.

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

At the end of the opening meeting, 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 and with internet access.

7.2.2. Visit to facilities and document analysis

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

7.2.3. interviews

Professionals involved in writing and developing the investigator's protocol and brochure, developing the statistical analysis plan, managing and monitoring clinical trials, quality system, reporting adverse events/ pharmacovigilance, files, contracts, database management data and other activities applicable to each company will be interviewed and questioned in relation to any clarifications or doubts that arise during the inspection. These interviews may be conducted remotely, as needed.

7.2.4. Closing meeting

At the end of the inspection, the team of inspectors will hold the closing 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 classification of the findings 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/ORPC of the study via electronic letter and to the IP, by email.

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

- **Critical:** findings directly related to the safety of the research participant, which may result in death, risk of death or unsafe conditions; when related to the study data, they can 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 participant's health or data invalidation
- **Minor:** findings that do not fit into critical or major observations, but that indicate deficiency and/or deviation; such findings should be cited for the purpose of implementing improvements in conducting studies
- **Informative:** descriptive and/or complementary findings

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

Upon receipt of the inspection report, the Sponsor/CRO will have 120 calendar days to manifestation, according to Art. 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 estimated deadlines and those responsible for each action. In addition, the impact and risk of the finding should be evaluated for all studies and not just for inspected clinical trials. For minor findings, only corrective actions need to be sent to Anvisa.

The following is an example of a response:

Finding #XX		
clarification		
Root cause		
Finding impact/risk for all company studies		
Corrective action	Responsible	Deadline
Preventive action	Responsible	Deadline

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

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

The response to the inspection report must be sent as an Electronic Addendum to the Sanitary Investigation Dossier to Anvisa. Once petitioned, the sponsor/CRO must inform the file number and the filing date to the e-mail inspecaobpc@anvisa.gov.br.

Following the Sponsor/CRO statement, the team of inspectors will review the response and collectively decide on the GCP compliance in the study. Further inquiries may be made to the inspected party. At the end of the evaluation, Anvisa will issue the Final Inspection Opinion, which will be sent via letter (or e-mail) to the sponsor/ORPC. The deadline for sending the final opinion is up to 30 days from the date of receipt of the response to the inspection report. In exceptional cases, this period may be extended and will be informed to the inspected party with due justification.

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

- **GCP Compliant:** Being GCP compliant does not mean that no findings were found or no action was required. However, the observations found were corrected or did not critically affect the GCPs, not leading to the determinations described in the next item.

- **Non-compliant with GCPs:** Non-compliance with GCPs means that, after evaluating the response to the findings identified in the inspection, Anvisa concludes that the study was not conducted in accordance with GCPs. In case of non-compliance with the BPC, Anvisa may, according to Art. 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 centers in Brazil; or
IV - invalidation of data from a clinical trial center.

It is noteworthy that systemic findings may have repercussions in clinical studies that were not evaluated during the inspection.

A new inspection may be carried out to assess the CAPA implementation, if any need.

8. ITEMS TO BE CHECKED IN SPONSORS OR ORPCs

In this section are listed the items that, in general, inspectors check during an inspection of sponsors/CROs. However, depending on the focus of the inspection, not all items will be evaluated, or it may be necessary to check items that are not mentioned here.

Importantly, the sponsor is responsible for ensuring that clinical trials comply with GCPs and local regulations. As per items 5.2.1 and 5.2.2 of the ICH E6(R2) guide, a sponsor may transfer any or all of the sponsor's tasks and roles relating to the clinical trial to the CRO, but the ultimate responsibility for the quality and integrity of the research data is of the sponsor. The CRO must implement quality assurance and quality control. These procedures must be documented in writing before the start of the study.

8.1. Organization and team

The purpose of this item is to assess whether the company's organization is capable of ensuring 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:

The. 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.

ç. Quality department as an independent department.

d. Description of the positions, qualifications and training of each employee involved in any stage of the clinical trial.

and. List of employees participating in the clinical trial(s) selected for inspection, including name, title, role in the study, date of entry and exit from the study (if applicable), signature and initials (manual or electronics).

f. Procedures for changing staff during a clinical trial.

