Inspection Guide in Good Clinical Practices (GCP) regarding clinical trials with drugs and biological products – Inspection in Clinical Trial Centers

Guide No. 35/2020 - version 2

National Health Surveillance Agency - Anvisa

2022

Inspection Guide in Good Clinical Practices (GCP) referring to clinical trials with drugs and biological products - Inspection in Test Centers Clinical

EFFECTIVE FROM 01/27/2022

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
CAPA – *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*
DDCM - Clinical Development Dossier of Experimental Drug
FAEC- Clinical Trial Submission Form
ICH – *International Council for Harmonization*
IN - Normative Instruction
IP – Principal Investigator
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
SUSAR – *Suspected Unexpected Serious Adverse Reaction*
TCLE - Free and Informed Consent Form
ICU - Intensive Care Unit

1. SCOPE

This guide deals with the procedures for conducting a Good Clinical Practice (GCP) inspection regarding clinical trials with drugs and biological products in clinical trial centers. 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 sites, 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 Normative Instruction (IN) in force No. 20 of October 2, 2017, in order to harmonize and guide those involved in the inspection procedures, thus ensuring 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 procedures for inspection 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 FOR THE CLINICAL TRIAL AND THE PLACE TO BE INSPECTED

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

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

- Studies not internationally inspected by other regulatory agencies;
- Studies with populations considered vulnerable, such as pediatricians, the elderly, 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.

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

- High number of participants included;
- High recruitment in a short period of time;
- Geographic region (preference for regions with few inspections performed);

- Principal Investigator with a large number of clinical trials active at the same time;
- Problems identified during the evaluation of the annual/final monitoring reports and adverse events;
- Results of previous inspections carried out by 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 ORPC responsible for the study before Anvisa. A copy of the letter will be sent to the principal investigator to the email address that was provided on the Clinical Trial Submission Form (FAEC).

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 center and 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, some documents will be requested in advance to assist the inspectors in conducting the inspection. The following list is an example of what is often requested. However, the list can be changed, according to the needs of each study.

I. List of study activities with their respective guardians.
Example: activities carried out by the sponsor, by CROs and other partners (also called *vendors).* (Model in Annex 1)

II. List of all inspected center departments involved in the study, including co-participating institutions. Example: pharmacy, local laboratory, imaging center, co-participating hospital where the study procedure is performed, etc. (Model in Annex 2)

III. List with all versions of the study protocol and their amendments applicable to Brazil. Versions of non-substantial amendments already implemented but which have not yet been petitioned at Anvisa must3.4(Art.46) be forwarded

IV. List of all study manuals provided by the sponsor to clinical trial sites.
Example: central laboratory manual, central image, case report form (CRF), randomization system (Interactive Voice or Web Response System - IVRS or IWRS), from the pharmacy, etc.

v. List of all versions of the investigator's brochure. Versions that have not yet been petitioned at Anvisa must3.4 (Art. 41) be forwarded.

SAW. Free and Informed Consent Terms (ICFs) and Consent Terms, if applicable – all versions already used, including plant-only versions (if applicable).

VII. Document listing the screening and randomization of participants included in the center to be inspected, containing the screening date, randomization date and screening failure date, if applicable *(Screening/ Enrollment Log).*

VIII. Electronic spreadsheet with current data of all participants screened at the center to be inspected, containing participant number, screening date, randomization date, discontinuation date (if applicable), date of signature of all informed consents obtained for each participant and justifications for participants considered screening failure and discontinued. (Model in Annex 3)

IX. Electronic spreadsheet containing number of screened participants, screening failure, randomized, active, discontinued and who completed the study for each Brazilian center and the study total. (Model in Annex 4)

X. Date of the first visit of the first participant screened and of the last visit of the last participant randomized to all Brazilian centers and worldwide. (Model in Annex 5)

XI. List of the sponsor or ORPC team responsible for each activity directly related to the study in Brazil, including the name of each team member, whether they are part of the blind or non-blind team, if applicable, start date and end date for each role performed in the study. (Model in Annex 6)

XII. Delegation of responsibilities form for the center to be inspected, including blind and non-blind members, if applicable.

XIII. Electronic spreadsheet containing the name of each team member of the center to be inspected, activities performed, start and end date (if applicable) of the delegation in the activity performed, date of all applicable training carried out (including BPC, versions of the protocol and procedures of the center or sponsor). (Model in Annex 7)

XIV. Electronic spreadsheet listing the Standard Operating Procedures (SOPs) used since the beginning of the study, containing the title and version of both the center to be inspected and the sponsor. (Model in Annex 8)

XV. Electronic spreadsheet with all Serious Adverse Events (SAEs) and all suspected and unexpected serious adverse reactions (SUSARs) that occurred in Brazil and worldwide, containing participant number, SAE name, start and end date of the event, outcome/ evolution (if applicable), relationship to study drug, severity criteria (eg, death, hospitalization), action taken with SAE. (Model in Annex 9)

XVI. Electronic spreadsheet containing all clinical trial protocol deviations and violations identified so far regarding the center to be inspected. (Model in Annex 10)

XVII. Contract between sponsor and center to be inspected (financial aspects may be obliterated) and listing of other contracts relevant to the center's activities

inspected (e.g. between center and back-end hospital, on-site laboratory, offsite archiving, etc.).

