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ANVISA
Agência Nacional de Vigilância Sanitária

PERGUNTAS & RESPOSTAS

RDC nº 945/2024 and IN nº 338/2024

5th

GUIDELINES AND PROCEDURES FOR

CONDUCTING CLINICAL TRIALS FOR

FOR REGISTRATION PURPOSES



CLINICAL RESEARCH COORDINATION IN
MEDICINES AND BIOLOGICAL PRODUCTS (COPEC)

SECOND DIRECTORATE (DIRE2)

CLI

SUS ANVISA Agência Nacional de Vigilância Sanitária MINISTÉRIO DA SAÚDE GOVERNO FEDERAL BRASIL UNIÃO E RECONSTRUÇÃO

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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 answer the most frequently asked questions received by Anvisa through formal public service channels such as *Contact Us and the Ombudsman.*
and *FalaBr*, related to the various clinical research topics covered in Collegiate Board Resolution – RDC No. 945/2024 and IN No.
338/2024. This also includes clarifications on the issues that have led to the recurring issuance of technical requirements in recent years, and specific instructions on the development of Fixed-Dose Associations (FDA).

This document does not create obligations and should be used by public and private agents as an aid to comply with specific regulations in force.

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1. GLOSSARY

Anvisa – National Health Surveillance Agency
ADF – Fixed-Dose Association
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
DM2 – Type 2 Diabetes Mellitus
DOU – Official Gazette of the Union
DPI – Product Dossier under Investigation
DSUR – *Development Safety* Update Report
(Development of Experimental Drugs)
EMA – *European Medicines Agency*
FAEC – Clinical Trial Submission Form
GPBIO – Biological Products Evaluation Management
GESEF – Safety and Efficacy Assessment Management
HbA1c – Glycated hemoglobin
ICH – *International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use* (ICH)
API – Active Pharmaceutical Ingredient
BMI – Body Mass Index
IMPD – *Investigational Medicinal Product Dossier*
IN – Normative Instruction
MAPA – Ambulatory Blood Pressure Monitoring
ORPC – Clinical Research Representative Organization
PAD – Diastolic Blood Pressure
PAE – Statistical Analysis Plan *(SAP)*
Systolic Blood Pressure (SBP)
PD – Pharmacodynamics
PDME – Experimental Drug Development Plan
PIP - Pediatric Investigation Plan (PIP)
PK – Pharmacokinetics
Q&A – Questions and Answers
RDC – Resolution of the Collegiate Board

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2. INTRODUCTION

This Questions and Answers (Q&A) 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 clinical research on medicines and biological products, in accordance with 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 and complementary acts.

The most frequently requested items related to primary petitions for Clinical Drug Development Dossiers (DDCM) and Specific Clinical Trial Dossiers (DEEC), as well as secondary petitions, were also included in this document in the form of questions and answers. The data were extracted from requests issued between January 2024 and August 2025.

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.

This document also addresses the regulatory and scientific aspects related to the clinical development of Fixed-Dose Combinations (FDCs) of synthetic and semi-synthetic drugs, based on frequently asked questions observed during the regulatory evaluation of clinical trials and drug registration applications containing combinations of active ingredients. The guidelines presented reflect current health legislation, national and international technical and scientific references, and aspects observed in the regulatory evaluation of FDCs.

The questions and answers are organized into a general section, which addresses principles applicable to the clinical development of ADF in a broad sense, and specific sections by therapeutic area, which present additional considerations for particular clinical contexts.

The answers presented in this document are for guidance only and do not replace the individual regulatory analysis of each study. The evaluation of each case is based on all the submitted documentation, the specific characteristics of the study, and compliance with applicable legislation and regulations.

This Questions and Answers (Q&A) document is a non-binding regulatory action with the purpose of educating and guiding clinical research processes. It is not intended to expand or restrict established technical or administrative requirements and should be interpreted in conjunction with current legislation and other relevant regulatory instruments.

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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.

Resolution of the Collegiate Board – RDC No. 753, of September 28, 2022, which provides for the registration of medicines for human use with synthetic and semi-synthetic active ingredients, classified as new, innovative, generic and similar.

4. OBJECTIVE

This Questions and Answers (Q&A) 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 for the evaluation of primary DDCM and DEEC petitions, secondary petitions, and guidance on relevant aspects of the clinical development of fixed-dose combinations of synthetic and semi-synthetic drugs, in order to support the planning of clinical development programs and the regulatory evaluation of these drugs.

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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?

No. The submission of the process to ANVISA (Brazilian Health Regulatory Agency) and the ethics committee can be done in parallel, and the decisions of the two bodies are independent; however, the trial for drug registration purposes can only begin after approval from both. Additionally, the As of February 27, 2018, the ethical evaluation report no longer needs to be submitted to Anvisa for approval of clinical protocols and subsequent amendments (RDC 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. There is a

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The possibility of submitting Phase I and II clinical trials simultaneously exists, but each case needs to be evaluated individually.

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).

Regarding the need to submit the DICD (Detailed Information and Communication Form), based on the risk classification, the interested party should consult the responsible area (GGTPS) to receive guidance, according to specific regulations.

5.3.4 - How should the submission be made in the case of a combination of drugs and/or medications?

- Fixed-Dose Association (FDA): the sponsor must submit a single DDCM.
containing all documentation relating to the investigational medicinal product (ADF) and relating to the drugs individually.

- Experimental drug + other drug(s) not registered in Brazil, for concomitant/simultaneous or sequential use: the sponsor must submit a DDCM (Document for Concomitant/Simultaneous Use) for each drug with all related documentation. The sponsor must choose the DDCM to which the DEEC (Document for Concomitant/ Simultaneous Use) will be linked and attach a letter to each DDCM explaining the relationship between them.