8.2. Infrastructure

The purpose 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:

The. Archive room, where company documentation and clinical trials are kept stored. Among others, the following will be evaluated:

1. Identification and organization of file folders
2. Adequate structure for document storage
3. Controlled access to the file
4. Procedure for filing and withdrawing documents
5. Action/contingency plan in case of fire, flood and pests
6. Archiving after completion of clinical trials

B. Location where the investigational drug and clinical trial supplies are located stored. Among others, the following will be evaluated:

1. Controlled access
2. Temperature and humidity control
3. Contingency plan in case of power outage 4.
Segregated and properly identified location for the products under investigation of each study to enable the products to be stored logically, allowing for prompt, agile location and without the possibility of errors in separation and dispensing.

5. Segregated location for quarantined, returned, expired or separated products for destruction

ç. Computerized systems. Among others, the following will be evaluated:

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 loss data (including in the case of software updates)
5. Procedures for handling the electronic record after the end of 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. System Access
8. Manuals and training on using the system

8.3. Operational procedures

During the inspection, it will be evaluated whether the company's procedures ensure proper conduct. clinical trial and in accordance with GCPs and local regulations.

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

8.3.1. Implementation and completion 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:

The. Document preparation: format, content and distribution of protocol, amendments to the protocol, documents related to informed consent, investigator's brochure, CRF and any other documents related to the clinical trial.

B. Document approval procedure.

ç. Procedure to ensure compliance with regulatory requirements, such as obtaining ethical approval by CEP/CONEP and regulatory approval by Anvisa.

d. Selection, training and monitoring of investigators.

and. Selection, training and monitoring of the sponsor/CRO team, including managers and monitors.

f. Comparison of critical dates: CEP/CONEP approval, Anvisa approval, start of the study, start date of each center, recruitment period, closing of centers, end of the study.

g. Applicable signed contracts.

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 management of clinical trials.

The following items can be checked, among others:

The. Management/supervision of all activities related to conducting tests clinicians.

B. Handling of issues, deviations, and major protocol, BPC, and local regulations (including root cause investigation).

ç. Sponsor/CRO control procedure to ensure that all ICFs applicable were obtained by the study participants.

d. Procedure to ensure that all ethical/regulatory approvals have been obtained when throughout the study (eg amendments, new versions of TCLEs, serious adverse events).

and. Systems used to control and manage the studies, including an appropriate system for recording protocol violations/deviations and problems/pending issues raised during the study (including recording the corrective and preventive measures adopted).

8.3.3. monitoring

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

The following items can be checked, among others:

The. Procedure for planning, frequency, extent and nature of the activities of monitoring.

B. Procedure for content, processing and monitoring of reports of monitoring.

ç. Monitoring plans used for inspected clinical trials.

d. Corrective actions arising from monitoring visits.

and. Communication flow between monitor and superiors for handling critical findings.

8.3.4. Experimental Medicine

The purpose 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 GCPs.

The following items can be checked, among others:

The. Procedure to ensure the integrity of the investigational drug from the manufacturing until receipt at clinical trial centers.

1. Evaluation of batch analysis certificates
2. Assessment of storage and transport conditions
3. Procedure for releasing the investigational drug, after receipt by the centers
4. Packaging and labeling evaluation
5. Comparison of labels used x labels approved by Anvisa
6. *Recall* and re-labeling procedure

B. Accounting for the investigational drug, including shipping, return and undoing.

1. Evaluation of the investigational drug inventory
2. Comparison between physical inventory x accounting records

ç. Procedures for randomization, blinding and code breaking.

8.3.5. sample management

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

8.3.6. Safety reporting and adverse events

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

The following items can be checked, among others:

The. Identification and monitoring by the investigator or sponsor/ORPC of an adverse event, serious adverse event, or unexpected and serious adverse drug reaction.

B. Procedure for assessing causality between the adverse event and the product under investigation.

ç. 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 reported to Anvisa, according to RDC 39/2008 or RDC 09/2015.

and. Reporting of serious adverse events by investigators to the CEP and the sponsor.

f. Management of investigator-reported serious adverse events, including sponsor/CRO procedures for receiving, evaluating, and monitoring events.

g. Security updates (including investigator brochure update) and periodic security reports, including verification of the need for an ICF update.

H. Communication of security updates to investigators, CEPs (through investigators) and Anvisa.

i. Procedures for interrupting the development or withdrawing from the market of an investigational drug from any country, for reasons of safety or failure to efficiency.

j. Full availability (24 hours, 7 days a week) of the team responsible for aspects of the investigational drug in the clinical trial.

