ANVISA
Agência Nacional de Vigilância Sanitária

PERGUNTAS & RESPOSTAS

RDC nº 945/2024 and IN nº 338/2024

GUIDELINES AND PROCEDURES FOR CONDUCTING CLINICAL TRIALS FOR

FOR REGISTRATION PURPOSES

CLINICAL RESEARCH COORDINATION IN MEDICINES AND BIOLOGICAL PRODUCTS (COPEC)

SECOND DIRECTORATE (DIRE2)

SUS

ANVISA
Agência Nacional de Vigilância Sanitária

MINISTÉRIO DA SAÚDE

GOVERNO FEDERAL
BRASIL
UNIÃO E RECONSTRUÇÃO

QUESTIONS AND DOCUMENT ANSWERS

RDC nº 945/2024 and IN nº 338/2024

GUIDELINES AND PROCEDURES FOR CONDUCTING CLINICAL TRIALS FOR RECORD PURPOSES

This Frequently Asked Questions (FAQ) document aims to clarify the most frequently asked questions received by Anvisa through formal public service channels such as *Contact Us, Ombudsman* , and *FalaBr,* related to various clinical research topics covered in Collegiate Board Resolution – RDC No. 945/2024 and IN No. 338/2024. It also includes clarifications...

Regarding the issues that have prompted the recurring issuance of technical requirements in recent years.

This document does not create new obligations and should be used by public and private entities as a reference for compliance with existing legislation.

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1. GLOSSARY

Anvisa – National Health Surveillance Agency
AREE – Equivalent Foreign Regulatory Authority
BI – Researcher's Brochure
GCP – Good Clinical Practices
Good Manufacturing Practices (GMP)
CETER – Therapeutic Equivalence Coordination
CNES – National Registry of Health Establishments
COPEC – Coordination of Clinical Research in Medicines and Biological Products
Datavisa - System of Products and Services under Sanitary Surveillance
DDCM – Drug Clinical Development Dossier
DEEC – Clinical Trial Specific Dossier
DI – Import Document
DICD - Medical Device Clinical Investigation Dossier
DOU – Official Gazette of the Union
DPI – Product Dossier under Investigation
DSUR – *Development Safety* Update Report
(Development of Experimental Drugs)
FAEC – Clinical Trial Submission Form
GPBIO – Biological Products Evaluation Management
GESEF – Safety and Efficacy Assessment Management
ICH – *International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use* (ICH)
API – Active Pharmaceutical Ingredient
IMPD – *Investigational Medicinal Product Dossier*
IN – Normative Instruction
ORPC – Clinical Research Representative Organization
PAE – Statistical Analysis Plan *(SAP)*
PIP - Pediatric Investigation Plan (PIP)
PDME – Experimental Drug Development Plan
RDC – Resolution of the Collegiate Board

2. INTRODUCTION

This Frequently Asked Questions (FAQ) document compiles the most frequently asked questions received by Anvisa through formal public service channels such as Contact Us, Ombudsman, and FalaBr, related to clinical research on medicines and biological products, as per the Collegiate Board Resolution –

RDC No. 945, of November 29, 2024, Normative Instruction No. 338, of November 29, 2024, and Normative Instruction No. 345, of February 20, 2025, which amended IN No. 338/2024.

The most frequently requested items related to primary applications for Clinical Drug Development Dossiers (DDCM) and Specific Clinical Trial Dossiers (DEEC), as well as secondary applications, have also been included in this document in the form of questions and answers. Other items are still being consolidated and require joint review, as they are the result of discussions, understanding, and alignment between the areas of clinical research and registration of synthetic and biological drugs (GESEF and GPBIO).

The data were extracted from the Health Surveillance Products and Services System (Datavisa) and include requirements issued between January 2024 and August 2025, related to 56 primary DDCM petitions and 80 DEEC petitions, in addition to 25 secondary petitions for amendments to the clinical protocol and 19 for modifications to products under investigation.

For each relevant topic, a corresponding section was created, based on the order of the articles in RDC No. 945/2024, in which questions and their respective clarifications were grouped. Some questions fall into more than one section, but repetition in other sections was avoided as much as possible.

The abbreviations used in this document have the same meaning as those described in RDC 945/2024 and IN No. 338/2024 and in the manuals related to the standard.

Finally, this Questions and Answers Document is a non-binding regulatory action adopted as a complement to the health regulation (RDC No. 945/2024), with the educational and guidance purpose for the instruction of clinical research processes, and is not intended to expand or restrict technical or administrative requirements established in current health regulations.

3. LEGAL BASIS

Resolution of the Collegiate Board - RDC No. 945, of November 29, 2024, which establishes the guidelines and procedures for conducting clinical trials in the country with a view to the subsequent granting of drug registration.

Normative Instruction No. 338, of November 29, 2024, which establishes, under the terms of RDC No. 945/2024, the list of Equivalent Foreign Regulatory Authorities (AREEs) and details the criteria for adopting the optimized procedure for analysis by *Reliance* and by risk and complexity assessment of petitions for DDCM, DEEC, substantial modifications to the product under investigation and substantial amendments to the clinical protocol.

4. OBJECTIVE

This Questions and Answers document aims to answer the most frequently asked questions received by Anvisa through formal public service channels such as Contact Us, Ombudsman and FalaBr, related to various clinical research topics covered in RDC No. 945/2024 and IN No. 338/2024. It also includes clarifications on the most recurring technical requirements regarding the evaluation of primary DDCM and DEEC petitions, as well as secondary petitions.

5. QUESTIONS AND ANSWERS

5.1 Scope of RDC No. 945/2024

5.1.1 - Should a clinical trial that is not intended to support the registration of a drug in Brazil, but is intended for registration in another country, be submitted to Anvisa for evaluation and approval?

The rule applies to any clinical trial intended for registration in Brazil or another country, but it is up to the company to submit clinical trials intended to support registration only in other country(ies) and not in Brazil for evaluation and approval by Anvisa.

5.2 Ethical Body for Clinical Research (INAEP)

5.2.1 - Is ethical approval of the clinical trial mandatory before submitting it for regulatory review and approval?

The decisions of the ethical and regulatory bodies are parallel and independent; however, the trial for drug registration purposes can only begin after approval from both. As of February 27, 2018, the ethical evaluation opinion is no longer required.

submitted to Anvisa for approval of clinical protocols and subsequent amendments.
(DRC No. 205/2017).