- Investigational drug + other drug(s) registered in Brazil, for concomitant/simultaneous or sequential use (without substantial changes to the registered drug(s)): the sponsor must submit a single DDCM (Document for the Development of the Medical Conduct) referring to the investigational drug with all related documentation and minimum information (package insert) regarding the registered drugs.

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The clinical protocol or DEEC can only be evaluated and approved if the corresponding DDCMs (Drug Development and Control Modules) for the medications involved have been submitted.

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 Anvisa's petitioning 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. The remaining documents are required.

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Documents may be submitted in another language (English or Spanish), but whenever possible, Portuguese is preferred.

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

All subject codes related to clinical research must be documented.
through the SOLICITA system.

In case of instability or persistent errors in the petitioning system, the sponsor can send a Contact Us (SAT) request to COPEC, accompanied by screenshots of the error screens.

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

Yes. Every DDCM (Drug Control and Monitoring Document) must have at least one DEEC (Drug Evaluation and Evaluation Document) linked to it for the analysis to begin. The DEEC must be filed within 15 (fifteen) business days from the date of filing of the DDCM, counted from the date of issuance of the DDCM document. Failure to file the DEEC within this period will result in the rejection of the DDCM, without technical analysis, except in cases of clinical trials involving more than one experimental 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.

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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 regulation requires that detailed toxicity, pharmacokinetic, and pharmacodynamic study reports be attached, supplementing the Information Bulletin (IB), as soon as they are available. Does Anvisa intend to publish a guidance document for compliance with 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?

Normative Instruction No. 457/2026 regulates the continuous submission of documents for the Drug Clinical Development Dossier (DDCM). It provides flexibility for the delivery of technical data on products under investigation in clinical trials in Brazil, including stability data.

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 state 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?

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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 publish guidelines outlining the minimum content of the PAE (Annual Action Plan) to be submitted. Until such guidelines are published, companies may submit their PAE/SAP considering the model, principles, and recommendations described in the ICH E9 and ICH M11 guidelines.

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 should clearly define the primary statistical objectives, which are measurable and testable translations of the primary clinical objectives. They should be

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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. 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?

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Yes. 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?

Yes. 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?

Yes. 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.

5.10.4 - 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.

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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 product 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 crucial to ensure that removing the medication from its original primary packaging does not compromise the inviolability of the medication, which could affect the robustness and credibility of the clinical trial data. Demonstrating that the API content in the medication and its physicochemical characteristics have not been critically altered, through a stability study, 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 by 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.

Additional labeling must be properly presented in the clinical trial documentation and batch records.

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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 Medicinal Product

5.12.1 - If the experimental drug is already registered in Brazil, the regulation states in article 29 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.

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5.13 Pharmacokinetic Interaction and Relative Bioavailability (BDR) or Bioequivalence (BE) Studies and other studies for Biosimilar products

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; however, results from pharmacokinetic interaction studies related to fixed-dose combinations (FDs) must be submitted to CETER for evaluation under subject code 10839 - Pharmacokinetic Interaction Studies for Clinical Trial Approval.

Pharmacokinetic (PC) and/or Pharmacodynamic (PD) studies required for the development of biosimilar products will be analyzed by the Biological Products Evaluation Management (GPBIO/GGBIO) and no longer by CETER.

The submission of DDCM to COPEC should only be carried out when there are protocols for “traditional” Phase 1, Phase 2, or Phase 3 clinical trials, as foreseen in RDC No. 945/2024. In this case, all the DDCM documentation required in the aforementioned RDC must be submitted.

Although Pharmacokinetic (PC), Pharmacokinetic and Pharmacodynamic (PC/PD), or Bioequivalence (BE) or Relative Bioavailability (RBA) studies may share, to some extent, the same characteristics and methodological design as a phase 1 clinical trial, for the purposes described here they are not considered trials.
“Traditional” phase 1 clinical trials.

Therefore, the exemption from submitting a DDCM for biosimilar products applies to cases involving comparative FC or FC/FD studies (relative bioavailability). Prior submission of a DDCM is also not required for FC/FD studies that present safety and immunogenicity results as secondary outcomes.

Regarding the procedures and/or technical and administrative criteria for the submission, evaluation, and issuance of opinions or reports, and other details about the execution and reporting of studies that will support the registration of biosimilar products, including the safety monitoring of these studies, the interested party must follow the specific rules and guidelines provided or consult the registration area itself (GPBIO), when it does not involve the submission of a DDCM.

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 available on the Anvisa website (http://portal.anvisa.gov.br/informes-medicamentos).

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The results of pharmacokinetic interactions should be considered when evaluating the rationale for ADF. Therefore, it is expected that this study will be conducted before the submission of the DDCM.

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, when not involving the changes mentioned in the previous item (“a”). Even in cases where other changes occur concurrently with the change in the expiration date (extension or reduction), subject code 10823 applies, provided that such changes are not substantial. The report with the results of the stability studies supporting the requested extension of 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 (code 10825), 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)?

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If the petition alters information contained in the Import Declaration (DI), such as the expiration date or storage conditions 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 be submitted to Anvisa either with the next substantive amendment request or as part of the final clinical trial protocol monitoring report in cases where there are no substantive amendments by 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.

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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

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It 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 Information) 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.

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It is the responsibility of the company holding/owning or that filed the DDCM to send the updated DI to the companies that filed the new DEECs 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 and other materials and supplies that qualify as products under investigation, according to RDC No. 945/2024, directly to the Research Centers, keeping them under the sponsor's responsibility until all ethical and regulatory approvals for the study are obtained?

Yes. Except for the experimental drug, active comparator, or placebo, which must be kept 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 and DEEC petitions published in the Official Gazette.

