Inspection Guide on Good Clinical Practices (GCP) on clinical trials with drugs and biological products - Inspection in Clinical Trial Sites

Guide No. 35/2020 - version 2

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EFFECTIVE AS OF 27/Jan/2022

This Guide expresses Anvisa's understanding of the best practices regarding procedures, routines and methods considered appropriate for compliance with technical or administrative requirements required by the Agency's legislative and regulatory frameworks.[1]

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

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

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

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ACRONYMS

ANVISA – Brazilian Health Regulatory Agency
GCP – Good Clinical Practices
CAPA – Corrective actions, preventive actions
CE – Special Notice
IEC - Independent Ethics Committee
CONEP – National Research Ethics Committee
COPEC – Clinical Research Coordination for Drugs and Biological Products
CRF – Case Report Form
DDCM – Dossier for the Clinical Development of Experimental Drug
FAEC – Clinical Trial Submission Form
ICH – International Council for Harmonisation
IN – Normative Instruction
PI – Principal Investigator
IVRS - Interactive Voice Response System
IWRS - Interactive Web Response System
CRO – Clinical Research Organization
SOP – Standard Operating Procedure
RDC – Collegiate Board Resolution
SUSAR – Suspected Unexpected Serious Adverse Reaction
ICF – Informed Consent Form
ICU – Intensive Care Unit

1. SCOPE

This guide deals with procedures for conducting a Good Clinical Practice (GCP) inspection of clinical trials with drugs and biological products in clinical trial sites. The guide is intended for everyone who is involved in clinical trials, including sites, sponsors, Clinical Research Organization (CRO) and Anvisa inspectors.

2. INTRODUCTION

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

The GCP inspections, which are foreseen in RDC No. 09, February 20th, 2015, Chapter VIII, Article 71, have as main objectives to verify the rights protection of clinical trial subjects, the degree of compliance with current Brazilian legislation and compliance with GCP, and the quality of data generated in clinical trials. Inspections can be performed at any location where study activities are

conducted, including clinical trial sites, sponsor, Clinical Research Organization (CRO), laboratories, and other institutions involved in the experimental drug development.

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

This guide describes how Anvisa conducts GCP inspections in clinical trial sites, based on the current Normative Instruction (IN) No. 20, October 20th, 2017, with the aim of harmonizing and guiding those involved in inspection procedures, thus ensuring a unified standard and the safety of all parties involved.

Throughout the text, the term "shall" is accompanied by the legal basis to which it refers (section 3 of this guide). E.g.: *The inspection shall[3.5 (Art. 5)] take place within a maximum of five (5) working days*. In this case, item 3.5 is the Normative Instruction No. 20/2017, therefore, the term refers to Article 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, January 26th, 1999, which defines the Brazilian National Health Surveillance System, creates the Brazilian Health Regulatory Agency, and provides other measures.

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

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

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

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

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

3.7. Good Clinical Practices: Document of Americas - IV Pan American Conference for harmonization of pharmaceutical regulations. March 2-4, 2005.

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

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

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

3.11. Operational Standard No. 001/2013 of the National Health Council (CNS), which provides for the organization and functioning of the IEC/CONEP System, and on the procedures for

submission, evaluation and monitoring of research and development involving human beings in Brazil, in terms of item 5, Chapter XIII, of CNS Resolution No. 466, December 12th, 2012.

4. INSPECTION SCOPE

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

5. INSPECTION TEAM AND DURATION

According to IN No. 20/2017, the inspection in GCP will be performed by employees of the effective staff of Anvisa, duly identified and qualified, respecting the attributions and competencies inherent to these positions.

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

The inspection shall[3.5 (Art.5)] take place within a maximum of five (5) business days. Exceptionally this period may be amended on the subject of due justification.

The inspection can take place both in person and remotely[3.8 (Art.71)].

6. CLINICAL TRIAL AND SITE TO BE INSPECTED SELECTION CRITERIA

The following are the most commonly used criteria for the selection of the clinical trial and the site to be inspected. 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 inspected internationally by other regulatory agencies;
- Studies with populations considered vulnerable, such as pediatrics, elderly, Indians, people with disabilities;
- Studies evaluated as complex by COPEC (e.g., studies with many procedures per visit, manipulation of experimental medication in an unusual way, etc.);
- Studies whose experimental medication is strategic for the country, such as for the treatment of diseases of endemic profile or that have socioeconomic impact;
- Studies initiated as provided for in Paragraph 1, Article 36 of RDC 09/2015;
- Results of previous inspections performed by Anvisa;
- Demand from other areas of Anvisa;
- Report.

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

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

- Principal Investigator with a large number of active clinical studies at the same time;
- Problems identified during evaluation of annual/final monitoring reports and adverse events;
- Results of previous inspections performed by Anvisa;
- Report.