5.3 Submission of the Clinical Drug Development Dossier (DDCM)

5.3.1 - If the sponsor decides to study new indications or develop new concentrations or pharmaceutical forms for registered medicines, different from those foreseen in the PDME, should a new DDCM be submitted to Anvisa?

No. Any change related to the same API/active substance for which there is an approved DDCM continues to be handled within that DDCM. In this case, the company must submit the DEEC petition with the new clinical protocol, depending on the intended change, and file the petition to modify the investigational product regarding the new form or new concentration, both linked to the approved DDCM.

5.3.2 - How to proceed in cases where a Phase II study is submitted and a Phase I study is still underway?

Generally, Phase II studies depend on the results of Phase I studies; if this is the case, it is necessary to wait for its completion before submitting the Phase II study. It is possible to submit Phase I and II clinical trials concurrently, but this needs to be evaluated on a case-by-case basis.

5.3.3 - How should the DDCM or DICD be submitted in the case of a product that is both an investigational medicinal product and an investigational medical device? What if the medical device is already registered?

The submission of DDCM/DICD should follow the same reasoning as for registration submissions; that is, if the registration will be joint (investigative drug + experimental device), the company must submit the DDCM for the experimental drug or the DICD for the medical device, considering in this case in which area the registration would occur, within the General Management of Health Products.

(GGTPS) or in the General Management of Medicines and Biological Products (GGMED).

If the registration of the medicinal product and the experimental device is carried out separately, the company must submit a DDCM (Document for the Development of Medical Products) with the quality information of the experimental medicinal product and a DICD (Document for the Development of Medical Devices) with the quality information of the medical device. In this case, it is important to mention in the DDCM that a DICD was submitted in parallel for the medical device and, if possible, to provide the corresponding process number.

If the drug is experimental but the medical device is registered, the company should only submit the DDCM (Document for the Development of Medical Devices).

5.3.4 - How should the submission be made in the case of a combination of two medications?

If it is a fixed-dose combination drug (ADF), the sponsor must submit a single DDCM.

If they are distinct medications for combined/joint use in all indications, a single DDCM (Dietary Data Sheet) should be submitted, and all quality documentation and...
An investigator's brochure for each medicine should be included.

If they are distinct medications for independent use in the clinical trial, one
A DDCM (Directly Responsible for Medical Care) for each medication must be formally established, and the sponsor must choose one of the DDCMs to which the DEEC (Digital Accounting and Evaluation Committee) will be linked. An official letter must be attached to each DDCM explaining the relationship between them.

In situations where a clinical trial involves different medications (DDCMs), the evaluation begins only when all DDCMs have been filed, and the Import Document (DI) will only be issued after the evaluation of both processes, including the DEEC, except for cases of DI anticipation, as provided for in the regulation.

Furthermore, the company responsible for the DDCM to which the clinical protocol was linked (DEEC) will be the one that must notify adverse events, submit annual and final reports, and comply with the other obligations related to the clinical trial described in RDC 945/2024. Additionally, the DI will be sent to this company.

5.3.5 - Who is responsible for filing DDCM requests, the primary sponsor or the secondary sponsor, in the situations foreseen in the regulation?

Given that the Anvisa system only accepts submissions from legal entities, the primary sponsor is responsible for this submission.

5.3.6 - If the clinical trial is initiated by a sponsoring investigator and the company donating the drug is not considered the sponsor, could the company submit the DDCM (previous item) to the sponsoring investigator?

The company should only file the DDCM (Document for Donation of Medical Data) in cases involving the donation of medicines already registered in Brazil for clinical trials, where the donor is the sponsor, and if there is an agreement for the transfer or ownership of the data obtained in the research to the donor.

In the case of research of interest to the research sponsor, without interest from the company, but involving the donation of unregistered medications, the primary sponsor (institution) is responsible for filing the DDCM (Document for the Donation of Unregistered Medications). However, it should be noted that the donor shares the responsibilities of the sponsor.

5.3.7 - Is it possible for a sponsor to submit a DDCM (Diploma of Clinical Trial Management) for a clinical trial conducted by an investigator-sponsor who will conduct the clinical trial in Brazil?

The sponsor can submit the DDCM (Detailed Diagnostic and Control Module) for an investigational drug; however, if the clinical trial is investigator-sponsored, it is the primary sponsor that must submit the specific protocol (DEEC). In the case of investigator-sponsor, the primary sponsor is the institution.

5.3.8 - Considering that a research sponsor wants to study a new indication for a drug that is already registered, does the company holding the registration that donates the drug for this new study, but has no interest in registering this new indication, have any responsibility regarding the filing of the DDCM (Drug Development and Control Plan)?

If the clinical trial is not for registration purposes, it does not fall within the scope of RDC 945/2024 and, therefore, should not be registered.

5.3.9 - Can the documents required for the processing of primary DDCM and DEEC petitions and secondary petitions for substantial amendment to the protocol and substantial modification to the product under investigation, to be filed with Anvisa, be in a foreign language?

The Development Plan (PDME), the Clinical Protocol, and the Researcher's Brochure (BI) must be submitted in Portuguese. All other documents should preferably be submitted in Portuguese.

5.3.10 - Which subject codes related to clinical research can be submitted through the SOLICITA system?

For now, only the codes listed below can be submitted through the SOLICITA system.

Soon, other matters can be filed through the SOLICITA system. The system has already been tested with the participation of the regulated sector, and adjustments suggested by the participants are being made. Anvisa will inform the sector in due course about the launch of the SOLICITA system for other matter codes.