5.19.4 - Direct delivery of medication to the patient is considered a decentralized activity of the clinical trial. For clinical trials in which 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 framework of the International Council for Harmonisation of Technical Requirements for Medicinal Products for Human Use (ICH), Annex 2 of the ICH E6 (R3) Guideline, which deals with Good Clinical Practices (GCP) and includes guidelines on the decentralisation of clinical trial activities. The proposal to develop a specific Guideline has been included in Anvisa's Regulatory Agenda (AR 2024-2026) and will be discussed with the regulated sector in 2026.

5.19.5 - 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 DI (Import Declaration) and before the date of publication of the petition's approval in the Official Gazette, the company may make the necessary changes to the FAEC (Simplified Tax Collection Form) that are related to and/or directly impact the...

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The purpose of the advance import of clinical supplies is to expedite the import process. It is recommended that other changes be made only after the petition has been approved in the Official Gazette.

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 specific clinical trial, unless otherwise defined in the protocol. Based on this definition, could the first act of recruitment 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 – DDCM Modification – Inclusion of

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Clinical trial protocol not included 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 (DEEC) that was not included in the previously approved PDME, and therefore was considered a modification to the DDCM. Following the enactment of RDC No. 945/2024, a new code was created.
Specific subject code 12373 – CLINICAL TRIALS – Development Plan Update Notification, for updating the PMDE, subject code 10818 is no longer necessary.

However, after the deactivation of subject code 10818, the petitioning system no longer accepts the filing of the cancellation request, which is currently done through SOLICITA, and was filed using that subject code.
(10818). Therefore, to avoid creating 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 be sent to COPEC informing the Amendment file number so that the technical area can proceed with the publication of the cancellation of the clinical trial.

6.0 Clinical Development of Fixed-Dose Combinations (FDCs)

6.1 Main points of attention related to ADF

6.1.1 What aspects should be considered when demonstrating the rationality of an ADF?

In general, the clinical development of an ADF should demonstrate the rationale of the combination, the contribution of each component, and the suitability of the combination for the intended therapeutic indication.

The proposed combination must have pharmacological and clinical rationale, being appropriate to the intended context of use, including the definition of the target population and the need for concomitant use of the components of the combination.

In this context, as stipulated in article 21 of RDC No. 753/2022, evidence must be presented of the clinical relevance of the function of each active ingredient in the intended indication, as well as a technical justification demonstrating the clinical and pharmacological rationale of the combination, including potential gains in efficacy, safety, bioavailability, or simplification of the therapeutic regimen.

Furthermore, each active ingredient is expected to contribute in a clinically relevant way to the therapeutic effect or to the benefit-risk profile of the combination, and the proposed doses are expected to be scientifically justified, considering the target population, the dosing regimen, and possible pharmacodynamic and pharmacokinetic interactions. When different potentially applicable dose combinations exist, it may be necessary to present data that allow for the evaluation of the dose-response relationship and to justify the choice of doses proposed for the clinical trial.

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6.1.2 In clinical trials for the development of an ADF, is it necessary to evaluate the contribution of each component of the combination?

In the clinical development of an ADF (anti-drug combination), the contribution of each component to the therapeutic effect of the combination must be adequately demonstrated. This demonstration must be based on the pharmacological and clinical rationale of the combination and on evidence supporting the clinical relevance of each component's function in the intended indication.

The clinical trial design should be defined according to the proposed therapeutic scenario for the combination and be able to robustly demonstrate the contribution of each component to the therapeutic effect of the combination, as well as characterize its efficacy and safety.

6.1.3 Should pharmacokinetic (PK) and pharmacodynamic (PD) interactions be evaluated in the development of an ADF?

The assessment of PK/PD interactions between the components of an ADF is a relevant aspect of drug development and a regulatory requirement for drug registration, including the registration of combinations, and must be considered in an integrated manner with the pharmacological and clinical rationale of the combination, as provided for in Article 21 of RDC No. 753/2022 and in Guides No. 59 and No. 60/2023.

In general, it is important to investigate the potential for interaction between the components that make up the combination based on a structured scientific approach, considering that each component can influence or have its exposure influenced by the others. This assessment should be based on pharmacological knowledge, available experimental data and, when necessary, specific studies that allow the characterization of any interactions.

The absence of relevant interaction must be duly justified based on adequate scientific evidence. When the risk of interactions is identified, these must be characterized in terms of their magnitude and clinical relevance, including the impacts on...
Systemic exposure, in the efficacy and safety profile of the association.

In addition to pharmacokinetic aspects, potential pharmacodynamic interactions, such as additive, synergistic, or antagonistic effects, must be considered, as these are fundamental to supporting the rationale for the combination.

The need to conduct specific studies will depend on the potential for interaction identified and the degree of uncertainty, and may be replaced by robust technical and scientific justification when supported by consistent data.

However, when the interaction between the components is part of the rationale for the combination (for example, increased bioavailability of one of the drugs), this interaction must be properly demonstrated and its benefits and risks clearly established.

In all cases, the assessment of PK/PD interactions should be integrated with the demonstration of the clinical benefit of ADF, contributing to the characterization of its benefit-risk ratio.

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6.1.4 Is it acceptable to use a placebo as a comparator in clinical trials for the development of an ADF when approved therapies already exist for the same clinical condition?

When the components of the combination, individually or in other combinations, already have approved therapeutic indications for the same clinical condition, the use of placebo as the sole comparator may not be methodologically adequate. In these scenarios, the use of placebo as the sole comparator may be insufficient to adequately assess the individual contribution of the components and the clinical relevance of the combination in relation to available therapeutic options.

In general, the clinical development of a combination drug (ADF) must demonstrate the benefit of the combination compared to the isolated components administered in appropriate dosage regimens. Additionally, for the registration of combination drugs, evidence of the clinical relevance of the function of each component of the combination in the intended indication must be presented, as stipulated in Article 21 of RDC No. 753/2022.