7. INSPECTION STEPS

7.1. Before inspection

7.1.1. Notice of Inspection

For each inspection, an administrative process (11407 - Health Investigation Dossier) will be instructed, which will contain all documentation related to the inspection. The inspection notification will be made through Electronic Letter to the sponsor or CRO responsible for the study before Anvisa. A copy of the letter will be sent to the principal investigator at the email address that was provided on the Clinical Trial Submission Form (FAEC).

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

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

7.1.2. Request for prior documentation

In the inspection notification letter, some documents will be requested in advance to assist the inspectors in conducting the inspection. The following list is an example of what is usually requested. However, the list may be changed as required by each study.

I. List of the study activities with the respective person in charge.
Example: Activities performed by the sponsor, ORPCs, and other partners (also called *vendors*). (Model of Annex 1)

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

III. List with all versions of the study protocol and its amendments for Brazil. Versions of non-substantial amendments that have already been implemented, but that have not been petitioned yet in Anvisa shall[3.4(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) completion, randomization system (Interactive Voice or Web Response System - IVRS or IWRS), pharmacy, etc.

V. List with all versions of the investigator's brochure. Versions that have yet been petitioned yet in Anvisa shall[3.4 (Article 41)] be forwarded.

VI. Informed Consent Forms (ICFs) and Assent Terms, if applicable – all versions already used, including exclusive site versions (if applicable).

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

VIII. Electronic spreadsheet with current data of all subjects screened in the site to be inspected, containing the subject's number, screening date, randomization date, discontinuation date (if applicable), signature date of all ICFs obtained for each subject and justifications for subjects considered as screening failure and discontinued. (Model of Annex 3)

IX. Electronic spreadsheet containing number of screened subjects, screening failure, randomized, active, discontinued and that completed the study for each Brazilian site and the study total. (Model of Annex 4)

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

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

XII. Delegation form of the site responsibilities to be inspected, including blinded and non-blinded members, if applicable.

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

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

XV. Electronic spreadsheet with all Serious Adverse Events (SAEs) and all suspected unexpected Serious Adverse Reactions (SUSARs) occurring in Brazil and worldwide, containing the subject's number, name of SAE, start and end date of the event, outcome/evolution (if applicable), relationship with the study drug, severity criterion (e.g., death, hospitalization), action taken with the SAE. (Model of Annex 9)

XVI. Electronic spreadsheet containing all deviations and violations identified so far referring to the site to be inspected. (Model of Annex 10)

XVII. Contract between sponsor and site to be inspected (financial aspects can be obliterated) and listing of other contracts relevant to the inspected site activities (e.g. between site and backup hospital, local laboratory, external filing, etc.).

XVIII. Information about the CRF format (paper or electronics) and a blank model of CRF.

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

XX. Monitoring reports of the site to be inspected, including that of the selection, initiation, and closure visit, if applicable.

XXI. Electronic spreadsheet with current data on monitoring visits in the site to be inspected, containing type of visit (e.g. screening, initiation, monitoring or closure), start and end date of the visit, name of the monitor(s) that performed the visit, date of report approval, name of the report approver and date of sending the follow-up letter to the site. (Model of Annex 11)

XXII. Form of monitoring visits performed in the site to be inspected signed by the representatives of the sponsor at each visit (Site Visit Log).

XXIII. All the site ethical approvals to be inspected, list of members of the Independent Ethics Committee (IEC), registration and renewal of the IEC registration in the National Research Ethics Commission (CONEP) or registration status, when the registration renewal is not available yet. For submissions and approvals, a printscreen of Plataforma Brasil is sufficient.

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

XXV. Accounting forms of the site investigational products to be inspected.

XXVI. Interactive Voice or Web Response System (IVRS or IWRS) data report for the site to be inspected, including all information related to the experimental drug (shipping, dispensing, disposal, etc.).

XXVII. Electronic spreadsheet containing experimental/placebo drug kit number, batch number, expiration date, date of shipment to the site to be inspected, date of receipt by the site, date of dispensation to the subject, subject's number for which the drug was dispensed. In the case of studies involving blind and non-blind teams, Anvisa inspectors shall instruct how to send this worksheet to avoid breaking the blind. (Model of Annex 13)

The models included in Annexes 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 elaborated/generated by the sponsor/CRO. The purpose of these spreadsheets is to facilitate the inspection preparation. In the cases of spreadsheets mentioned in items XII, XIII, XV and XVI, when it is not possible to generate spreadsheets, pdf reports with active copy/paste function can be forwarded.

Before submitting the documents and spreadsheets, the inspected one shall[3.6(4.8.10.n)] try not to forward any information that impairs the subject's confidentiality of the clinical trial.