1362 CLINICAL TRIALS - Request for Data Correction in the Database; 1363 CLINICAL TRIALS – Amendment; 1371 CLINICAL TRIALS - Reconstitution of documentation; 1379 CLINICAL TRIALS - Administrative Appeal; 10767 CLINICAL TRIALS CLINICAL TRIAL - Cancellation of Clinical Trial Protocol upon request; 10819 TRIALS CLINICAL - DDCM Modification - Exclusion of Clinical Trial Protocol; 10826 CLINICAL TRIALS - Cancellation of DDCM at request; 10828 ESSAYS CLINICAL TRIAL - Temporary suspension of DDCM; 10830 CLINICAL TRIALS - Temporary suspension of Clinical Trial Protocol; 10831 CLINICAL TRIALS - Reactivation of suspended Clinical Trial Protocol; 10917 COPEC - Withdrawal of petition/process upon request; 11568 COPEC - Copy of process or petition; 11577

COPEC - Copy of process or petition for appeal support; 11995 CLINICAL TRIALS - Publication Rectification – ANVISA; 11996 CLINICAL TRIALS - Correction of Publication – COMPANY; 12094 COPEC - Response to Official Letters; 12130 CLINICAL TRIALS - Global Transfer of Responsibility for Clinical Trial or Healthcare Program for Medicines and Biological Products; 12382 CLINICAL TRIALS - Authorization for Amendment by a third party.

5.3.11 - Once a DDCM is filed, is there a deadline for the company to file the DEEC?

Yes. Every DDCM (Document for Analysis and Control of Consumer Rights) must have at least one DEEC (Document for Analysis and Control) linked to it for the analysis to begin. The DEEC must be filed within 15 (fifteen) business days from the date the DDCM is filed, counted from the date the DDCM document is issued. Failure to file the DEEC within this period will result in its rejection. from the DDCM, without technical analysis, except in cases of clinical trials involving more than one investigational drug, whose DEEC has already been linked to one of the DDCMs for those drugs.

5.3.12 - Is it possible for a company (e.g., ORPC) different from the company that filed the DDCM to file a new DEEC, not foreseen in the last filed PDME, linked to the approved DDCM? In this case, how should the PDME update be performed?

Yes. The sponsor must submit the updated PDME (Plan for Development of Investigational Drugs) to the ORPC (Regional Planning Commission), and the ORPC must register it using subject code 12373 - CLINICAL TRIALS - Notification of Update to the Development Plan for Investigational Drugs, or the sponsor can register the updated PDME directly with the DDCM (Department of Drug Control and Monitoring), and the ORPC will issue a note that the updated plan has been registered by the sponsor. In this case, the analysis of the DEEC (Declaration of Evidence of Clinical Trials) petition will only be completed when all documents are available.

5.4 Drug Development Plan (DDP)

5.4.1 - When should a PMDE update be filed?

In cases where new DEECs are linked to the DDCM and protocols listed in the PDME are excluded for which the respective DEECs have not been filed, the company must file the updated version of the PDME, using subject code 12373 – CLINICAL TRIALS – Development Plan Update Notification.

5.5 Researcher's Brochure (RB)

5.5.1 - For phase 1 clinical trials involving the *first-in-human (FIH)* use of an investigational drug , the standard requires that detailed toxicity, pharmacokinetic, and pharmacodynamic study reports be attached.

In addition to the Business Intelligence (BI), as soon as they are available. Does Anvisa intend to publish a guidance document for fulfilling this requirement?

Yes. Anvisa will publish a specific guidance document. In the meantime, it is recommended that the company use the report template available in the ICH M4S CTD guideline. Other templates may be used, provided they contain the information described in this ICH guideline. Furthermore, it is necessary to clearly justify and substantiate in the Business Intelligence (BI) the choice of dose that will be used in this study.

5.6 Investigational Medicinal Product Dossier (IMPD)

5.6.1 - At the time of filing the DDCM (Drug Data Processing Method), can the company submit the results of accelerated stability studies for the investigational drug within 3 months and wait for a technical requirement to submit the supplementary data within 6 months?

The possibility of continuous submission of stability data and other data will be addressed within the scope of a specific Normative Instruction

5.6.2 - What type of documentation should be submitted when using an active comparator that is not registered in Brazil, but is registered in another country?

The company must inform in which country(ies) the drug is registered and the reason for not using a drug registered in Brazil as a comparator.
It is recommended to consult the registration area beforehand regarding future acceptance.
Application for registration based on clinical trials conducted with a comparator not registered in Brazil.

5.7 Clinical Trial Specific Dossier (DEEC)

5.7.1 - How should centers that do not have their own CNES (National Registry of Health Establishments), but are linked to an institution that does, proceed?

In this case, it is acceptable to submit the CNES (National Registry of Health Establishments) of the institution to which the center is affiliated.

5.7.2 - How do I inform Anvisa about the co-participating center?

Co-participating centers should be listed in the center list for each FAEC, considering “zero” participants and providing a brief description of the activities to be developed in these centers in the table footer. It is emphasized that even with more than one center, the principal investigator remains responsible for all activities performed, regardless of whether they occur in the main center or in a co-participating center.

5.8 Statistical Analysis Plan (SAP) or SAP

5.8.1 - Does COPEC intend to publish guidelines on the minimum content of the Statistical Analysis Plan (PAE) to be submitted to Anvisa?

COPEC will soon publish guidelines outlining the minimum content of the PAE (Environmental Assessment Plan) to be submitted. Until these guidelines are published, companies may submit the PAE/SAP (Environmental Assessment Plan/Sustainable Performance Assessment) considering the model, principles, and recommendations described in the ICH E9 and ICH M11 guides.

5.8.2 - What elements should be included in the Statistical Analysis Plan (SAP) and what is its purpose?

The Statistical Assessment Plan (SAP) is an independent technical document that complements the protocol and exhaustively details all statistical procedures to be applied. It must contain, at a minimum: sample size calculation (including the formula used, parameters, parameter references, and margins), study outcomes, margins (clarification of the margin definition, including references to previous studies and clinical relevance), definition of statistical hypotheses in data analysis, detailed definitions of all efficacy and safety variables, precise description of the analysis populations, algorithms and criteria for handling protocol deviations, specific statistical methods for each analysis (models, tests, significance criteria), strategies for handling missing data, and procedures for sensitivity and subgroup analyses.

In the case of interim analyses, all methodologies and objectives for carrying out these analyses must be defined beforehand in the clinical protocol or PAE (Patient Assessment and Evaluation).

It is possible to finalize the PAE (Environmental Assessment Plan) after the protocol has been developed, as established by ICH-E9, and it is important that at least a draft version be included with the protocol. At least the draft version of the PAE is a mandatory document for the initial submission of the DEEC (Department of Emergency and Control), according to RDC 945/2024.

5.8.3 - What are the primary statistical objectives that should be defined in the protocol and how do they relate to the clinical objectives of the study?