Thus, when the components of the combination, individually or in other combinations, already have an approved indication for the same clinical condition, it is expected that the study design will allow comparison of the combination under evaluation to the individual components or to already registered combinations, when applicable, and adequately demonstrate the contribution of each component to the therapeutic effect of the combination.

The use of placebos in clinical trials involving combinations may be acceptable in certain situations, such as when no effective therapies are available or when their use is methodologically justified for the adequate characterization of the effect of the investigational drug. In these cases, acceptability should be evaluated on a case-by-case basis, considering scientific, methodological, and ethical aspects.

6.1.5 What aspects should be considered when choosing between superiority and non-inferiority designs in clinical trials for the development of an ADF?

The choice between superiority and non-inferiority designs should be aligned with the study objective, the intended therapeutic indication, and the rationale for the combination.

In general, superiority studies are used when the goal is to demonstrate that the combination offers additional benefit compared to the comparator. Non-inferiority studies, on the other hand, may be appropriate when the objective is to demonstrate that the combination maintains similar efficacy to that of an established treatment, associated with other potential advantages, such as simplification of the therapeutic regimen, improved adherence, tolerability, or safety profile.

Regardless of the study design adopted, studies must be able to adequately demonstrate the contribution of each component of the combination and the clinical relevance of the combination for the intended indication.

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In non-inferiority studies, in addition to justifying the design, it is necessary to justify the adopted non-inferiority margin, which must be established in a way that preserves a clinically relevant effect in relation to the active comparator. The definition of the margin should consider, among other factors, the magnitude of the comparator effect, the fraction of the effect that is intended to be preserved, the variability of the outcome, the characteristics of the study population, and the evidence available in the scientific literature or in previous studies. The chosen margin must be clinically justifiable and supported by evidence that sustains the adopted value.

Finally, the choice of experimental design must be scientifically justified and compatible with the intended clinical use scenario for the combination.

6.2 ADF for the Treatment of Arterial Hypertension

6.2.1 How should the choice of doses evaluated in clinical trials of an ADF for the treatment of hypertension be justified?

The selection of doses evaluated in the clinical development of an ADF (antidiuretic derivative) must be adequately justified based on pharmacological and clinical evidence, in order to demonstrate the contribution of each component to the therapeutic effect of the combination.

In general, the choice of doses should consider the previously established doses for the single drugs that make up the combination, the dose-response relationship of each component and of the combination, the potential for pharmacodynamic interaction between the components, and evidence of efficacy and safety of the combination at the proposed doses.

International guidelines indicate that, whenever possible, clinical development should allow for the evaluation of the individual contribution of the components of the combination and the adequacy of dosage combinations, for example, through appropriate designs such as factorial studies, as described in the Guideline *on clinical investigation of medicinal products in the treatment of hypertension* (EMA, 2016).

Evaluating only one dosage combination may be acceptable in specific situations, provided it is properly justified. However, additional justification may be necessary when multiple doses of the components are available or used in clinical practice, in order to ensure that the proposed dose in the combination is appropriate.

6.2.2 Is it necessary to include elderly patients in the clinical development of antihypertensive medications?

Elderly patients constitute a significant portion of the population affected by hypertension and, therefore, should be adequately represented in the clinical development of antihypertensive medications.

In general, clinical trials are expected to include participants with characteristics compatible with the population for which the drug will be used in clinical practice. In this context, the inclusion of elderly patients is particularly relevant, considering that the prevalence of hypertension increases with age and that

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Factors related to aging can influence the response to treatment and the safety profile of the medication.

The assessment of this population should consider aspects such as physiological changes associated with aging, the presence of comorbidities, concomitant use of other medications, and greater susceptibility to adverse events, including postural hypotension, dizziness, and falls.

Furthermore, when applicable, the dosing strategy should be appropriately characterized for elderly patients, especially those in older age groups, to ensure that usage recommendations are supported by appropriate clinical evidence.

6.2.3 What efficacy outcomes can be considered in clinical trials of antihypertensive drugs?

The goal of treating hypertension is to reduce morbidity and mortality associated with elevated blood pressure.

In general, the reduction in systolic blood pressure (SBP) is the most commonly used primary efficacy variable in clinical trials of antihypertensive drugs, and is usually assessed through standardized measurements performed in the office. Diastolic blood pressure (DBP) is frequently evaluated as a secondary outcome.

Additionally, outcomes related to the proportion of patients who achieve previously defined blood pressure targets or who show a clinically relevant response to treatment may be used.

Complementary methods for assessing blood pressure, such as ambulatory blood pressure monitoring (ABPM) or home blood pressure monitoring, can provide additional information on the duration of the antihypertensive effect, blood pressure variability, and blood pressure control over the dosing interval. However, these methods are generally considered complementary to office measurements for regulatory purposes.

In addition to blood pressure-related outcomes, parameters associated with target organ damage, including cardiac, renal, vascular, or retinal changes, can be evaluated. These outcomes can contribute to characterizing the effects of treatment and are particularly relevant when specific claims related to target organ protection are made. However, in general, they are considered supportive outcomes and do not replace the demonstration of the antihypertensive effect.

Clinical outcomes related to cardiovascular morbidity and mortality, such as myocardial infarction, stroke, heart failure, or cardiovascular death, are highly relevant clinically. However, their evaluation generally requires large-scale, long-term studies and is not usually necessary for the initial demonstration of antihypertensive efficacy.

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The choice of outcomes should be compatible with the objectives of clinical development, the mechanism of action of the drug, the population studied, and the intended therapeutic indication.