These documents shall[3.4 (Art.41)] be forwarded to Anvisa by Electronic Addition to the Sanitary Investigation Dossier (informing the office number and date for the inspection e-mail). The deadline for sending the documents is usually 1 to 2 weeks, depending on the complexity of the documentation requested.

It shall be emphasized that, before the inspection beginning, Anvisa inspectors must[3.6 (5.1.2)] have access to all computerized systems used, including for cases of closed 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 for the inspection.

7.2. During inspection

The inspection process is usually composed of the following steps:

- Opening meeting,
- Visit to facilities,
- Interview with the study team,
- Document analysis,
- Closure meeting.

7.2.1. Opening meeting

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

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

The principal investigator (PI) makes a brief description of the clinical trial site, study team and the activities that PI is conducting. The PI shall[3.5 (Art.4)] be present throughout the meeting as well as the

sponsor representative/CRO. It is recommended that a representative of the institution's management also be present. Exceptional cases where the PI or sponsor/CRO representative cannot be present will be discussed with COPEC prior to inspection.

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

A member of the study team, preferably from the site, shall be designated, who will accompany inspectors throughout the inspection process, not necessarily the PI.

The attendance list 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 shall preferably stay in a separate room from the site staff and with internet access.

7.2.2. Visit to facilities and document analysis

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

7.2.3. Interviews

Before starting interviews, inspectors will request that all documentation regarding curricula, professional experiences, and training of the entire study team be available for 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 questioned regarding any clarifications or doubts arising during the 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 inspection, but this may vary depending on the logistics and focus of the inspection.

7.2.4. Closure meeting

At the inspection end, the team of inspectors will hold the closure meeting, in which a summary of the inspection activities will be made, and any findings will be informed. At this time, inspectors will not classify the findings found. The findings classification will be reported in the inspection report.

During the meeting, it will also be clarified about the procedures and post-inspection deadlines. The meeting will be conducted by the lead inspector. The PI and sponsor representative must[3.5(Art.4)] be present throughout the meeting. It is recommended that a representative of the institution's management also be present. Exceptional cases where the PI or sponsor/CRO representative cannot be present will be discussed with Anvisa prior to 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/CRO of the study via electronic letter and to PI, by email.

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

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

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

Upon receipt of the inspection report, sponsor/CRO will have 120 calendar days for demonstration, according to Article 8 of IN No. 20/2017.

The answer to each critical or major finding must be given by identifying the root cause and proposing corrective and preventive actions (CAPA) with the estimated deadlines and those responsible for each action. In addition, the impact and risk of the finding shall be evaluated for the entire study and not only for the inspected site, as applicable. For minor findings, only corrective actions need to be sent to Anvisa.

The following is an example of an answer:

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 the evidence justifying the response. For example, if the preventive action for the finding was the elaboration of a SOP, this SOP shall be sent to Anvisa along with the response.

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

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

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

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

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

- **Compliant with GCP:** Compliance with GCP does not mean that no findings have been found or no action has been required. However, the observations found were corrected or did not critically affect GCP, not leading to the determinations described in the following item.

- **Non-compliant with GCP:** Not complying with the GCP means that, after evaluating the response to the findings identified in the inspection, Anvisa's conclusion is that the study was not conducted according to the GCP. In case of non-compliance with the GCP, Anvisa may, according to Article 11 of IN No. 20/2017, determine:

I - temporary discontinuation of the clinical trial;

II - the definitive cancellation of the clinical trial, in the site concerned;

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

IV - the data invalidation from the site concerned or the clinical trial.

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

8. ITEMS TO BE CHECKED AT CLINICAL TRIAL SITES

This section lists items that inspectors generally check during an inspection at clinical trial sites. However, depending on the inspection focus, not all items will be evaluated, or it may still be necessary to check for items that are not mentioned herein.

8.1. APPROVALS AND AGREEMENTS/CONTRACTS

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

8.1.1. Regulatory approval

The following items can be checked, among others:

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

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

8.1.2. Ethical approval (IEC/CONEP)

The following items can be checked, among others:

a. IEC (and CONEP, if applicable) approval for protocol (and its amendments) and ICF with the identified version
b. Nature and frequency of correspondence with the local IEC. This item may include:
1. Submission and approval of study documents, such as protocol and amendments, materials to be distributed to study subjects, other materials that require ethical approval.
2. Notifications of reports of adverse events and serious adverse events
3. Notification of deviations and violations

4. Notification of change of the principal investigator
5. Partial and final reports
6. Safety information
7. List of IEC members and declaration on renewal of IEC registration in CONEP
8. Letter of exemption from voting of IEC members who are directly involved with the inspected clinical trial

8.1.3. Contracts/Agreements

The following items can be checked, among others:

a. Contracts/agreements signed between the parties involved (e.g. between the site (PI and institution)/sponsor or CRO, site/clinical analysis laboratory, site/radiology sector, site/backup hospitals, site/co-participant institution, site/archiving company, site/health service waste management company).
b. Evidence that the clinical trial subject and his/her companion (as applicable) was duly reimbursed for transportation and food.
c. Agreement between sponsor/CRO and site for archiving the study documentation.
d. In the agreements/contracts will be verified mainly scope, effective period, responsibilities defined by each party, in line with the approved protocol.