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

XIX. Monitoring Plan - all versions already used in the study applicable to the center to be inspected.

XX. Monitoring reports from the center to be inspected, including the selection, initiation and closing visit, if applicable.

XXI. Electronic spreadsheet with current data on monitoring visits at the center to be inspected, containing type of visit (e.g. selection, initiation, monitoring or closing), start and end date of the visit, name of the monitor(s) who performed it (aram) the visit, date the report was approved, name of the report approver, and date the follow-up letter was sent to the center.
(Model in Annex 11)

XXII. Form of monitoring visits carried out at the center to be inspected signed by the sponsor representatives at each visit *(Site Visit Log).*

XXIV. All ethical approvals of the center to be inspected, list of members of the Research Ethics Committee (CEP), registration and renewal of registration of the CEP with the National Commission for Ethics in Research (CONEP) or registration status, when the registration is renewed is not yet available. For submissions and approvals, the screen capture *(printscreen)* of Plataforma Brasil is sufficient.

XXV. Electronic spreadsheet on CEP documentation, containing the name of the document submitted to the CEP, submission/notification date and approval date (if applicable). (Model in Annex 12)

XXVI. Accounting forms for the products under investigation of the center to be inspected.

XXVII. Data report from the Interactive Voice or Web Response System (IVRS or IWRS) for the center to be inspected, including all information related to the investigational drug (shipment, dispensing, disposal, etc.).

XXVIII. Electronic spreadsheet containing the experimental/placebo drug kit number, batch number, expiration date, date sent to the center to be inspected, date received by the center, date of dispensing to the participant, number of the participant to which the drug was dispensed. In the case of studies involving blind and non-blind teams, Anvisa inspectors will instruct how to send this worksheet to avoid breaking the blind character.
(Model in Annex 13)

The templates included in Appendices 1 to 13 are optional and do not necessarily need to be used.

The electronic spreadsheets mentioned in items VIII, XI, XII, XIII, XV, XVI, XXI, XXV and XXVIII are control spreadsheets that can be prepared/generated by the sponsor/CRO. The purpose of these worksheets is to facilitate inspection preparation. In the case of the spreadsheets mentioned in items XII, XIII, XV and

XVI, when it is not possible to generate electronic spreadsheets, pdf reports with active copy/paste function can be forwarded.

Before sending the documents and spreadsheets, the inspected party must3.6(4.8.10.n) be careful not to forward any information that could jeopardize the confidentiality of the clinical trial participants.

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 1 to 2 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 by the center during the study, including for closed case studies.

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 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 analysis,
- 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 center and clinical trial for the inspection, in the case of routine inspection. 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 principal investigator (PI) gives a brief description of the clinical trial site, the study team, and the activities that the IP is conducting. The IP must3.5 (Art.4) be present throughout the meeting as well as the sponsor/CRO representative. It is recommended that a representative of the

management of the institution is also present. Exceptional cases where the IP or sponsor/CRO representative cannot be present will be discussed with COPEC prior to the inspection.

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 center or 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 study team member, preferably from the center, should be designated
will accompany inspectors throughout the inspection process, not necessarily the IP.

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 should preferably stay in a separate room from the center's staff 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

Before starting the interviews, the inspectors will request that all documentation regarding the CVs, professional experiences and training of the entire study team is already available to
the interview.

The professionals involved in the clinical trial (PI, sub-investigators, study coordinator, pharmacists, nurses, study monitors, study managers, etc.) will be interviewed about their activities in the study and asked about any clarifications or doubts that arise during the clinical trial. inspection. In addition, the presence of any team members may be requested if necessary.

Interviews usually take place on the second or third day of the inspection, but this can vary depending on the logistics and focus of the inspection.

7.2.4. Closing meeting

At the end of the inspection, the team of inspectors will hold the closing meeting, in which a summary of the inspection activities will be made and any findings will be reported. At this time, inspectors will not classify the findings found. 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 sponsor's IP and representative must3.5(Art.4) be present during the entire meeting. It is recommended that a representative of the institution's management

also be present. Exceptional cases in which the IP or representative of the sponsor/ORPC cannot be present will be discussed with Anvisa before the inspection.

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, as well as those responsible for each finding (center or sponsor).

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 the entire study and not just for the inspected center, as applicable. 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
Impact/risk of the finding for the study

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.

In some situations, the inspection report may contain site-directed findings and sponsor/CRO-directed findings. In this case, only a single response to the report must be sent, containing clarifications from both the center and the Sponsor/CRO.