6.2.4 Is ambulatory blood pressure monitoring (ABPM) mandatory in clinical trials of antihypertensive drugs?

Ambulatory blood pressure monitoring (ABPM) is not mandatory in clinical trials of antihypertensive medications. However, it is a tool frequently used as a complementary measure, as it provides additional information about blood pressure behavior over 24 hours.

This method allows for the evaluation of aspects such as circadian variation in blood pressure, nocturnal reduction in blood pressure, and the duration of the antihypertensive effect throughout the dosing interval. Furthermore, it can contribute to a more comprehensive characterization of the pharmacodynamic profile of the treatment and reduce the influence of variability associated with isolated measurements.

Despite its usefulness, ABPM (Ambulatory Blood Pressure Monitoring) is generally considered complementary to standardized measurements performed in the office for the purpose of demonstrating effectiveness, and should be interpreted within the context of the body of available clinical evidence.

6.2.5 Is a *run-in* period necessary in clinical trials of antihypertensive drugs? What is the recommended duration?

In clinical trials of antihypertensive drugs, the use of a run-in period before randomization is a well-established practice, especially in designs that involve the discontinuation of previous therapies or the evaluation of the treatment effect under stable baseline conditions.

In these contexts, the run-in period usually lasts at least 2 weeks, and can extend to approximately 4 weeks, being considered important for stabilizing blood pressure, confirming baseline values, and reducing biases, such as the phenomenon of regression to the mean.

However, the need for and duration of the run-in period should be determined according to the study design and the characteristics of the population included, and may not be applicable to all scenarios, such as in add-on studies, where maintenance of background therapy may be necessary for clinical reasons.

6.2.6 Is it necessary to include a *washout* period in clinical trials of antihypertensive drugs?

The need for a *washout* period in clinical trials of antihypertensive drugs depends on the study's objective, the study design adopted, and the population included.

Washout can be *used* in certain studies to minimize the influence of previous antihypertensive therapies, allowing for a more direct evaluation of the effect of the experimental drug. However, its use should be carefully evaluated, especially in patients with higher blood pressure levels, considering the potential risks to participant safety.

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In many cases, particularly in add-on studies or in already treated populations, maintaining baseline therapies may be more appropriate. In these scenarios, it is important that the protocol clearly defines the permitted prior and concomitant antihypertensive therapies, as well as the criteria for their maintenance, adjustment, or discontinuation throughout the study.

Regardless of the strategy adopted, the study design must ensure that the influence of prior treatments is adequately controlled and considered in the data analysis, in order to allow for a robust interpretation of the efficacy and safety results.

6.2.7 Do clinical trials of antihypertensive drugs need to include formal monitoring of diet or exercise?

Diet, physical activity, and other non-pharmacological measures are important components of the management of hypertension and can influence the results of clinical trials evaluating antihypertensive medications.

However, the implementation of formal intervention programs on diet or physical exercise is not, in general, a requirement for the clinical development of these medications.

Regardless of the adoption of structured interventions, it is recommended that non-pharmacological factors with potential impact on blood pressure, such as dietary habits, level of physical activity and other behavioral measures, be adequately identified, recorded and, whenever possible, kept relatively constant throughout the study and between treatment arms, so as not to introduce biases into the study results.

This approach helps to reduce sources of variability and to properly assess the effect of the experimental drug on blood pressure.

6.2.8 What is the recommended duration for clinical trials of antihypertensive drugs?

In general, studies aimed at characterizing the dose-response relationship and demonstrating antihypertensive efficacy should last at least 3 months, preferably 6 months. When more than one dose is evaluated, it is generally recommended that each dose be maintained for at least 4 weeks to allow for adequate characterization of its effect.

Controlled studies with an active comparator may require follow-up periods of approximately 6 months in order to allow for adequate comparison of efficacy and safety between treatments.

Thus, the duration of the studies must be sufficient to allow for adequate characterization of the antihypertensive efficacy, dose-response relationship, and safety profile of the combination, with the design and follow-up time being compatible with the specific objectives of each stage of clinical development.

6.2.9 What safety aspects should be considered in clinical trials of antihypertensive drugs?

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Safety assessment is an essential part of the clinical development of antihypertensive drugs and should consider both general adverse events and specific events related to the mechanism of action of the components of the combination.

In general, safety monitoring should include the assessment of events potentially associated with a reduction in blood pressure, such as hypotension, orthostatic hypotension, dizziness, and syncope, as well as other known adverse events from the pharmacological classes involved.

Additionally, specific monitoring related to laboratory, electrocardiographic, or metabolic parameters may be necessary, depending on the pharmacological profile of the medications being studied. Electrolyte imbalances, renal function, heart rate, blood glucose, and lipid profile are examples of parameters that may be relevant in certain contexts.

Safety assessments should also consider potentially more vulnerable populations, such as elderly patients, individuals with multiple comorbidities, and patients concomitantly using other antihypertensive medications.

The security monitoring plan must be compatible with known or potential risks and allow for an adequate characterization of the benefit-risk profile of the proposed partnership.

6.3 ADF for the Treatment of Flu and Common Cold

6.3.1 What aspects should be considered when designing clinical trials for the treatment of influenza and the common cold?

The design of clinical trials to evaluate the effectiveness of antiviral medications should consider the characteristics of the clinical conditions being treated, which are generally acute, self-limiting, and composed of multiple symptoms.

In this context, the following aspects, among others, should be considered:

- Clear definition of the target symptoms to be evaluated (e.g., pain, fever, nasal congestion, and cough); • Use of clinical outcomes directly relevant to the patient, assessed using validated tools; • Selection of outcomes that allow for the evaluation of the magnitude and time of response to treatment, such as the time to improvement or resolution of symptoms;
- Defining appropriate comparators, including placebo or active comparators, according to the study objective and the availability of effective therapies; • Controlling and standardizing the use of concomitant and rescue medications, considering their potential impact on efficacy assessment; • Adopting measures to ensure standardization of clinical assessments throughout the study.