8.2. ORGANIZATION AND CLINICAL TRIAL SITE TEAM

The purpose of this item is to verify whether the site organization is able to guarantee an adequate conduct of the clinical trial as well as guarantee adherence to Good Clinical Practices. In relation to 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:

a. Organization chart of the site.
b. List of all clinical trials conducted by the investigator, including information on the protocol code, protocol title, name of the experimental drug, sponsor name and study start and end dates.
c. Address of all locations where the clinical trial subject is served and where the study is conducted.
d. Site's operation flow, such as:
    1. Flows to obtain medical records
    2. Communication flows within the study team
e. Quality assurance system (refer to section 8.4 of this guide).
f. List of task delegations duly completed and signed.
g. Curricula of the team involved in the study and professional licenses.
h. Record of training in Good Clinical Practices, protocol, procedures, study manuals and any other applicable training. The records must contain, at a minimum, the training date,

subject or material used (including version, if applicable), form of training (example: individual reading, lecture, class), responsible for the training and identification of trained employees (for example, through subscriptions).

i. Training certificate for emergency procedures, when applicable.
j. Compatibility between the team's 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 described in the Good Clinical Practices and that he/she is aware of the study protocol.

8.3. INFRASTRUCTURE

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

It shall be emphasized that health service facilities must also comply with the relevant local laws. If local legislation does not include the issues already regulated by Anvisa, federal legislation shall be applied.

A compiled of the main regulations can be found in the document "Health Services Library" (version 03/Jan/2020 and subsequent updates), via link: http://portal.anvisa.gov.br/documents/33880/4967127/Biblioteca+dos+Temas+de+Servi%C3%A7os+de+Sa%C3%BAde_Portal.pdf/55e4ab14-e99f-41c1-aea9-cc6e8875b5e4. The main standards related to health services include 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 facilities are those that are usually checked. However, other locations can be checked, depending on the characteristics of each study.

8.3.1. Study file

a. Identification and organization of file folders.
b. Appropriate structure for document storage.
c. Restricted access to the file.
d. Action plan/contingency plan in cases of fire, flood and pests.
e. Filing after completion of the clinical trial.
f. Record of the location of essential documents, including source documents.

8.3.2. Pharmacy or storage location of the investigational products

a. Restricted and controlled access to the pharmacy or the location where the investigational products are stored.

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

c. Contingency plan in case of power failure (nobreak and generator).

d. Segregated and duly identified location for the investigational products of each study to enable the products to be stored in a logical manner, allowing for prompt, agile location and without the possibility of errors in separation and dispensing. The local segregation and identification should be mainly in relation to the study (for example: study “X”, “Y”, “Z”) and in relation to the product status (e.g.: expired or quarantined products must be completely separate from stock in use).

8.3.3. Offices

a. Evidence that the site maintains the confidentiality and privacy of clinical trial subjects for the discussion and obtaining of the ICF, and for clinical evaluations performed during the clinical trial.

8.3.4. Inpatient ward or infusion room

a. Access to a study doctor throughout the hospitalization period, if this procedure is part of the protocol.
b. Availability of ICU in the clinical unit (according to RDC 07/2010) or contract with mobile ICU (advanced support ambulance - ambulance type D, according to Ordinance MS 2.048/2002) and backup hospital.
c. Presence of an emergency trolley in an easily accessible location. The trolley does not necessarily need to be in the inpatient/infusion ward, but rather where the experimental drug is administered. In the emergency trolley, it will be checked mainly if it is sealed and checked with adequate frequency. The presence, validity and functioning of emergency trolley 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 trolley'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. Collection and handling room for biological samples

a. Collection area.
b. Storage of samples before analysis or sending to external laboratory, national or international.
c. Shipping conditions to external laboratory, if applicable.

8.3.6. Clinical laboratory

The clinical laboratory shall follow the guidelines of RDC No. 302/2005. During the inspection, the following items can be checked:

a. Validated procedures for collection, processing, handling and transport and analysis of biological samples.
b. Certificate of external proficiency, certificate of accreditation, reference values and SOPs.
c. Record room temperature control, refrigerator, freezer or water bath when needed.