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 response, the team of inspectors will review the response and collectively decide on 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 by letter to the sponsor/ORPC and via email to the IP. 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 at the center in question;

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

IV - invalidation of data from the center in question or from the clinical trial.

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

8. ITEMS TO BE CHECKED IN CLINICAL TEST CENTERS

This section lists items that inspectors generally check during an inspection of clinical trial sites. 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.

8.1. APPROVALS AND AGREEMENTS / CONTRACTS

The objective is to verify if the study was conducted with the proper ethical and sanitary approvals, and if the necessary contracts/agreements were signed correctly, observing their specificity, their validity and if they are being followed.

8.1.1. regulatory approval

The following items can be checked, among others:

The. Regulatory approval for the study: Special Notice (EC) or Document for Importation of Product(s) under investigation from the Clinical Development Dossier of Experimental Medicine (DDCM) listing the inspected clinical trial or, in the case of studies approved according to RDC No. 39/ 2008, EC of clinical trial listing inspected site.

B. Approval of substantial amendments: Special Notice (EC) or Document for Importation of Product(s) under investigation by the DDCM listing the version of the approved amendment

8.1.2. Ethical approval (CEP/CONEP)

The following items can be checked, among others:

The. CEP approval (and CONEP, if applicable) for protocol (and its amendments) and TCLE with the identified version

B. Nature and frequency of correspondence with the local zip code. This item may include:

1. Submission and approval of study documents, such as protocol and amendments, materials to be distributed to study participants, other materials that require ethical approval.
2. Reports of Adverse Events and Serious Adverse Events

3. Notification of deviations and violations
4. Principal Investigator Change Notification
5. Partial and final reports
6. Security Reports
7. List of CEP members and declaration of renewal of CEP registration with CONEP
8. Letter of exemption from voting by CEP members who are directly involved with the inspected clinical trial

8.1.3. Contracts/Agreements

The following items can be checked, among others:

The. Contracts/agreements signed between the parties involved (for example, between the center (IP and institution)/ sponsor or CRO, clinical analysis center/laboratory, radiology center/sector, center/background hospitals, center/ institution with the participant , filing center/company, healthcare waste management center/company).

B. Evidence that the clinical trial participant and his/her companion (as applicable) have been properly reimbursed for transportation and food.

ç. Agreement between sponsor/CRO and center for archiving the documentation of the study.

d. In the agreements/contracts, the scope, period of validity, responsibilities defined by each party, in line with the approved protocol will be verified.

8.2. CLINICAL TEST CENTER ORGANIZATION AND TEAM

The objective of this item is to verify if the organization of the center is capable of guaranteeing an adequate conduction of the clinical trial as well as guaranteeing adherence to Good Clinical Practices. Regarding the team, the objective is to verify the qualification, responsibilities, delegation, experience, training and availability of the study team.

The following items can be checked, among others:

The. Center organization chart.

B. List of all clinical trials conducted by the investigator, including information on protocol code, protocol title, investigational drug name, sponsor name, and study start and end dates.

ç. Address of all locations where the clinical trial participant is attended and where the study is conducted.

d. Flows of the center's operation, such as:

1. Flows for obtaining medical records 2.
Communication flows within the study team

and. Quality Assurance System (refer to section 8.4 of this guide).

f. List of task delegations duly completed and signed.

g. Resumes of the staff involved in the study and professional licenses.

H. Record of training performed in Good Clinical Practice, protocol, procedures, study manuals and any other applicable training. The records must contain, as a minimum, the date of training, subject or material used (including version, if applicable), form of training (example: individual reading, lecture, class), responsible for training and identification of trained employees (for example, through subscriptions).

i. Certificate of training for emergency procedures, where applicable.

j. Compatibility between staff workload and clinical trial requirements.

k Availability, involvement and supervision of the principal investigator in the clinical trial.

l. Evidence that the principal investigator fulfills the responsibilities outlined in the Good Clinical Practice and is familiar with the study protocol.

8.3. INFRASTRUCTURE

The purpose of this item is to confirm that the facilities are suitable for conducting the test clinical practice and if they are in accordance with the Good Clinical Practices.

It is noteworthy that health service establishments must also comply with relevant local legislation. If local legislation does not include topics already regulated by Anvisa, federal legislation must be applied.

A compilation of the main regulations can be found in the document “Library of Health Services” (version 01/03/2020 and subsequent updates), through the link: http://portal.anvisa.gov.br/documents/33880/ 4967127/Library+of+Themes+of+Service%C3%A7os+of+Sa%C3%BAde_Portal.pdf/55e4ab14-e99f-41c1-aea9-cc6e8875b5e4. The main standards related to health services include those of infrastructure (RDC No. 50/2002), Good Operating Practices for health services (RDC No. 63/2011), guidelines and standards for the prevention and control of hospital infections (Ordinance No. 2,616/1998) and patient safety actions (RDC 36/2013).

The following installations are the ones that are generally verified. However, other locations can be verified, depending on the characteristics of each study.

8.3.1. Study file

The. Identification and organization of file folders.