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In general, the study design should allow for a clear assessment of the drug's effect on the symptoms it is intended to treat, ensuring the interpretability of the results and the adequate characterization of its efficacy.

6.3.2 What efficacy outcomes can be considered in clinical trials for the treatment of influenza and the common cold?

The primary efficacy outcomes in studies with antiviral medications should reflect the direct clinical benefit to the patient for whom the medication is being investigated, considering the nature of those clinical conditions.

Examples of frequently used outcomes include time to symptom improvement or resolution, change in the intensity of specific symptoms such as pain, fever, nasal congestion, and cough, and composite measures that assess the evolution of clinically relevant symptom sets (e.g., combined symptom scores), provided that the contribution of each component and the clinical interpretation of the result are duly justified.

The choice of outcome should consider clinical relevance, sensitivity to detect changes over time, and suitability to the mechanism of action of the investigational drug. Whenever possible, the use of validated instruments and scales, including patient-reported measures, is recommended for symptom assessment.

In this context, standardization of symptom assessment is essential to ensure data reliability. Assessments should be conducted at defined and consistent times, using standardized instruments and under similar conditions throughout the study.

Additionally, the variability of symptoms over time should be considered, since conditions such as the common cold and flu-like syndrome have fluctuating courses. Therefore, it is recommended that the study design include repeated assessments throughout the study period and use outcomes capable of capturing this temporal evolution, allowing for the differentiation between the effect of treatment and the natural progression of the disease.

Studies based solely on vague global outcomes may limit the interpretation of results, especially when they do not allow for the identification of the treatment effect on individual symptoms.

The occurrence of intercurrent events, such as the use of rescue medication, early remission of symptoms, or discontinuation of treatment, should also be considered, as these can impact the interpretation of the outcomes evaluated. In such cases, it is recommended that such events be defined beforehand, with objective characterization criteria and clear treatment strategies in the analyses, in order to ensure the proper interpretation of the results.

6.3.3 Is it appropriate to use global symptom outcomes as the primary outcome?

The use of global symptom outcomes, based on composite scores that aggregate multiple symptoms (such as pain, fever, nasal congestion, and cough), may be acceptable as a primary outcome in clinical trials of influenza medications, provided that

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duly justified and evaluated using appropriate instruments to capture clinically relevant changes. This approach can be particularly useful considering that these conditions are characterized by the simultaneous presence of multiple symptoms and that therapeutic benefit often translates into overall clinical improvement.

However, the use of global outcomes may present some limitations. In particular, these outcomes may not, in isolation, adequately characterize the effect of treatment on specific symptoms, nor may they be sufficient to characterize the individual contribution of the components of the association.

Since these conditions are characterized by multiple symptoms with different pathophysiological mechanisms and variable evolution over time, the interpretation of results obtained through composite scores must consider the behavior of individual symptoms. In this context, it is important that the study includes complementary assessments of the evolution of specific symptoms, especially in the development of ADF, where it may be necessary to demonstrate the contribution of the different components of the association to the observed therapeutic effect.

Thus, although global outcomes can be used as the primary outcome, the study design must allow for adequate characterization of the effect of the experimental drug on the symptoms it is intended to treat, ensuring the interpretability of the results and the assessment of the clinical relevance of the combination, especially with regard to the contribution of its components.

6.3.4 How should the choice between superiority and non-inferiority delineations be defined?

As discussed in the general section on clinical development of ADF, the choice between superiority or non-inferiority designs should be aligned with the study objective, the intended therapeutic indication, and the clinical rationale for the combination.

For example, when the goal is to demonstrate an additional benefit of the combination compared to its individual components or other available therapies, such as greater efficacy in symptom relief, faster onset of action, or clinically relevant improvement in overall symptom control, a superiority study is necessary. This design is particularly relevant considering that these combinations aim to act on multiple symptoms in a complementary way.

Non-inferiority studies may be considered in specific situations, such as when the combination aims to replace established treatments, maintaining similar efficacy but offering other advantages, such as improved safety profile, tolerability, or dosing convenience.

Additionally, it should be considered that studies with antiviral drugs are subject to high variability in symptoms and a high placebo response, characteristics that may limit the ability of non-inferiority designs to demonstrate clinically relevant differences. Thus, in many scenarios, superiority designs tend to be more informative and more suitable for characterizing the therapeutic value of the combination.

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6.3.5 What are the considerations regarding the use of rescue medication?

In general, it is recommended that the protocol provide for the use of rescue medication when necessary to ensure the well-being of participants, especially in studies involving moderate to severe symptoms, observation periods during which participants may experience significant discomfort, or designs that include a placebo as a comparator.

In these cases, the protocol must clearly define the type of rescue medication allowed, the dose and administration schedule, the criteria for use, and the procedures for recording and monitoring its consumption.

Additionally, the use of rescue medication should be considered in the analysis of the results, since it may interfere with the evaluation of the efficacy of the experimental drug.

6.3.6 What aspects should be considered regarding the start of treatment and the timing of effectiveness assessment?

The start of treatment and the timing of efficacy assessment are critical aspects in the design of clinical trials with antiviral medications, since the therapeutic response can vary according to the phase of the disease, which is acute, self-limiting, and characterized by rapid symptom progression.

In this context, it is important to consider:

- The interval between the onset of symptoms and inclusion in the study, which must be clearly defined and clinically justified, considering the mechanism of action of the experimental drug; • The time between randomization and the effective start of

treatment, which must be minimized and standardized in order to avoid variations in treatment exposure;

- The timing of the effectiveness assessment, which must be defined in advance and consistent among participants, allowing for adequate comparison between groups;

- The duration of treatment and the follow-up period, which should be sufficient to capture the evolution of symptoms and the effect of the medication over time.