8.3.7. Data collection and processing

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

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

The. CRF drawing

B. Database development and validation

ç. Data entry and cleaning

d. Database closure

and. data reconciliation

f. Access Profile

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

g. Protocol adherence

H. Whether the data is complete, readable and completed in the expected time

i. CRF fixes and audit trails

j. Comparison of dates of the first and last participant included with the start and end dates of the study as well as with the date of submission of the investigational drug

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

k Procedure to ensure the integrity of data collected from clinical trial centers

1. Evaluation of data processing, data analysis and control procedures
2. Audit trails (both for paper and electronic systems)

l. Procedures for preparing the clinical trial report

m. Data management

no. Statistical analysis (as established in the protocol)

O. Clinical trial report content and review process

for. Quality control applied to data processing

8.3.8. Quality warranty

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

The following items can be checked, among others:

The. Audits for critical clinical trial processes, including monitoring activities, data management, safety reporting, clinical trial reporting, filing and validation of computerized systems.

B. Audit of contracted/subcontracted services.

ç. Process for communicating and addressing audit findings, including format and distribution of audit reports.

d. Procedures for dealing with BPC adherence issues that are severe or recurrent.

and. Procedures for designing and implementing audit programs/plans.

f. Audit reports, if applicable.

g. Qualification of auditors.

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

H. Preparation of SOPs

i. Maintenance of SOPs, including periodic review

j. Master POP List

k List of SOPs applicable for each clinical trial inspected

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 may be verified, among others:

The. Prior selection and continuous evaluation of contracted/subcontracted services.

B. Documentation on the service delegation, including the signed contract/agreement.

ç. Handling amendments to the contract.

d. Contract review (both the specific contracts and the draft model of the contract).

and. Communication between the parties involved.

8.3.10. File

The purpose of this item is to verify that the system established by the sponsor/CRO guarantees that the general documentation that must be filed with the sponsor/CRO (according to the GCPs) is available, complete and being maintained in good condition during the expected period.

The following items can be checked, among others:

The. Preparation, review and approval of documents.

B. Document update.

ç. Control of document versions.

d. Filing form.

and. Archiving of essential documents, according to BPC.

f. Document retention as required by GCPs and local regulations.

9. GLOSSARY

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

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

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

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

Good Clinical Practice (GCP): standard for planning, conducting, conducting, monitoring, auditing, recording, analyzing and reporting clinical trials that provides assurance that the data and reported results are credible and credible. accuracy, and that the rights, integrity, and confidentiality of clinical trial participants are protected, in accordance with the GCP guidelines set forth in the Americas Document and Good Clinical Practice Manual of the International Conference on Harmonization (Document E6(R2)) . [Reference: RDC 09/2015]

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

Research Ethics Committee (CEP): an interdisciplinary and independent collegiate, of public relevance, of an advisory, deliberative and educational nature, created to defend the interests of research participants in their integrity and dignity and to contribute to the development of research within standards ethical. [Reference: RDC 09/2015]

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

Free and Informed Consent: Process by which a research subject voluntarily confirms their willingness to participate in a particular study, after having been informed of all aspects relevant to their decision to participate. Free and informed consent is documented through an informed consent form, in writing, signed and dated. [Reference: Americas Document and E6(R2)]

Clinical Trial Protocol Deviation: Any failure to comply with the procedures or requirements defined in the approved version of the clinical trial protocol, with no major implications for trial integrity, data quality, or the rights and safety of clinical trial participants.
[Reference: RDC 09/2015]

Essential Documents: Documents that individually or collectively allow evaluating 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 humans with the aim of discovering or confirming the clinical and/or pharmacological effects and/or any other pharmacodynamic effects of the investigational drug and/or identifying any adverse reaction to the investigational drug and/or studying the absorption, distribution , metabolism and excretion of the investigational drug to verify its safety and/or efficacy. [Reference: RDC 09/2015]

Adverse Event (AE): Any adverse medical occurrence in a patient or clinical trial participant to whom a pharmaceutical product was administered that does not necessarily have a causal relationship to the treatment. As a result, an AE can be any unfavorable and unintended sign, symptom, or illness (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: one that results in any adverse experience with drugs, biologics or devices, occurring at any dose and resulting in any of the following outcomes:

a) death;

b) threat to life;

c) persistent or significant disability/disability;

d) requires hospitalization or prolongs hospitalization;

e) congenital anomaly or birth defect;

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

g) clinically significant event.