The protocol must clearly define the primary statistical objectives, which are measurable and testable translations of the primary clinical objectives. These should be specified as precise statistical hypotheses, including the parameter to be estimated (e.g., difference of means, hazard ratio) and the direction of the test. The study's conclusion is based on the result of the statistical test of this objective, which in turn directly answers the main clinical question. A lack of clarity in this definition is a critical nonconformity.

5.8.4 - What are the points to consider when calculating the sample size?

Sample size calculations must be presented in sufficient detail to allow for reproducibility. The calculation should be performed using variables related to the primary outcome. It must include all hypothesis comparisons or groups foreseen in the study design. In the case of co-primary outcomes, sample size calculations are necessary for each outcome, using the worst-case scenario (most conservative). In the case of a primary secondary outcome, sample size calculations must be presented. The calculation description must include the formula, statistical parameters (ÿ, ÿ, dropout, significance level, margin, etc.), and bibliographic references. Justification for the parameters used must be included, along with references or previous data supporting these choices. For non-inferiority margins, the clinical rationale and studies supporting the adopted value must be presented.

5.8.5 - What are the points to consider when choosing and describing subgroup analysis procedures?

Subgroup analysis should be pre-specified in the clinical protocol to avoid random findings. For each subgroup, the following should be described at a minimum:

Clinical Justification/Rationale: Why is this subgroup of interest?

Defining Variable: How the subgroup will be defined (e.g., age range, disease severity, biomarker).

Statistical Method: How the treatment effect will be estimated within the subgroup.

Interaction Analysis: It is recommended that, when applicable, a formal statistical test for interaction between the treatment and the subgroup variable be performed to assess whether the difference in effect between the subgroups is statistically significant. Interpretations should be cautious, given the reduction in statistical power.

5.9 Pediatric Research Plan (PIP)

5.9.1 - Is it possible for companies to submit the PIP along with the DDCM documentation and, in the corresponding item of the DEEC subject checklist, add a justification for absence stating that the document was submitted along with the DDCM petition?

The PIP can be attached to the PMDE/DDCM, and if the relevant DEEC is included in the PIP, we recommend that it be reported in the DEEC. The PIP template is the document generated by the authorities themselves (e.g., EMA and FDA).

5.10 Sample Label for Investigational Drugs

5.10.1 - What information is required in label templates? Is there any legislation regarding this?

Normative Instruction No. 136/2022 and its updates discuss the information that must be included on the labeling of products under investigation. In addition, the Manuals for Submitting Quality Requirements for Investigational Products Used in Clinical Trials provide some recommendations for labeling.

5.10.2 - In the case of a comparator drug to be used in a clinical study, if the drug is purchased in Brazil, can its original labeling be maintained, or is it necessary to include a label with labeling information in accordance with the Quality Requirements Manual available on the ANVISA website?

If it is an open-label study, there is no need for new labeling of the already registered comparator drug. In the case of blinded studies, the provisions of IN No. 136/2022 must be followed, since the label must contain the information required for the investigational drug.

5.10.3 - What are the specific labeling statements for Clinical Trials?

- Name, address, and phone number of the sponsor, contracted research organization, or investigator (the main contact for product, clinical trial, and emergency information);

- Subject identification number/treatment number and, whenever relevant, the visit number;

- Researcher's name (if not included in the information in sections I or IV);

- Instructions for use (reference may be made to a package insert or other explanatory document intended for the trial participant or the person administering the product); “for clinical trial use only” or similar text.

5.10.4 - The label must include: “FOR USE IN TESTS ONLY”
"CLINICAL," "ALL MEDICATIONS SHOULD BE KEPT OUT OF THE REACH OF CHILDREN" for medication for hospital use?

We recommend that the phrase "FOR EXCLUSIVE USE IN CLINICAL TRIALS" be placed on the labels of any medication, regardless of whether it is for hospital use or not.
This phrase is important so that, if someone outside the clinical trial team accidentally gains access to the medication, they will be able to identify that the product is an experimental drug.

The phrase "KEEP ALL MEDICINE OUT OF THE REACH OF CHILDREN" does not need to be included on the labeling of experimental medicines for hospital use.

5.10.5 - What are ANVISA's guidelines regarding the removal of a medication from its original packaging for the purpose of masking the product under investigation during the conduct of a clinical trial?

The company must evaluate ways to mask the comparator drug without compromising its quality. However, the study of how the comparator drug can be masked is at the discretion of the company, which must research alternatives and prove to ANVISA (Brazilian Health Regulatory Agency) that it did not affect its quality. A risk assessment must be carried out regarding the process and the possible consequences of altering the product packaging, considering its characteristics. Stability studies (including in use) and proof of no interaction between the product and the packaging are also important. It is important to ensure that removing the drug from its original primary packaging does not compromise the inviolability of the drug, which could affect the robustness and credibility of the clinical trial data. Demonstration that the API content in

The drug and its physicochemical characteristics have not been critically altered through stability studies, which is essential for this evaluation.

5.10.6 - Can the label of the experimental drug be changed in cases where there has been a change in the expiration date?

According to IN No. 136/2022, an additional label may be superimposed over the old expiration date, but it cannot be superimposed over the original batch number for quality control reasons. To maintain traceability, it is important that the previous batch number remains visible. This operation must be performed at a duly authorized manufacturing site. However, exceptionally, provided it is duly justified, the operation may be performed at a site authorized by the clinical trial sponsor, by a pharmacist, or another authorized healthcare professional. Provided it is duly justified, the operation may be performed at the research site under the supervision of the clinical trial center pharmacist, or another healthcare professional, in accordance with national regulations, or when this is not possible, by the clinical trial monitor(s), who must be adequately trained. The operation must be performed in accordance with GMP principles, standard and specific operating procedures, and under contract, if applicable, and must be verified by a second person. The additional labeling must be properly presented in the clinical trial documentation and batch records.

5.11 Declaration on compliance with GMP

5.11.1 - Is it necessary for the production line to be GMP certified when producing the experimental drug?

No. RDC 945/2024 requires that production occur under GMP conditions, but certification of the plant or production line is not required. GMP certificates, when available, may be from the main manufacturers or from all locations involved in the manufacturing stages of the investigational drug (including packaging, labeling, and release). RDC No. 945/2024 requests that a declaration be submitted if another document, such as a certificate, is not available.