The lack of definition and control of these parameters can introduce significant variability, making it difficult to distinguish between the effect of treatment and the natural progression of the disease, especially in conditions with a high placebo response, and compromising the interpretability of the results.

6.4 ADF for the Treatment of Type 2 Diabetes Mellitus (DM2)

6.4.1 How should the clinical and pharmacological rationale for an ADF in the treatment of type 2 diabetes be demonstrated?

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The development of ADF for the treatment of type 2 diabetes mellitus (DM2) must be supported by a consistent pharmacological and clinical rationale that justifies the combined use of the components.

This rationale should consider, among other aspects, the complementarity of the mechanisms of action, the potential for an additive or synergistic effect in reducing blood glucose levels, and the possibility of acting on different pathophysiological pathways of the disease.
Additionally, it should be considered that the management of type 2 diabetes is multifactorial and individualized, so the combination must be able to offer relevant clinical benefit in the context of the patient's profile and the intended therapeutic scenario.

The composition of the combination should consider the safety profile of each active ingredient and the potential impact of the combination on the occurrence of adverse events, including the risk of hypoglycemia and other effects specific to the classes involved. The assessment of the balance between benefit and risk should also consider aspects such as the complexity of the therapeutic regimen, the number of medications, and the potential impact on adherence to treatment.

In the regulatory context, clinical development is expected to demonstrate not only the efficacy of the combination, but also the contribution of each component to the observed therapeutic effect, as well as the adequacy of the proposed doses. This demonstration should show that the combination offers additional benefit or a relevant clinical advantage compared to the components administered individually or to available therapeutic alternatives.

Therefore, the rationale for the combination must be clearly described and supported by pharmacological and clinical evidence in order to justify its use in the intended therapeutic setting.

6.4.2 How should the intended use scenario of an ADF be defined in clinical development for the treatment of type 2 diabetes?

The use scenario for an ADF should be clearly defined in clinical development, considering the intended role of the combination in clinical practice, such as initial therapy, add-on therapy, or replacement of previously established regimens, since this context guides the definition of the objectives and design of the clinical trials to be conducted.

Furthermore, the intended therapeutic scenario should consider that the management of type 2 diabetes is dynamic and individualized, guided by the patient's clinical characteristics, the presence of comorbidities (such as cardiovascular or renal disease), the risk of hypoglycemia, and specific therapeutic goals.

Additionally, it must be aligned with the clinical rationale of the association, the characteristics of the study population, and the evidence generated throughout the development. Clinical trials should be designed to reflect the context.

intended use, including appropriate selection of comparators, inclusion criteria, and outcomes.

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In the case of initial therapy, the use of the combination in treatment-naïve or limitedly treated patients must be justified. In add-on scenarios, the combination should be evaluated in conjunction with stable background therapies. In replacement situations, it must be demonstrated that ADF maintains or improves clinical control compared to the previous regimen.

The proposed use scenario must also be consistent with the expected clinical benefit of the combination, including potential advantages in efficacy, safety, or simplification of the therapeutic regimen, when applicable.

Consistency between the proposed use scenario, study design, and intended therapeutic indication is essential for proper regulatory assessment.

6.4.3 In what situations can the use of initial combination therapy be considered in the treatment of type 2 diabetes?

The use of initial combination therapy may be considered, especially when there is a need to achieve faster and more effective glycemic control, or when the baseline HbA1c level is above the therapeutic target.

Clinical guidelines consider initiating dual-agent therapy in patients with HbA1c above target, especially when there is a greater distance from the target or a need for faster and more sustained glycemic control, within the context of an individualized approach based on the patient's clinical profile *(Standards of Care in Diabetes — 2026, American Diabetes Association;* Management of antidiabetic therapy in type 2 diabetes — 2025, Brazilian Diabetes Society; *Comprehensive Type 2 Diabetes Management Algorithm — 2023 Update, American Association of Clinical Endocrinology).*

In the context of developing an ADF, this scenario is particularly relevant, provided that the proposed combination is consistent with established clinical practice and supported by evidence demonstrating additional benefit compared to monotherapy.

On the other hand, more intensive strategies from the start of treatment, such as the use of combinations with multiple components, must be carefully justified, considering the clinical rationale, the available evidence, and the balance between benefit and risk, including aspects such as safety, tolerability, and complexity of the therapeutic regimen, as well as its suitability to the intended use scenario.

In general, the rationale for using combinations from the start of treatment should be based on consistent clinical rationale, evidence of clinically relevant additional benefit, and alignment with current clinical practice and therapeutic guidelines.

6.4.4 Is it acceptable to adopt early intensification strategies, such as the direct introduction of triple therapy, in the development of ADF?

The adoption of early intensification strategies, such as the direct introduction of triple therapy, should be carefully justified in the context of the clinical development of ADF.

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According to the guideline “Management of antidiabetic therapy in type 2 diabetes mellitus”, from the Brazilian Diabetes Society (2025), the management of DM2 is generally based on a structured therapeutic progression, with gradual intensification of treatment according to the clinical response, which should be continuously reassessed and adjusted over time.

In this context, the introduction of more complex therapies, such as triple therapy, is generally considered an intensification strategy in patients who remain above their glycemic target after using dual therapy or in specific clinical situations, such as after stabilization of insulin-based therapy. These approaches are associated with reassessment of glycemic control and adjustment of the therapeutic strategy to the patient's clinical profile.