8.3.7. Equipment

The objective is to verify that the equipment used in all facilities where the clinical trial is conducted is in proper conditions for use.

The following items will be checked, among others:

a. Certificate of calibration or periodic maintenance.
b. Operation and location (specific equipment must be available at the place of use).
c. Procedures established for use of each equipment, such as equipment manual or SOP.

8.3.8. Waste management

The objective is to verify if the health service waste was properly managed, according to RDC 222/2018, from segregation, packaging, identification, treatment, transport to final disposal.

The following items can be checked, among others:

a. Container with lid identified for each type of residue and that is rigid and resistant to puncture, breakage and leakage.
b. Collector/incinerator suitable for sharp cutting materials, available at the procedure location.

8.3.9. Computerized systems

a. Purpose of using the system.
b. Procedures for creating, modifying, deleting, maintaining or transmitting electronic records.
c. Types of access profiles.
d. Presence of an audit trail to identify any data entry and changes in the system.
e. Security system (for example, who has access and how this access is controlled).
f. Presence of backup, data recovery or contingency plan to avoid data loss (including in cases of software updates).
g. Procedures for handling electronic data after the study end.

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 the use of 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 Americas and ICH E6 (R2).

The following items can be checked, among others:

a. 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 forwarding reports given to issues verified in monitoring visits.
   4. Evidence of follow-up given by PI to the findings observed in monitoring visits.
   5. Evidence of adequate communication between monitor and superior staff for the treatment of critical findings.
   6. Record of monitoring visits in appropriate form, as well as the scope and frequency of the same.

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 IEC or other regulatory authorities, if applicable.

c. Treatment of deviations, investigation and identification of the root cause and adoption of corrective and preventive measures.
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 the site has written and controlled processes, flows or procedures of the study.

Procedures that are protocol-specific shall[3.6 (5.1.1)] be provided by the sponsor to ensure that all sites are performing the procedure in a standardized manner (for example, study unblinding procedure, notification of adverse events conditions, preparation and administration of the experimental drug). Documented manuals and instructions are examples of these procedures.

Where there are divergences between the procedures of the site and the sponsor, the site shall follow those of the sponsor in order to ensure harmonization between the data collected in the 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 site must define in advance, and together with the sponsor/CRO, which procedures will be necessary during the conduct of the clinical trial. The following are examples of procedures that inspectors may require for a clinical trial.

a. Training and continuing education of the study team
b. Recruitment and screening of clinical trial subjects
c. Application of ICF and Assent Term
d. Completion, correction and verification of data from the Case Report Form (CRF)
e. Record in medical records (physical or electronic)
f. Use, calibration and maintenance of equipment/instruments
g. Transportation, receipt, storage, control and accounting of the experimental drug
h. Preparation and administration of the experimental drug
i. Destruction or return of the experimental drug
j. Electricity failure and contingency plan in the storage area of the experimental drug
k. Collection, transport, preparation, identification and analysis of laboratory samples
l. Disposal of biological and non-biological materials
m. Unblinding of study
n. Notification of adverse events and serious adverse events (including pregnancy cases), containing deadlines for reporting
o. Preparation and maintenance of files (including information on the retention time of study documents)

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

p. Existence and adherence to written processes, flows and procedures.
q. Check whether processes, flows, and procedures have a version control and change history.
r. Record of team training in the processes, flows and procedures available and in force.
s. Check whether the processes, flows and procedures are available and accessible.
t. Update and frequency of reviews of study processes, flows and procedures, proven 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. 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:

a. Version of the ICF approved by IEC.
b. Signature, date and heading of the ICF by the subject or his/her legal representative and by the person who conducted the consent process, prior to any clinical trial procedure.
c. Evidence that a signed copy of ICF was given to the subject or his/her legal representative.
d. Evidence that the consent process was conducted appropriately and before any other procedure of the clinical trial, and the record of this process is in the subject's medical records.
e. Assent Term approved by the IEC, in the case of underage or legally incapacitated subjects along with a copy of the ID or birth certificate.
f. Presence of an impartial witness or legal representative, where applicable, including the need and identification of such persons. The witness's impartiality shall[3.6 (1.26)] be proven.
g. Need for subjects to re-consent and obtain it shortly after ethical approval (for example, at the next study visit or immediately after approval in safety cases, etc.).

8.5.2. Data collected from clinical trial subjects

The objective is to confirm that the data collected from the subjects were obtained and recorded according to the approved protocol and the GCP.