5.12 Registered Experimental Drug

5.12.1 - If the experimental drug is already registered in Brazil, Article 29 of the regulation states that only data supporting the proposed post-registration changes should be submitted. If the experimental drug has already been submitted to Anvisa for registration but is still awaiting analysis, should all data on the experimental drug be attached to the DDCM?

Yes. Assuming that registration has not yet been approved, all data must be submitted. However, the company must inform that the drug is awaiting registration approval, as well as describe the therapeutic indications for which registration was requested in Brazil, and the respective registration process number at Anvisa.

5.12.2 – To conduct a clinical trial with an already registered investigational drug, how should one proceed to verify if that drug already has a DDCM (Drug Development Plan for Clinical Medicines) submitted to or approved by ANVISA (Brazilian Health Regulatory Agency)?

If the intended clinical trial falls within the scope of the standard, i.e., a clinical trial with a drug for registration purposes (in this case, post-registration), the trial must be submitted to the DDCM. If it is a trial exclusively for academic purposes (the data obtained in the trial cannot support any intention of registration), then it does not fall within the scope of the standard. In this case, only ethical approvals are applicable.

To verify if the product already has a DDCM (Development Data Classification) submitted or approved by Anvisa (Brazilian Health Regulatory Agency), it is necessary to check this information with the holder of the drug registration and verify if they authorize the applicant to use the information previously submitted by them. If the registration holder does not authorize the use of this information, then the sponsor-investigator must submit literature information that supports the rationale of the proposed development.

5.13 Pharmacokinetic Interaction and Relative Bioavailability (RBA) or Bioequivalence (BE) Studies

5.13.1 - In what situations should the clinical trial protocol be sent to CETER?

There is no need to submit a clinical trial protocol to CETER, but rather the results of pharmacokinetic studies or literature, depending on the case, as defined in the specific Technical Notes.

Technical Note 09/2015: Related to Relative Bioavailability studies for demonstrating pharmacokinetic interaction in ADF cases through subject 10839 - Pharmacokinetic Interaction Studies for Approval in Clinical Trials. In this case, it is a primary petition for which COPEC needs the data from this study in order to begin evaluating ADF clinical trials, as the assessment of relative bioavailability will guide the development plan regarding the conduct of Phase 2 or 3 clinical trials.

Technical Note 118/2016: Comparative pharmacokinetic studies for biosimilar DDCMs. In this case, the evaluation between COPEC/CETER is done jointly. COPEC evaluates pharmacodynamic data and CETER evaluates pharmacokinetic data, as explained in the technical note.

Therefore, the document to be sent to CETER is a secondary petition to the DDCM (10900- Comparative Pharmacokinetic Studies for Investigational Drugs – Biosimilars – submitted as DDCM).

Additional information can be obtained through the Technical Notes available on the Anvisa website (http://portal.anvisa.gov.br/informesmedicamentos).

The two technical areas are consolidating a guidance document for the sector, which will be published soon, especially related to studies involving biosimilar products.

5.13.2 - How do I know if a Pharmacokinetic/Bioequivalence study needs to be a primary petition submitted for CETER review? How do I know when this petition should be submitted; before or concurrently with the DDCM submission?

The submission of petitions to CETER must be in accordance with Technical Notes 09/2015 and 118/2016, available on the Anvisa website (http://portal.anvisa.gov.br/informes-medicamentos).

5.13.3 - Regarding pharmacokinetic interaction studies, what is the timeframe for analysis by CETER?

There is no regulatory or legal deadline for CETER to respond, and since the interaction study is a document that must be part of the DDCM, the company must send the study to CETER before submitting the DDCM. Otherwise, if a parallel analysis (CETER and COPEC) is awaited, the 90-business-day deadline established in RDC No. 945/2024 may be exceeded.

5.14 Substantial modifications to the investigational product

5.14.1 - Is it mandatory to submit subject code 10849 - CLINICAL TRIALS - Modification of DDCM - Change of expiration date, every time the company wishes to change the expiration date of the investigational drug?

No. There are two distinct situations for extending the expiration date and/or changing storage instructions:

a) The registration of subject code 10849 - CLINICAL TRIALS - Modification of DDCM - Change of validity period is mandatory when there is a change in the previously established stability assessment criteria (previously approved by the DPI or IMPD), or when the results of any stability parameter are not within the established specification limits, or when the change in the validity period is being supported by extrapolations based on reduced stability study plan models (grouping and matrixing);

b) Protocoling of subject code 10823 - CLINICAL TRIALS – Changes to the Clinical Trial Submission Form are permitted when there are no changes to the previously established stability assessment criteria (previously approved by the DPI or IMPD), provided that all stability parameter results are within the established specification limits, or that the change in the expiration date is not supported by extrapolations based on reduced stability study plan models (grouping and matrixing). In this case, the report with the results of the stability studies that supported the requested change in the expiration date must be submitted to Anvisa in the next petition for substantial modification to the product under investigation or as part of the DSUR, whichever occurs first.

5.14.2 - In the event of substantial modifications to the Product under Investigation (subject code 10820), will the technical area always update the Import Document (DI)?

If the petition alters information present in the DI (Declaration of Importation), such as the expiration date of the product under investigation, the company will receive the updated DI.

5.15 Substantial Amendments to the Clinical Protocol

5.15.1 - In the case of a non-substantial amendment to the clinical trial protocol, is it necessary to file an updated FAEC (Financial Assessment and Evaluation Form) to change the protocol version?

No. Non-substantial amendments to the clinical trial protocol must always be submitted to Anvisa either with the next substantive amendment petition or as part of it.

from the final clinical trial protocol monitoring report in cases where there are no substantial amendments until the end of the clinical trial.

5.16 Deadlines for Anvisa's response regarding clinical trials

5.16.1 - When to request and what are the deadlines for Anvisa's response regarding primary and secondary clinical research petitions prioritized according to the criteria of RDC No. 205/2017 (rare diseases) and RDC No. 1001, of December 11, 2025?

DRC No. 205/2017:

When to request:

- at the time the petition to be prioritized is filed.

Deadline for qualification in the priority category:

- 45 consecutive days (RDC No. 811/2023).