B. Structure suitable for document storage.

ç. Restricted access to the file.

d. Action/contingency plan in case of fire, flood and pests.

and. Archiving after completion of the clinical trial.

f. Record the location of essential documents, including source documents.

8.3.2. Pharmacy or place of storage of the products under investigation

The. Restricted and controlled access to the pharmacy or to the place where the products under investigation.

B. Temperature and humidity control when applicable (room, refrigerator or freezer).

ç. Contingency plan in case of power outage (UPS and generator).

d. Segregated and duly identified location for the products under investigation of each study to enable the products to be stored logically, allowing for a prompt, agile location and without the possibility of errors in separation and dispensing. Segregation and site identification should be primarily in relation to the study (e.g. study “X”, “Y”, “Z”) and in relation to the status of the product (e.g. expired or quarantined products must be fully separated of stock in use).

8.3.3. offices

The. Evidence that the location protects the confidentiality and privacy of clinical trial participants for the discussion and obtaining the informed consent, and for clinical evaluations performed during the clinical trial.

8.3.4. Inpatient ward or infusion room

The. Access to a study physician for the entire length of stay if this procedure be part of the protocol.

B. Availability of an ICU in the clinical unit (according to RDC 07/2010) or contract with a mobile ICU (advanced support ambulance – type D ambulance, according to Ordinance MS 2048/2002) and a back-up hospital.

ç. Presence of an emergency cart in an easily accessible location. The cart does not necessarily need to be in the inpatient/infusion ward, but rather in the place where the investigational drug is administered. In the emergency cart, it will be checked mainly if it is sealed and checked with adequate frequency. The presence, validity and functioning of emergency cart items that guarantee immediate care in the event of a medical emergency will also be verified. During the inspection, the inspector may request that the cart's seal be broken to verify its contents.

d. Number of beds and infusion pumps in the infusion room, if applicable for the clinical trial.

8.3.5. Room for collection and handling of biological samples

The. Collection area.

B. Storage of samples before analysis or sending to an external laboratory, national or International.

ç. Shipping conditions to external laboratory, if applicable.

8.3.6. Clinical laboratory

The clinical laboratory must follow the guidelines of RDC nº 302/2005. During the inspection, the following items may be verified:

The. Validated procedures for the collection, processing, handling and transport and analysis of biological samples.

B. External proficiency certificate, accreditation certificate, reference values and POPs.

ç. Room temperature control record, refrigerator, freezer or water bath, when required.

8.3.7. Equipments

The objective is to verify that the equipment used in all the facilities where the test clinic is conducted are in proper condition for use.

The following items will be checked, among others:

The. Calibration or periodic maintenance certificate.

B. Operation and location (specific equipment must be available on site of its use).

ç. Procedures established for the use of each equipment, such as the equipment or POP.

8.3.8. Waste management

The objective is to verify whether health care waste has been properly managed, according to RDC 222/2018, from segregation, packaging, identification, treatment, transport to final disposal.

The following items can be checked, among others:

The. Container with lid identified for each type of waste and that is rigid and resistant to puncture, rupture and leakage.

B. Collector/incinerator suitable for sharps, available on site procedure.

8.3.9. computerized systems

The. Purpose of using the system.

B. Procedures for creating, modifying, deleting, maintaining or transmitting records electronics.

ç. Access profile types.

d. Presence of an audit trail to identify any data entry and changes in the system.

and. Security system (eg who has access and how this access is controlled).

f. Presence of *backup,* data recovery or contingency plan to prevent data loss (including in the case of software updates).

g. Procedures for handling electronic data after study closure.

H. System validation, based on references such as *PIC/S Guidance PI 011-3: Good Practices for Computerized Systems in Regulated GXP Environments, 2007.*

i. Manuals and training on using the system.

8.4. QUALITY SYSTEM

The objective is to confirm the existence of a quality system to ensure that all procedures performed at the clinical trial site are in accordance with the approved protocol and the Good Clinical Practices available in Document of the Americas and ICH E6 (R2).

The following items can be checked, among others:

The. Monitoring and follow-up by the sponsor/CRO

1. Monitoring plan and adherence to the plan.
2. Number of monitoring visits performed at the clinical trial site.
3. Monitoring and referral reports given to problems found during visits of monitoring.
4. Evidence of follow-up given by the IP to the findings observed in the visits of monitoring.
5. Evidence of adequate communication between monitor and superiors for treatment of critical findings.
6. Record monitoring visits in an appropriate form, as well as their scope and frequency.

B. Audits and inspections

1. Certificate of Audits, if applicable.
2. Report of audits performed by the sponsor/CRO, if applicable.
3. Inspection report performed by CEP or other regulatory authorities, if applicable.

ç. Treatment of deviations, investigation and identification of the root cause and adoption of measures corrective and preventive.

d. Written and controlled study procedures (see item 8.4.1).

8.4.1. Written and Controlled Study Procedures

The objective is to verify if in the center there are processes, flows or written procedures and study controls.