[Reference: RDC 09/2015]

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

Inspection: The act by a regulatory authority to conduct an official review of documents, facilities, records and any other resources deemed by the authority to be related to the clinical trial and which may be located where the trial is conducted, on the premises of the sponsor, the Clinical Research Representative Organization (ORPC) or such other locations as the regulatory authority deems appropriate. [Reference: RDC 09/2015]

Investigator: person responsible for conducting a clinical trial at the site where the trial is being 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, object of the DDCM, to be used in the clinical trial, in order to obtain information for its registration or post-registration.
[Reference: RDC 09/2015]

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

Clinical Research Representative Organization (ORPC): any company regularly installed in the national territory contracted by the sponsor or by the sponsor-investigator, which assumes, in whole or in part, with Anvisa, the sponsor's attributions. [Reference: RDC 09/2015]

Sponsor: person, company, institution or organization responsible for initiating, managing, 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)]

Product under investigation: 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 of a computerized system can be consistently met from design through decommissioning the system or transitioning 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 participants and the reliability of study results.
[Reference: E6(R2)]

Clinical trial protocol violation: deviation from clinical trial protocol that could affect data quality, compromise the integrity of the study, or could affect the safety or rights of clinical trial participants.
[Reference: RDC 09/2015]

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11. VERSION HISTORY

VERSION	DATE	AMENDMENT	JUSTIFICATION
1	09/11/2020	Initial issue	Not applicable
two	01/26/2022	Changes made based on contributions received during the Public Consultation period (09/14/20 to 03/11/21):	
		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	Regulations update of ethical and inclusion 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, elderly, **pregnant women,** Indians, 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(s).	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(s). Include in this organizational chart contracted external services (for example: statistics department, database, medication 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 systems computers used to conduct clinical trials (eg, 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 Free and Informed Consent Form **applicable for Brazil** with the changes highlighted, including the specific versions of the center, if applicable.	To clarify which versions are applicable for Brazil.
		Section 7.1.2 (Request for prior documentation): In the last paragraph of this section, the part in bold has been added and the strikethrough part has been deleted: It should be noted that, before the start of the inspection, Anvisa inspectors must have access to all the systems computers used **or your data,** including for cases ~~the systems are~~ **deactivated** ~~due to~~ **the fact that the studies are** closed.	To clarify that if the systems computers are more no active due to the end of the study, their data must be available.
		Section 7.1.3 (Preparatory meeting for inspection) was included	A virtual pre-inspection meeting will make it easier how to line up inspected logistical details of the inspection.
		Section 7.2.1 (Opening Meeting): about the attendance list, the part in bold was included - The attendance list **prepared by Anvisa**	To clarify that the attendance list is prepared by Anvisa.

		must be signed by all present.	
		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 in which the person responsible is not in person inspection (for at activities carried out by employees ex, 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 date of receipt of the response to the inspection report. In exceptional cases, this period may be extended **and will be informed to the inspected party** with due justification.	To clarify that the new deadline will be informed to the inspected party, with the reason for the extension of the deadline.
		Section 8.1 (Organization and Team): Added the part in bold: The. 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): Added the part in bold: and. List of employees participating **in the** trial(s) clinician(s) **selected for inspection,** containing name, title, role in the study, date of entry and exit from the study (if applicable), signature and initials **(manual or electronic).**	To clarify that the list to be to be evaluated is of employees participating in the clinical trial site inspected for and to clarify that the signature/initial can be either manual or electronic.
		Section 8.2 (Infrastructure): Added the part in bold: ç. 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 suggestion for validation of computerized systems was for included.
		Section 8.3.6 (Safety and Adverse Event Reporting) - the bolded part was added and the strikethrough part deleted:	To comply with Brazilian regulations (RDC 09/2015) and clarify the types of events

		ç· 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 CEPs.	adverse events that must be immediately notified for each instance.
		Section 10 (References Bibliographic): inclusion of the following reference: **PHARMACEUTICAL INSPECTION CO-OPERATION SCHEME (PIC/ S): PIC/S Guidance: Good Practices for Computerized systems in regulated GXP environments. PI 011-3 of September 25, 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: template for sponsor
  - Annex 1b: model for CRO
- **Annex 2:** Spreadsheet template with the number of participants screened in the study
- **Annex** 3: Model document with the date of the first visit of the first screened participant and the last visit of the last randomized participants in Brazil
- **Annex 4:** Spreadsheet template with all study serious adverse events

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