Procedure when accepting classification in the priority category:

- proceed with the technical analysis.

Procedure when the application for priority status is not accepted (within 45 days):

- to dismiss the petition, which is the subject of the prioritization request, without analysis.

Procedure when the application for priority status is not accepted (outside the 45-day period).

The petition, which is the subject of the prioritization request, must be included in the queue for the analysis of ordinary petitions, in a position corresponding to its filing date.

Deadline for Anvisa's final decision:

- 75 consecutive days.

DRC No. 1001/2025:

When to request:

- at the time the petition to be prioritized is filed, or at any later time, using a specific subject code.

Deadline for qualification in the priority category:

- up to 15 consecutive days.

Procedure when accepting classification in the priority category:

- proceed with the technical analysis.

Procedure when the application for priority status is not accepted (within 15 days):

- To dismiss the petition, which is the subject of the prioritization request, without analysis.

Procedure when the application for priority status is not accepted (outside the 15-day period).

The petition, which is the subject of the prioritization request, must be included in the queue for the analysis of ordinary petitions, in a position corresponding to its filing date.

Deadline for Anvisa's final decision:

- 60 (sixty) consecutive days.

(*) In any situation where 90 working days have elapsed from the date of submission of the petition to be prioritized or not, without a response from Anvisa, the petition will be released due to the expiration of the deadline.

5.17 Technical Requirements

5.17.1 - Considering that Anvisa may request clarifications and additional documents only once, through a technical requirement, during the analysis of primary and secondary clinical research petitions, and that the company has 30 working days to comply with the technical requirement, in cases where only part of the responses are not satisfactory, will it be possible for COPEC to issue a "conditional approval" with the company's commitment to provide the pending information before the start of the clinical trial?

No. If the responses to the requirements are not satisfactory, the petition will be rejected and the documentation must be resubmitted, if the company wishes, with complete information for analysis from the beginning. Upon realizing that it will not fully meet the requirements, the company has the option to withdraw the petition using subject code 10917 - COPEC - Withdrawal of petition/process at request. It is important that the company discusses clinical development with Anvisa whenever possible before submitting the DDCM. It is public knowledge that Anvisa has faced challenges in providing technical advice and guidance, especially for novice developers, but is implementing measures and actions to promote conditions for developers to be supported and guided before submitting DDCMs.

5.17.2 - In cases where only part of the responses are unsatisfactory, will COPEC be able to issue a "conditional approval" with the company committing to provide the pending information before the start of the clinical trial?

No. There is no regulation for conditional approval in these cases.

5.18 Inspections in Good Clinical Practices (GCP)

5.18.1 - In BPC inspections, what findings are most frequent?

The findings from GCP inspections can be accessed in the Good Clinical Practice (GCP) Inspection Metrics Report available on the Anvisa portal.

Annual reports — National Health Surveillance Agency - Anvisa

5.19 Importation of Product under Investigation

5.19.1 - The new RDC no longer mentions the issuance of a Special Communication (CE). Can we understand, then, that the Import Document (DI) will be issued and the final approval will only be published in the Official Gazette? Or will there be some additional official communication to be issued?

During the validity of RDC No. 9/2015, the CE (Certificate of Enforcement) was considered an authorizing document. However, it was replaced by the Import Document (DI) according to RDC No. 945/2024. The DI (Import Declaration) is not an authorization document and is sent to the company for the purpose of importing clinical supplies. It may even be issued by Anvisa (Brazilian Health Regulatory Agency) before approval by DDCM/DEEC (Department of Clinical Management/Department of Clinical Engineering and Economic Studies), as provided for in the new regulation. The authorization document is the Resolution-RE published in the Official Gazette of the Union (DOU).

5.19.2 - For each new clinical protocol submitted, will the company that submitted the petition receive an updated Import Document (DI)?

Yes. The updated DI (Declaration of Intent) will always be sent to the company registered in the system as the holder, which filed the DDCM (Declaration of Disposal of Clinical Trials). Even after the updated DI has been sent to the company in advance (art. 53, § 2°), after the publication of the petition in the Official Gazette, the company will receive a new updated DI. This update is necessary because the advance DI contains a note that the clinical trial has not yet been approved and, therefore, the company should not distribute the investigational product to the centers. It is the responsibility of the holding/holder company or the company that filed the DDCM to send the updated DI to the companies that filed the new DEECs (Declaration of Intent for Clinical Trials) with the DDCM.

5.19.3 - According to article 83, § 3, if COPEC anticipates sending the DI (Declaration of Importation) to the company, the products under investigation must be stored in a protected area, under the sponsor's control, and may only be distributed to the locations where they will be used after the approval of the DDCM (Declaration of Ethical and Regulatory Compliance) and DEEC (Declaration of Ethical Compliance) petitions published in the Official Gazette. Considering that the lab kits will only be used in the screening phase of the specific study participants, is it possible to import the lab kits directly to the Research Centers, keeping them under the sponsor's responsibility until all ethical and regulatory approvals for the study are obtained?

No. By definition, an investigational product is a product used as an experimental drug, active comparator, or placebo, or any other product to be used in a clinical trial. Therefore, lab kits, as well as other materials and supplies, fall under the category of investigational products.

5.19.4 - How to import an experimental drug whose clinical trial is not for the purpose of sanitary registration?

For clinical trials that are not for registration purposes and that require importing the product under investigation, the company must consult RDC No. 172, of September 8, 2017, and RDC No. 81, of November 5, 2008, and their updates. For further information, the interested party should contact the responsible area of Anvisa, in this case the General Management of Ports, Airports and Borders (GGPAF).

5.19.5 - What is the best time to make a change to the Clinical Trial Submission Form (FAEC) in the case of a change in the materials to be imported for a clinical trial that is still awaiting review by Anvisa?

Between the date of issuance and delivery to the company of the advance Import Declaration (DI) and before the date of publication of the petition's approval in the Official Gazette (DOU), the company may make the necessary changes to the FAEC (Authorization for Clinical Imports) that are related to and/or directly impact the importation of clinical supplies, which is the purpose of the advance DI. It is recommended that other changes be made only after the petition's approval in the Official Gazette (DOU).

5.19.6 - When can the advance submission of the Import Declaration (DI) be requested from Anvisa?