Procedures that are protocol-specific should3.6(5.1.1) be provided by the sponsor to ensure that all sites are performing the procedure in a standardized manner (e.g., study breakout procedure, reporting of serious adverse events , preparation and administration of the investigational drug). Manuals and documented instructions are examples of these procedures.

When there are discrepancies between the site's and the sponsor's procedures, the site must follow the sponsor's procedures to ensure harmonization between the data collected at different sites participating in the same study.

The processes, flows and procedures will depend on the type of clinical trial to be conducted. COPEC understands that the center must define in advance, and together with the sponsor/ORPC, which procedures will be necessary during the conduction of the clinical trial. Listed below are examples of procedures that inspectors may require for a clinical trial.

The. Training and continuing education of the study team
B. Recruitment and selection of clinical trial participants
ç. Application of TCLE and Term of Assent
d. Completion, correction and verification of Case Report Form (CRF) data
and. Record in source document (physical or electronic)
f. Use, calibration and maintenance of equipment/instruments
g. Transport, receipt, storage, control and accounting of the drug experimental
H. Preparation and administration of the investigational drug
i. Destruction or return of the investigational drug
j. Electricity failure and contingency plan in the medicine storage area experimental
k Collection, transport, preparation, identification and analysis of laboratory samples
l. Disposal of biological and non-biological materials
m. Breaking study blinding
no. Reporting of adverse events and serious adverse events (including cases of pregnancy), containing reporting deadlines
O. Preparation and maintenance of files (including information on retention time of the study documents)

The following items of processes, flows and procedures can be verified, among others:

for. Existence and adherence to written processes, flows and procedures.
q. Verification that processes, flows and procedures have version and history control of changes.
a. Record of staff training in the processes, flows and procedures available and in force.
s. Verification that processes, flows and procedures are available and accessible.
t. Update and frequency of reviews of study processes, flows and procedures, as evidenced by a master list or other control document.
u. Historical file of replaced processes, flows and procedures, if applicable.

8.5. SOURCE DOCUMENTATION AND CASE REPORT FORM

8.5.1. Free and Informed Consent Form

The objective is to confirm whether the informed consent was obtained in accordance with Good Clinical Practices and local regulations.

The following items can be checked, among others:

The. Version of the TCLE approved by the CEP.

B. Signature, date and initials in the consent form by the participant or his/her legal representative and by the person who conducted the consent process, prior to the performance of any clinical trial procedure.

ç. Evidence that a signed copy of the informed consent was given to the participant or his/her representative cool.

d. Evidence that the consent process was conducted properly and prior to any other clinical trial procedure, and recording of this process in the participant's medical record.

and. Term of Assent approved by the CEP, in the case of underage participants or legally disabled together with a copy of the RG or birth certificate.

f. Presence of an impartial witness or legal representative, when applicable, including the need and identification of these persons. The impartiality of the witness must 3.6 (1.26) be evidenced.

g. Requirement for participant re-consent and obtaining soon after ethical approval (e.g. at the next study visit or immediately after approval in safety cases, etc.).

8.5.2. Data collected from clinical trial participants

The objective is to confirm that the data collected from the participants were obtained and recorded in a accordance with the approved protocol and GCPs.

The following items can be checked, among others:

The. Handling of clinical trial participants' data within medical confidentiality.

B. Proof of participant identification, such as copy of ID or certificate of birth.

ç. Participant history

1. Fulfillment of inclusion and exclusion criteria (medical records must support all these criteria). For cases in which participants violating these criteria were allowed to enter, the justification for doing so must be duly documented.

2. Participant's visit schedule.

3. Safety data (report of adverse events and their follow-up according to the protocol, including clear medical justification for the causal or non-causal relationship pointed out; procedures performed; reason for early discontinuation of treatment, among others).

4. Effectiveness data (verification of procedures for analysis of primary objectives, among others).

d. List of screened and randomized participants, including those considered screening failures with the respective failure reason.

and. Randomization process according to Sponsor/POP instructions.

f. Appropriate administration of the investigational drug (including dose, frequency, route of administration and duration established by the protocol) and adherence to treatment.

g. Source document (medical records, exams, reports, etc.)

1. Organization (chronology of information, archiving, etc.).
2. Completion (data must3.6(4.9.0) be completed in a contemporary, exact manner, with identification of the person responsible for recording the data, legible, original and complete).

8.5.3. Case Report Form (CRF)

The objective is to confirm that the data recorded in the CRF correspond to the data of the source documents.

The following items can be checked, among others:

The. Completion, correction and verification of data by a person formally delegated to this function.

B. Completion of the CRF within the deadline stipulated by the sponsor.

ç. Signed and dated CRF pages.

d. Agreement between source data x CRF x clinical trial report prepared for registration of the drug (if applicable).

8.6. PRODUCT UNDER INVESTIGATION

The purpose of this item is to verify that all activities related to the product under investigation were carried out in accordance with protocol and local regulations.