The following items can be checked, among others:
a. Handling of data from clinical trial subjects within medical confidentiality.
b. Proof of identification of the subject, for example, ID or birth certificate copy.
c. Subject's history
    1. Compliance with the inclusion and exclusion criteria (medical records must support all these criteria). For cases in which subjects were allowed to enter in violation of these criteria, the justification for this must be properly documented.
    2. Visits calendar of the subject.
    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. Efficacy data (checking of procedures for analysis of primary objectives, among others).
d. List of screened and randomized subjects, including those considered screening failures with the respective failure ratio.
e. Randomization process according to sponsor/SOP instructions.
f. Appropriate administration of the experimental 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 must[3.6(4.9.0)] be filled in in a contemporary, accurate manner, with identification of the data registration officer, legible, original and complete).

8.5.3. Case Report Form (CRF)

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

The following items can be checked, among others:

a. Filling, correcting and verifying the data by person formally delegated to this function.
b. Completion of the CRF within the time stipulated by the sponsor.
c. Signed and dated CRF pages.
d. Agreement between source data x CRF x clinical trial report prepared for drug registration (if applicable).

8.6. INVESTIGATIONAL PRODUCT

The purpose of this item is to verify that all activities related to the investigational product were performed in accordance with local protocol and regulations.

The following items can be checked, among others:

a. Registration of receipt, preparation, administration or dispensation to the subject and destruction or return to the sponsor.
b. Record of conservation care (such as, temperature and humidity record) during the medication transport to the clinical trial site and during its storage at the site.
c. Experimental drug label, according to the model sent in the DDCM.
d. Available quantity and validity of the investigational products.
e. Inventory/accounting record of the experimental drug. This item includes:
    1. Date and quantity of experimental drug received, dispensed, returned or destroyed at the site.
    2. Batch number, expiration date, and allocation code number for the experimental drug.
    3. Adherence of study subjects to treatment.
f. Documentation related to allocated treatment, randomization and unblinding, if applicable.
g. Blinding code maintenance plan, when there is blinded and non-blinded staff, if applicable.
h. Registration of the procedure according to the protocol/SOP in case of study unblinding.
i. Documentation related to the change in the expiration date/re-labelling of the experimental 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 is generally available, dated, signed (where applicable) and how it is archived in the clinical trial site.

The following items can be checked, among others:

a. Form of organization with the items that compose the investigator file.
b. Versioning of documents.
c. Correspondences between the site and the sponsor.
d. Internal correspondence from the site (for example, minutes of team meetings).
e. Supporting document that ensures the compensation for the clinical trial subjects who will suffer any damage during the study.
f. Communication of serious adverse event or adverse event of special interest within the time limit stipulated in the protocol and in good clinical practices.
g. Serious adverse event notification form.
h. All ICFs submitted and approved by the IEC.
i. All protocol versions submitted and approved by the IEC.
j. All recruitment materials and other documents submitted and approved by the IEC.
k. Investigator's brochures updated and notified to IEC.
l. Protocol signature pages and their amendments signed and dated by the investigator and sponsor.
m. Record of protocol deviations and violations by the investigator.
n. Other study-specific documents (e.g., guides and manuals for specific procedures; *Newsletters*).

9. GLOSSARY

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

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

Minor findings: findings that do not fit critical or larger observations but indicate deficiency and/or deviation; such findings shall be cited for the 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 Practices (GCP): standard for planning, conducting, performing, monitoring, auditing, recording, analyzing and reporting clinical trials that provides assurance that the data and results reported have credibility and accuracy, and that the rights, integrity and confidentiality of clinical trial subjects are protected, in accordance with the GCP guidelines set out in the Document of Americas and the Good Clinical Practices Manual of the International Harmonization Conference (Document E6(R2)). [Reference: RDC 09/2015]

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

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

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

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

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

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

Source Documents: Original documents, data and records (e.g., hospital records, clinical and office records, laboratory notes, memoranda, evaluation checklist or journals of the research subjects, registration of drugs 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, radiological test results, archives of research subjects and records archived in pharmacies, laboratories and medical/technical departments involved in the clinical study). [Reference: E6 (R2) and Document of Americas]

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

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

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

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

Serious Adverse Event: one that results in any adverse experience with medications, biological products 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/inability;
d) requires hospitalization or prolongs hospitalization;
e) congenital anomaly or birth defect;
f) any suspected transmission of infectious agent by means of a drug or;
g) clinically significant event.