At the time of submitting the DDCM and DEEC petitions, the company can request the issuance of the DI (Declaration of Importation). It can also be requested for each new DEEC filed, simply by attaching a declaration of commitment that the product under investigation will only be distributed to the locations where the clinical trial will be conducted after the approval and publication of the related petition in the Official Gazette. The DI will be issued within 30 business days from the date of filing of the DEEC that already includes the Declaration.

5.20 Commencement, termination, suspension or cancellation of a clinical trial or DDCM

5.20.1 - When a clinical trial is prematurely cancelled, should a Clinical Trial Termination Notification be sent or is a Study Cancellation at the request of the participant sufficient?

In this case, cancellation of the study at the request of the participant is sufficient. However, the company should consider that the cancellation request will prevent future information from being linked to the DEEC, since it will have a cancelled status in the system. On the other hand, if any participant decides to remain in the study, it cannot be suspended, since only the recruitment activity will be interrupted and not the study itself (cancellation only after everything is finished).

5.20.2 - As defined by RDC 945/2024, the Clinical Trial Start Date is the first act of recruiting a potential participant for a clinical trial.

specific, unless otherwise defined in the protocol. By this definition, can the first recruitment act be considered the first screening/selection or the first randomization?

This is considered to be the first act of recruiting the first potential participant for a specific clinical trial, unless otherwise defined in the protocol.

5.20.3 - When should the subject code “10917- COPEC - Withdrawal of petition/process at request” and the subjects “10826 - CLINICAL TRIALS – "Cancellation of DDCM at request", "10767 - CLINICAL TRIALS – Cancellation of Clinical Trial Protocol at request"?

The subject of withdrawal at the request of the applicant (10917) should only be used when it has not yet been accepted. The approval or rejection of the petition was published in the Official Gazette of the Union (DOU). Cancellation (10826 or 10767) should only be used when the approval or rejection of the petition has already been published in the DOU.

5.20.4 - How to proceed to request the cancellation of a clinical trial registered under subject code 10818 - CLINICAL TRIALS – Modification of DDCM – Inclusion of a clinical trial protocol not foreseen in the initial development plan, considering that this subject code was deactivated after the publication of RDC No. 945/2024?

Subject code 10818 was the only code for clinical protocol registration (DEECs) that was not included in the previously approved PDME and was therefore considered a modification to the DDCM. Following the enactment of RDC No. 945/2024, a specific subject code was created for updating the PMDE (12373 – CLINICAL TRIALS – Notification of Development Plan Update), making subject code 10818 no longer necessary.

However, after the deactivation of subject code 10818, the petitioning system no longer accepts the filing of cancellation requests for protocols that were filed under this subject code. Therefore, to avoid the creation of a new subject code, we recommend that the cancellation request be filed under subject code 1363 CLINICAL TRIALS – Amendment and, in parallel, that a SAT (Service Request Authorization) be sent informing the Amendment's file number so that the technical area can proceed with the publication of the clinical trial cancellation.

6.0 General Questions

6.1 - Direct delivery of medication to the patient is considered a decentralized activity in clinical trials. For clinical trials where participants, for some reason, cannot go to the center to receive the experimental medication, is it possible for the company to use this option?

No. Anvisa is discussing, within the scope of the International Council for Harmonisation of Technical Requirements for Medicinal Products for Human Use (ICH), Annex 2 of the ICH Guideline E6 (R3), which deals with Good Clinical Practices (GCP) and includes guidelines on...

Decentralization of clinical trial activities. The proposal to develop a specific guide was included in Anvisa's Regulatory Agenda (AR 2024-2026) and will be discussed with the regulated sector in 2026.

6.2 - In accordance with Article 6 of IN No. 163/2022, which governs the conduct of Clinical Research with lenalidomide-based medications and other substances listed in list C3, except thalidomide, in Brazil, establishments must
Submit the research protocol to COPEC, in accordance with RDC No. 945/2024, along with risk minimization measures. In this case, which document should be submitted to COPEC?

Risk minimization measures are generally included in the clinical protocol; however, if these measures are not properly detailed in the clinical protocol, it is recommended that the company attach an additional document detailing such risk minimization measures, as provided for in specific regulations (RDC No. 735, of July 13, 2022).

7. RECOMMENDATIONS

This section lists some recommendations regarding documents submitted to DDCM. These recommendations are not mandatory, but they are suggestions proposed by the technical area to expedite the completion of the process analysis, based on analyses conducted since the implementation of the standard.

7.1. Dossier Organization

ÿ Include a general index to facilitate document retrieval.

ÿ Include explanatory notes, if applicable, to justify the absence of a document in the corresponding section or to inform that a particular document or piece of information can be found in another section.

7.2. Dossier of the Investigational Medicinal Product

ÿ Submit a summary/comment on the RDC items and manuals. We noted that dossiers containing a file with a complete description of the items requested by RDC 945/2024 and following the guidelines of the “Manuals for Submitting Quality Requirements for Investigational Products Used in Clinical Trials” (or referencing another section of the dossier containing more complete information) were analyzed more quickly than other dossiers that only referenced the documentation.

ÿ Follow the order described in the RDC and in the specific manuals of Anvisa. If any item is not applicable, we recommend marking it as "not applicable" instead of not describing the item.

7.3. Compliance with requirements

ÿ Send the answers in Portuguese.

8. BIBLIOGRAPHIC REFERENCES

Resolution of the Collegiate Board - RDC No. 9, of February 20, 2015. Provides for regulations for conducting clinical trials with medicines in Brazil. Official Gazette of the Union, March 1, 2015 (revoked).

Resolution of the Collegiate Board - RDC No. 735, of July 13, 2022. Provides for the control of the substance lenalidomide and medications containing it, and takes other measures. Official Gazette of the Union, September 15, 2022.

Resolution of the Collegiate Board - RDC 1001/2025, of December 11, 2025.
This document outlines the priority classification of applications for registration, post-registration, prior approval for clinical trials, and Good Manufacturing Practices (GMP) certification for medicines and active pharmaceutical ingredients.

Resolution of the Collegiate Board - RDC 205, of December 28, 2017. Establishes a special procedure for the approval of clinical trials, certification of good manufacturing practices, and registration of new medicines for the treatment, diagnosis, or prevention of rare diseases. Official Gazette of the Union, December 29, 2017.