The following items can be checked, among others:

The. Record of receipt, preparation, administration or dispensing to the participant and destruction or return to the sponsor.

B. Record of conservation care (such as recording of temperature and humidity) during drug transport to the clinical trial center and during storage in the center.

ç. Label of the investigational drug, according to the model sent in the DDCM.

d. Available quantity and validity of the products under investigation.

and. Record of investigational drug inventory/accounting. This item includes:

1. Date and quantity of investigational drug received, dispensed, returned or destroyed in the center.
2. Batch number, expiration date and drug allocation code number experimental.
3. Study participants' adherence to treatment.

f. Documentation related to allocated treatment, randomization and code breaking blind, if applicable.

g. Blind code maintenance plan, when there is a blind and non-blind team, if applicable.

H. Registration of the procedure according to the protocol/SOP in case of breach of study blinding.

i. Documentation related to change in expiration date/re-labeling of the investigational drug, if applicable.

j. Correlation between accounting documentation, source documents and CRF.

8.7. INVESTIGATOR FILE

The purpose of this item is to verify that the documentation in general is available, dated, signed (when applicable) and how it is filed at the clinical trial site.

The following items can be checked, among others:

The. Form of organization with the items that make up the investigator's file.

B. Versioning of documents.

ç. Correspondence between the center and the sponsor.

d. Internal mailings from the center (eg, minutes of staff meetings).

and. Evidence document that ensures compensation for trial participants clinical trials that may suffer any harm during the study.

f. Reporting a serious adverse event or adverse event of special interest within the timeframe stipulated in the protocol and in good clinical practice.

g. Serious adverse event notification form.

H. All TCLEs submitted and approved by the CEP. i. All protocol versions submitted and approved by the CEP.

j. All recruitment materials and other documents submitted and approved by the ZIP CODE.

k Investigator brochures updated and notified to the CEP.

l. Protocol signature pages and their amendments signed and dated by the investigator and sponsor.

m. Record of deviations and protocol violations by the investigator.

no. Other study-specific documents (such as guides and specific procedures; *newsletters).*

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 Document of the Americas and Manual of Good Clinical Practice of the International Conference of 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)]

Source Documents: Original documents, data, and records (e.g., hospital records, clinical and office records, laboratory notes, memos, assessment checklist or research subjects' journals, drug records provided by the pharmacy, data recorded by automated instruments, copies or transcripts validated after verification of their authenticity and accuracy, microfiche, photographic negatives, microfilms or magnetic records, results of radiological examinations, files of research subjects and records filed in pharmacies, laboratories and medical/technical departments involved in the study clinical).

[Reference: E6 (R2) and Americas Document]

Document for Importing Product(s) under investigation from the Clinical Development Dossier of Medicines (DDCM): Document issued by Anvisa, necessary for the import or export request for a clinical trial, in cases of non-manifestation about the DDCM.
[Reference: RDC 09/2015]

Clinical Drug Development Dossier (DDCM): compiled from documents to be submitted to Anvisa in order to evaluate the steps inherent to the development of an experimental drug in order to obtain information to support the registration or post-registration changes of said product . [Reference: RDC 09/2015]

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]

Co- **participating institution:** the one in which there will be the development of some stage of the research. This is, therefore, an institution that will participate in the project, just like the proponent, despite not having proposed it. [Reference: Letter No. 0212/CONEP/CNS of 10/21/2010]

Proposing institution: the one in which the main researcher has a link, therefore, the one from which the project will be proposed. [Reference: Letter No. 0212/CONEP/CNS of 10/21/2010]

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]

Legal Representative: An individual, legal entity, or other body authorized under applicable law to consent, on behalf of a potential participant, to the participant's participation in the clinical trial. [Reference: E6(R2)]

Impartial witness: A person, who is independent of the trial, who cannot be unduly influenced by those involved with the trial, who participates in the informed consent process if the participant or the participant's legal representative cannot read, and who reads the informed consent form and any other written information provided to the participant. [Reference: E6(R2)]

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 the 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]

10. BIBLIOGRAPHIC REFERENCES

ANVISA **Resolution of the Collegiate Board (RDC) No. 09, of February 20, 2015,** which provides for the regulation for conducting clinical trials with drugs in Brazil.

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

ANVISA **COPEC Activities Report - 2017.** 1st edition, 08/13/2018, section 5

ANVISA **Health Services Library.** Updated on 03/01/2020. Management of Regulatory Processes (GPROR) / General Management of Regulation and Good Regulatory Practices (GGREG)

ANVISA **Resolution of the Collegiate Board of Directors (RDC) nº 50, of February 21, 2002,** which provides for the Technical Regulation for planning, programming, elaboration and evaluation of physical projects of health care establishments.

ANVISA **Resolution of the Collegiate Board of Directors (RDC) No. 63, of November 25, 2011,** which provides for the Requirements for Good Operating Practices for Health Services.