[Reference: RDC 09/2015]

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

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

Co-participant 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 21/Oct/2010]

Proposing institution: the one in which the principal investigator is bond to, therefore the one from which the project will be proposed. [Reference: Letter No. 0212/CONEP/CNS of 21/Oct/2010]

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

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

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

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

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

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

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

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

Legal Representative: An individual, legal person or other body authorized under the laws in force to consent, on behalf of a potential subjects, to the participation of the clinical trial subject. [Reference: E6(R2)]

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

Computerized systems validation: a process that establishes and documents that specific requirements for a computerized system can be consistently met from design up to system deactivation or transition to a new system. The validation approach shall be based on a risk

assessment that takes into account the intended use of the system and the system potential to affect the subject's protection and reliability of the study results. [Reference: E6(R2)]

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

10. BIBLIOGRAPHIC REFERENCES

ANVISA. **Resolução da Diretoria Colegiada (RDC) nº 09, de 20 de fevereiro de 2015**, que dispõe sobre o regulamento para a realização de ensaios clínicos com medicamentos no Brasil.

ANVISA. **Instrução Normativa (IN) nº 20, de 02 de outubro de 2017**, que dispõe sobre procedimentos de inspeção em Boas Práticas Clínicas para ensaios clínicos com medicamentos.

ANVISA. **Relatório de Atividades da COPEC - 2017**. 1ª edição, de 13/08/2018, seção 5

ANVISA. **Biblioteca de serviços de saúde**. Atualizada em 03/01/2020. Gerência de Processos Regulatórios (GPROR)/ Gerência Geral de Regulamentação e Boas Práticas Regulatórias (GGREG)

ANVISA. **Resolução da Diretoria Colegiada (RDC) nº 50, de 21 de fevereiro de 2002**, que dispõe sobre o Regulamento Técnico para planejamento, programação, elaboração e avaliação de projetos físicos de estabelecimentos assistenciais de saúde.

ANVISA. **Resolução da Diretoria Colegiada (RDC) nº 63, de 25 de novembro de 2011**, que dispõe sobre os Requisitos de Boas Práticas de Funcionamento para os Serviços de Saúde.

ANVISA. **Resolução da Diretoria Colegiada (RDC) nº 36, de 25 de julho de 2013**, que institui ações para a segurança do paciente em serviços de saúde e dá outras providências.

ANVISA. **Resolução da Diretoria Colegiada (RDC) nº 07, de 24 de fevereiro de 2010**, que dispõe sobre os requisitos mínimos para funcionamento de Unidades de Terapia Intensiva e dá outras providências.

ANVISA. **Resolução da Diretoria Colegiada (RDC) nº 302, de 13 de outubro de 2005**, que dispõe sobre o regulamento técnico para funcionamento de laboratórios clínicos.

ANVISA. **Resolução da Diretoria Colegiada (RDC) nº 222, de 28 de março de 2018**, que regulamenta as Boas Práticas de Gerenciamento dos Resíduos de Serviços de Saúde e dá outras providências.

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

EUROPEAN COMISSION. **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, versão 28/05/2008.

EUROPEAN COMISSION. **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, versão 28/05/2008.

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

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

FOOD AND DRUG ADMINISTRATION. **Information Sheet Guidance for IRBs, Clinical Investigators and Sponsors**. FDA inspectons of clinical investigators, versão Junho, 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. Versão de 20/08/2008.

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

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

ISP (INSTITUTO DE SALUD PÚBLICA DE CHILE). **Guía de inspección de estudios clínicos farmacológicos**. Resolución nº 5174, de 30 de dezembro de 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, 28/10/2016, Coreia do Sul.

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.** Período do relatório entre 01/04/2016 a 31/03/2017. Data do documento 11/05/2018.

MINISTÉRIO DA SAÚDE. **Portaria nº 2616, de 12 de maio de 1998**, que dispõe sobre diretrizes e normas para prevenção e o controle das infecções hospitalares.

MINISTÉRIO DA SAÚDE. **Portaria nº 2048, de 05 de novembro de 2002**, que aprova o regulamento técnico dos sistemas estaduais de urgência e emergência.

ORGANIZAÇÃO PAN-AMERICANA DA SAÚDE/ OMS. **Boas Práticas Clínicas: Documento das Américas**. IV Conferência pan-americana para harmonização da regulamentação farmacêutica. 2-4 de Março de 2005.

PHARMACEUTICAL INSPECTION CO-OPERATION SCHEME (PIC/S): PIC/S Guidance: **Good Practices for Computerised systems in regulated GXP environments**. PI 011-3 de 25 de setembro de 2007.