Resolution of the Collegiate Board - RDC No. 763, of November 25, 2022. Amends Resolution of the Collegiate Board - RDC No. 205, of December 28, 2017. Official Gazette of the Union, December 1, 2022.

Normative Instruction - IN No. 163, of July 13, 2022 - Defines, in a complementary manner to Collegiate Board Resolution - RDC No. 735, of July 13, 2022, the special control criteria for conducting studies and research, including laboratory tests and assays with lenalidomide and other substances listed.

C3 of Annex I of Ordinance SVS/MS No. 344/1998, as well as medications containing them, except thalidomide.

Manual for submitting a clinical drug development dossier (DDCM) and a specific clinical trial dossier. 4th Edition, 2025. COPEC.

Manual for Submitting Quality Requirements for Investigational Products Used in Clinical Trials - Biological Products. 3rd Edition, 2019. COPEC.

Manual for Submitting Quality Requirements for Investigational Products Used in Clinical Trials – Synthetic and Semi-synthetic Drugs. 3rd Edition, 2019. COPEC.

Technical Note 09/2015, dated September 3, 2015. Clarifications regarding relative bioavailability studies for demonstrating pharmacokinetic interaction for the purpose of registering Fixed-Dose Combinations or obtaining approval in the Clinical Development Dossier of the Drug – DDCM. CETER/COPEC/GGMED/ SUMED/ANVISA.

Available on the Anvisa website:

https://www.gov.br/anvisa/pt-br/centraisdeconteudo/publicacoes/medicamentos/pesquisa-clinica/notas-tecnicas/nota-tecnica-no-09-de-2015.pdf

Technical Note 118/2016, dated April 15, 2016. Clarifications on pharmacokinetic studies of comparative biological products CETER/COPEC/GGMED/ANVISA. Available on the Anvisa website:

https://www.gov.br/anvisa/pt-br/centraisdeconteudo/publicacoes/medicamentos/pesquisa-clinica/notas-tecnicas/nota-tecnica-118-2016.pdf

ICH E9: Statistical principles for clinical trials. 05 de fevereiro de 1998, ICH (International Consil on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use).

ICH M11: Clinical study protocol template and technical specifications. 2025, ICH (International Consil on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use).

9. CHANGE HISTORY

v.1	N/A	Original version
v.2	Layer: Version update (from 1 to 2) and year update (from 2015 to 2016)	Changed to reflect the current version.
v.2	Counter-layer: • Update of the management name (Superintendency to General Management • Inclusion of the Effectiveness and Safety Assessment Management of Medicines • Update of full/alternate members	Changes made to reflect current management and membership.
v.2	Header: Replace the word "frequent" with "answers" and include "version 2"	Changes were made to standardize the document name and include the version number for better document traceability.
v.2	Summary: Update to reflect the new sections included (9. Investigator-Sponsor; 11. Recommendations, 12. Annexes, 13. History of Changes).	Inclusion of new items that were necessary after reviewing the document.
v.2	1. Introduction: The final paragraph was added: *"A history of changes has been added to the document for better tracking of modifications made since the last version."*	Inclusion to explain the reason for having a change history.
v.2	2. Submission Question 1: Items in bold have been added: *"Documents to be submitted to Anvisa may be submitted in a* ***foreign language (e.g.,*** *English,* ***Spanish, German, French...)?"***	This question has been updated due to inquiries regarding various foreign languages, not just English.
v.2	2. Submission Question 15 from v1: "Is it possible to pay the fee as an individual (principal investigator)?" has been moved to Question 5 of Section 9 of v2.	The question has been moved to a more specific section, created in v2.
v.2	2. Submission: Questions 16 to 19 of version 1 have been renumbered as questions 15 to 18.	Renumbering to reflect the removal of Question 15 from v1.
v.2	2. Submission: Questions 19 to 52 have been added.	Inclusion of questions asked after the publication of v1.
v.2	2. Submission: The item "RECOMMENDATIONS" has been moved to section 11 of v2.	Transferring the item to a more specific section, created in v2.
v.2	3. Amendments, Modifications, Suspensions and Cancellations: Renumbering of questions 20 to 32 from v1 to 1 to 13 in v2.	Renumbering to standardize all sections of the document. The idea of restarting the numbering for each section is to avoid confusion.

		When new questions are added, subsequent versions will be created in.
v.2	3. Amendments, Modifications, Suspensions and Cancellations: addition of questions 14 to 26.	Inclusion of questions asked after the publication of v1.
v.2	4. Quality Aspects: Questions 7 through 14 have been added.	Inclusion of questions asked after the publication of v1.
v.2	5. Importation: Question 1: Add the phrase *"This form should be added to the petition for the clinical trial approved by RDC 39/2008 and not to the DDCM."* to the answer.	Inclusion of the phrase to clarify where the form should be amended.
v.2	5. Importation: Questions 5 through 10 have been added.	Inclusion of questions asked after the publication of v1.
v.2	6. Deadlines: Questions 6 through 11 have been added.	Inclusion of questions asked after the publication of v1.
v.2	7. Reports: Questions 7 through 10 have been added.	Inclusion of questions asked after the publication of v1.
v.2	8. Adverse Events: Questions 5 through 8 have been added.	Inclusion of questions asked after the publication of v1.
v.2	Inclusion of Section 9: Investigator-Sponsor	Due to the number of questions related to the investigator - a Sponsor, a new section has been created to make searching easier.
v.2	The former section 9 of v1 has been renumbered as section 10 (Miscellaneous).	Renumbering due to the inclusion of new sections.
v.2	10. Miscellaneous: Questions 4 through 15 have been added.	Inclusion of questions asked after the publication of v1.
v.2	Inclusion of Section 11: Recommendations	Due to the amount of information related to this item, a new section has been created to facilitate the search.
v.2	Inclusion of Section 12: Annexes	The need for a new section arises from the content of section 11.
v.2	Inclusion of Section 13: History of Changes	Insertion of a comparative table of the wording between versions for a more transparent monitoring of the updates made.
v.2	Inclusion of questions already described in V.1 that have been modified.	Proofreading includes corrections for spelling, grammar, or formatting, without altering the content of the text.
v. 3	Compliance with the new RDC No. 945/2024 and IN No. 338/2024	Fully updated version