ANVISA **Resolution of the Collegiate Board (RDC) No. 36, of July 25, 2013,** which institutes actions for patient safety in health services and other measures.

ANVISA **Resolution of the Collegiate Board of Directors (RDC) No. 07, of February 24, 2010,** which provides for the minimum requirements for the operation of Intensive Care Units and other measures.

ANVISA **Resolution of the Collegiate Board (RDC) No. 302, of October 13, 2005,** which provides for the technical regulation for the operation of clinical laboratories.

ANVISA **Resolution of the Collegiate Board of Directors (RDC) No. 222, of March 28, 2018,** which regulates the Good Practices for the Management of Waste from Health Services and makes other provisions.

EUROPEAN COMMISSION. **Guidance documents containing the common provisions on the conduct of GCP inspections by competent authorities of the different member states.** Guidance for the preparation of good clinical practice inspections, version 05/28/2008.

EUROPEAN COMMISSION. **Guidance documents containing the common provisions on the conduct of GCP inspections by competent authorities of the different member states.** Guidance for the conduct of good clinical practice inspections, version 05/28/2008.

EUROPEAN COMMISSION. **Guidance documents containing the common provisions on the conduct of GCP inspections by competent authorities of the different member states.** Annex I - To guidance for the conduct of good clinical practice inspections – investigator site, version 05/28/2008.

EUROPEAN MEDICINES AGENCY. **Annual report of the Good Clinical Practice Inspectors Working Group 2016.** EMA/INS/GCP/763873/2016. Dated 06/15/2017

FOOD AND DRUG ADMINISTRATION. **Compliance program guidance manual. Chapter 48 - Bioresearch monitoring.** Clinical Investigators and Sponsor-Investigators, version 08/05/2008.

FOOD AND DRUG ADMINISTRATION. **Information Sheet Guidance for IRBs, Clinical Investigators and Sponsors.** FDA inspectors of clinical investigators, version June, 2010.

FOOD AND DRUG ADMINISTRATION. **Bioresearch Monitoring Program (BIMO) Metrics – FY' 16.**

HEALTH CANADA. **Classification of observations made in the conduct of inspections of clinical trials.**

Guide-0043. Version of 20/08/2008.

HEALTH CANADA. **Inspectorate Program. Annual Inspection Summary Report 2015-2016.** Chapter 4 - Drug Good Clinical Practices Inspection Program (GCP)

INTERNATIONAL CONFERENCE ON HARMONISATION. **ICH harmonized tripartite guidelines. Guideline for Good Clinical Practice E6 (R2).** Current Step 4 version, 09 Nov 2016.

ISP (INSTITUTE OF PUBLIC HEALTH OF CHILE). **Inspection guide for clinical pharmacological studies.** Resolution No. 5174, of December 30, 2016.

MFDS (MINISTRY OF FOOD AND DRUG SAFETY). **Specifications for Clinical Trial Control (KGCP) of Pharmaceutical Drugs.** Regulation on Safety of Pharmaceutical Drugs. Article 30, 10/28/2016, South Korea.

MEDICINES AND HEALTHCARE PRODUCTS REGULATORY AGENCY (MHRA). **Good Clinical Practice Guide.** Annex 1 – Introduction to GCP inspections. 2012

MEDICINES AND HEALTHCARE PRODUCTS REGULATORY AGENCY (MHRA). **GCP inspections metrics report.** Report period between 04/01/2016 to 03/31/2017. Document date 05/11/2018.

MINISTRY OF HEALTH. **Ordinance No. 2616, of May 12, 1998,** which provides for guidelines and norms for the prevention and control of hospital infections.

MINISTRY OF HEALTH. **Ordinance No. 2048, of November 5, 2002,** which approves the technical regulation of state urgency and emergency systems.

PAN AMERICAN HEALTH ORGANIZATION/WHO. **Good Clinical Practices: Document of the Americas.** IV Pan-American Conference for Harmonization of Pharmaceutical Regulations. March 2-4, 2005.

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.

11. EDITIONS HISTORY

VERSION	DATE	AMENDMENT	JUSTIFICATION
1	09/11/2020	Initial issue	Not applicable
two	01/26/2022	Amendments made based on contributions received during the Public Consultation period (09/14/20 to 03/11/21):	
		The acronyms CAPA, CRF, ICH, IVRS, IWRS, SUSAR have been updated with the English nomenclature.	As the acronyms originate from English, the meaning of the English acronym is included. clarification was for in
		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 7.1.2 (Request for Prior Documentation): item III - The part in bold was included in the text - List with all versions of the study protocol and their amendments **applicable to Brazil.** The **amendment** versions do not **already implemented, but** which have not yet been petitioned at Anvisa should be forwarded.	To make it clear that the amendments are applicable in Brazil. In addition, the submission of versions not submitted to Anvisa are those already implemented (and therefore not substantial), but which were not on time to be sent to the agency.
		Section 7.1.2 (Request for Prior Documentation): renumbering of items after VIII.	Incorrect was numbering.
		Section 7.1.2 (Request for Prior Documentation): item XVI - The part in bold has been included: Spreadsheet containing all **clinical trial protocol** deviations and violations identified to date referring to the center to be inspected. (Model in Annex 10)	To clarify that they are deviations and protocol violations.
		Section 7.1.2 (Request for Prior Documentation): item XXVIII - The part in bold has been included: Spreadsheet containing experimental/ placebo drug kit number, batch number, expiration date, date sent to the center to be inspected, date of	To clarify special what procedure will be done if the study has blind and non-blind teams to avoid breaking the blind character.