11. EDITION HISTORY

VERSION	DATE	CHANGE	JUSTIFICATION
1	11/Sep/2020	Initial issue	Not applicable
2	26/Jan/2022	Changes made based on contributions received during the Public Consultation period (14/Sep/20 to 11/Mar/21):	
		The acronyms CAPA, CRF, ICH, IVRS, IWRS, SUSAR have been updated with the English nomenclature.	As the acronyms originate from English, the meaning of the acronym in English has been included for clarification.
		Section 3 (Legal Basis): References 3.8 to 3.11 have been included	Update of regulations and inclusion of ethical regulations, which were not in the first version.
		Section 5 (Team and Duration of Inspection): Remote inspection expected date 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**. Versions of **non-substantial amendments already implemented, but** which have not yet been petitioned at Anvisa, must be submitted.	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 within the deadline to be sent to the agency.
		Section 7.1.2 (Request for prior documentation): renumbering of items after VIII.	The numbering was incorrect.
		Section 7.1.2 (Request for prior documentation): item XVI	To clarify that they are deviations and protocol

			– The part in bold was included: Electronic spreadsheet containing all deviations and violations of **clinical trial protocol** identified so far referring to the site to be inspected. (Model in Annex 10)	violations.
			Section 7.1.2 (Request for prior documentation): item XXVIII - The part in bold has been included: Electronic spreadsheet containing the experimental drug/placebo kit number, batch number, expiration date, date sent to the site to be inspected, date of receipt by the site, date of dispensing to the subject, number of the subject 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 spreadsheet to avoid breaking the blind**. (Model in Annex 13)	To clarify what special procedure will be done if the study has blind and non-blind teams to avoid breaking the blind.
			Section 7.1.2 (Request for prior documentation): In the last paragraph of this section, the part in bold was added: It is emphasized that, before the inspection start, Anvisa inspectors must have access to all computerized systems used **by the site during the study**, including for closed case studies.	To clarify it refers to computerized systems used by the site during the study.
			Section 7.1.3 (Preparatory meeting for inspection) was included	A pre-inspection virtual meeting will make it easier to align with the inspected party the inspection's logistical details.
			Section 7.2.1 (Opening Meeting): on the attendance list, the part in bold was included - The attendance list **prepared by Anvisa** must be signed by all those present.	To clarify that the attendance list is prepared by Anvisa.
			Section 7.3 (After inspection): The part in bold has been included: For each finding, the appropriate references to the Document of Americas or International Council for Harmonization (ICH E6 (R2)) and local legislation will be listed, **as well as those responsible for**	To facilitate the identification of the person responsible for each finding.

			each finding (site or sponsor).	
			Section 7.3 (After inspection): The part in bold has been included: The deadline for sending the final opinion is up to 30 days from the receipt date of the response to the inspection report. In exceptional cases, this period may be extended and the **inspected party will be informed** with due justification.	To clarify that the new deadline will be informed to the inspected party, with the reason for the deadline extension.
			Item 8.3.4 (Inpatient ward or infusion room): item c - the bolded part was added and the strikethrough part deleted: Presence of an emergency trolley ~~sealed and checked with adequate frequency (including oxygen and available accessories),~~ in easily accessible location. **The trolley does not necessarily need to be in the inpatient/infusion ward, but rather where the experimental drug is administered. In the emergency trolley, it will be checked mainly if it is sealed and checked with adequate frequency. The presence, validity and functioning of emergency trolley 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 trolley's seal be broken to verify its contents.**	Added more details about the emergency trolley to clarify what trolley information is typically 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 study procedures): item 6 - the bolded part was added and the strikethrough part was excluded: Record in ~~medical chart~~ **source document** (physical or	To correct the term “medical chart” to “source document”

		electronic)	
		Item 8.5.1 (Informed Consent Form): item f – the part in bold was added and the strikethrough part was excluded: The witness impartiality must be ~~proven~~ and **evidenced**.	To clarify that it is necessary to have evidence of the witness impartiality. The word "proof" could be understood as the need for a supporting document.
		Section 10 (Bibliographic References): 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 25th, 2007.**	To update the reference used after reviewing the guide. .

12. ANNEXES

- **Annex 1:** Study activity list template with the respective person in charge
- **Annex 2:** Model list of all departments of the inspected site involved in the study
- **Annex 3:** Spreadsheet model with all screened subjects in the site to be inspected
- **Annex 4:** Spreadsheet model with the number of subjects screened in study
- **Annex 5:** Document model with the first visit date of the first screened subject and the last visit of the last randomized subject in Brazil
- **Annex 6:** Model list of the sponsor/CRO team responsible for each study activity in Brazil
- **Annex 7:** Spreadsheet model with information from the site team members to be inspected
- **Annex 8:** Model of SOPs list of the site and sponsor used in the study
- **Annex 9:** Spreadsheet model of SAEs and SUSARs occurred in study
- **Annex 10:** Spreadsheet model of deviations and violations of the site to be inspected
- **Annex 11:** Spreadsheet model on monitoring visits performed at the site to be inspected
- **Annex 12:** Spreadsheet template with IEC documentation for the site to be inspected
- **Annex 13** Spreadsheet model with inventory of investigational products