		receipt by the center, date of dispensing to the participant, number of the participant to whom the drug was dispensed. **In the case of studies involving blind and non-blind teams, Anvisa inspectors will instruct how to send this worksheet to avoid breaking the blind character.** (Model in Annex 13)	
		Section 7.1.2 (Request for Prior Documentation): In the last paragraph of this section, the part in bold was added: It should be noted that, before the start of the inspection, Anvisa inspectors must have access to all computerized systems used **by the center during the study,** including for closed case studies.	To clarify what it refers to The systems computers used by the center during the study.
		Section 7.1.3 (Preparatory meeting for inspection) was included	A virtual pre-inspection meeting will make it easier to align with the inspected party the logistical details of the inspection.
		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 7.3 (After inspection): The part in bold has been included: For each finding, the appropriate references to the Document of the Americas or International Council for Harmonization (ICH E6 (R2)) and local legislation, **as well as those responsible for each finding (center or sponsor).**	To facilitate the identification of the person responsible for each finding.
		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.
		Item 8.3.4 (Inpatient ward or infusion room): item c - the part in bold has been added and the strikethrough part has been deleted: Presence of an emergency cart sealed and ~~checked with~~	Were More details about the stroller included emergency to clarify what cart information is usually

		~~adequate frequency (including oxygen and available accessories)~~, in an easily ~~accessible loca~~tion. **The cart does not necessarily need to be in the inpatient/infusion ward, but in the place where the medication experimental is administered. In the emergency cart it will be checked mainly if it it is sealed and checked with adequate frequency. The presence, validity and functioning of emergency trolley items will also be verified to guarantee immediate assistance in the event of a medical emergency. During the inspection, the inspector may request that the cart's seal be broken to verify its contents.**	checked during inspection.
		Item 8.3.4 (Inpatient ward or infusion room): item d – the part in bold was added: Number of beds and infusion pumps in the infusion room, **if applicable for the clinical trial.**	To clarify that this item will be checked only if applicable to the study.
		Item 8.3.9 (computerized systems): item h – the part in bold has been included: 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.
		Item 8.4.1 (Written and controlled procedures of the study): item 6 - the part in bold was added and the strikethrough part was excluded: Record in medical record **source document** (~~physical or~~ electronic)	To correct the term “record” “source document” for
		Item 8.5.1 (Free and Informed Consent Form): item f - the part in bold has been added and the strikethrough part has been deleted: The impartiality of the witness must be proven **evidenced.**	To clarify that it is necessary to have evidence of the impartiality of the witness. The word “proof” could give an understanding of the need for a supporting document.
		Section 10 (References Bibliographic): inclusion of the following reference: **PHARMACEUTICAL INSPECTION CO-OPERATION SCHEME (PIC/S):**	To update the reference used after reviewing the guide.

		PIC/S Guidance: Good Practices for Computerized systems in regulated GXP environments. PI 011-3 of September 25, 2007.	

12. ANNEXES

- **Annex 1:** Model list of study activities with their respective guardians
- **Annex 2:** List template of all inspected center departments involved in the study
- **Annex 3:** Spreadsheet template with all participants screened at the center to be inspected
- **Annex 4:** Spreadsheet template with the number of participants screened in the study
- **Annex 5:** Document template with the date of the first visit of the first screened participant and the last visit of the last randomized participant in Brazil
- **Annex 6:** List template of the sponsor/CRO team responsible for each activity of the study in Brazil
- **Annex 7:** Spreadsheet template with information from team members of the center to be inspected
- **Annex 8:** SOP list template of the center and sponsor used in the study
- **Annex 9:** Spreadsheet template of EAGs and SUSARs occurred in the study
- **Annex 10:** Spreadsheet template of deviations and violations of the center to be inspected
- **Annex 11:** Spreadsheet template on monitoring visits carried out at the center to be inspected
- **Annex 12:** Spreadsheet template with CEP documentation referring to the center to be inspected
- **Annex 13:** Spreadsheet template with the inventory of the products under investigation

Agência Nacional de Vigilância Sanitária – Anvisa

SIA Trecho 5, Área Especial 57, Lote 200

CEP: 71205-050

Brasília – DF

www.anvisa.gov.br

www.twitter.com/anvisa_oficial

Anvisa Atende: 0800-642-9782

ouvidoria@anvisa.gov.br