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International guidelines indicate that the treatment of type 2 diabetes should be continuously monitored, with periodic reassessment of glycemic control and adjustment of therapy when targets are not met, characterizing a model of therapeutic intensification based on the response to the current treatment *(Standards of Care in Diabetes* — 2026, *American Diabetes Association).*

Thus, therapeutic intensification generally occurs sequentially, with treatment adjusted according to the observed response, and the direct introduction of more complex regimens, such as triple therapy, is not a standard initial approach and requires consistent clinical justification. Additionally, the suitability of this strategy should be analyzed in light of the profile of the studied population.

The rationale for more intensive strategies should consider the balance between benefit and risk, including the potential increase in treatment complexity and the risk of adverse events, as highlighted in clinical guidelines.

6.4.5 Is it appropriate to allow wide variation in the dose of medications used as background therapy in the development of an ADF?

In the context of type 2 diabetes mellitus (DM2), clinical trials are frequently conducted in an add-on regimen, in which participants remain on a previously established baseline therapy. In these scenarios, the evaluation of the effect of the experimental drug, including outcomes such as changes in glycated hemoglobin (HbA1c), depends on relatively stable treatment conditions over time. Therefore, it is recommended that the baseline therapy be maintained, whenever possible, at a stable dose throughout the study.

Although the use of different dose levels may be considered in well-designed studies, this approach requires prospective definition of dose levels, sufficient sample size, and a statistical strategy capable of evaluating the impact of this variability, including the relationship between dose and therapeutic response. In the absence of these elements, dosage variability can compromise the interpretation of results and the estimation of the effect of the experimental drug.

Additionally, even when accompanied by broad stratifications, dose heterogeneity may not ensure the comparability necessary for

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Regulatory assessment, especially when there is no adequate statistical planning to support confirmatory inferences.

It should be noted that when the ADF under development includes the background therapy as one of its components, the dosage variability of this medication during the study may hinder the adequate assessment of the specific dose to be incorporated into the combination, as well as the interpretation of the efficacy and safety of the ADF at the dosage proposed for registration. This aspect is particularly relevant, since the regulatory evidence must directly support the efficacy and safety of the combination at the proposed fixed doses.

Additionally, changes in baseline therapy throughout the study may introduce further variability and confound the assessment of treatment effect, and should be defined, controlled, and considered in advance during data analysis.

6.4.6 What parameters can be used for stratification in randomization and for subgroup evaluation?

The definition of parameters for stratification in randomization and for subgroup analysis should be based on prognostic factors relevant to the study outcome and on clinical characteristics that may influence the response to treatment.

In the context of type 2 diabetes mellitus (DM2), risk stratification is an important element not only for the methodological planning of studies, but also for the proper clinical interpretation of results. Factors such as cardiovascular risk, presence of kidney disease, risk of hypoglycemia, baseline HbA1c level, disease duration, body mass index (BMI), and previous treatment can influence both the choice of therapy and the magnitude of the expected benefit.

Randomization, by itself, tends to promote balance between study groups. However, stratification may be considered in specific situations, especially for factors with a potentially significant impact on results, such as baseline metabolic control and prior treatment.

Other population characteristics, such as age, renal function, presence of comorbidities, and the patient's overall clinical profile, may be considered in defining subgroups, provided there is clinical plausibility of influence on the response to the treatment.
treatment.

Additionally, when the rationale for the intervention is associated with specific benefits in certain risk profiles (e.g., cardiovascular, renal, or metabolic effects), assessing the consistency of results in these subgroups becomes particularly relevant, allowing the exploration of possible differences in the magnitude of the effect between distinct populations.

Therefore, factors potentially influencing the response to treatment should be prospectively identified, and the consistency of the observed effects among clinically relevant subgroups should be evaluated.

The selected parameters must be justified based on clinical and statistical rationale. Subgroup analyses must be pre-specified in the protocol and...

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Interpreted with caution, especially when they lack sufficient statistical power to support confirmatory inferences, they should generally be considered exploratory analyses when not adequately sized.

6.4.7 What outcomes can be considered in clinical trials of an ADF for the treatment of type 2 diabetes?

In clinical development, efficacy outcomes should reflect relevant clinical benefit and be appropriate to the mechanism of action of the combination and the intended therapeutic setting.

The variation in HbA1c is widely accepted as a primary outcome in confirmatory studies of antidiabetic drugs, being considered a validated surrogate outcome for reducing the risk of microvascular complications. However, demonstrating efficacy should not be limited exclusively to this parameter. It is important to consider, in addition to glycemic control, relevant clinical outcomes such as those related to cardiovascular risk, renal function, body weight, blood pressure, lipid profile, risk of hypoglycemia, and quality of life, especially in pharmacological classes that offer additional benefits beyond blood glucose reduction.

Additionally, glycemic parameters other than HbA1c can be used as complementary outcomes to characterize the drug's action profile. Among these, fasting blood glucose, postprandial blood glucose, and metrics derived from continuous glucose monitoring, such as time in range, stand out. These parameters can contribute to the assessment of glycemic variability and the risk of hypoglycemia, and are generally considered secondary or exploratory outcomes, not replacing HbA1c as the primary outcome for confirmatory demonstration of efficacy (Diabetes Mellitus: *Efficacy Endpoints for Clinical Trials Investigating Antidiabetic Drugs and Biological Products — 2023, Food and Drug Administration).*

In this context, the selection of endpoints should be aligned with the pharmacological profile of the components of the combination and with the expected clinical benefits. When applicable, additional endpoints, such as major cardiovascular events, hospitalization for heart failure, or renal endpoints, may be relevant, especially for therapeutic classes with demonstrated effects on these clinical endpoints. The inclusion of these endpoints should be justified based on the expected additional clinical benefit of the combination.

Additionally, safety assessments should consider not only general adverse events, but also specific events associated with the classes involved, including hypoglycemia and relevant metabolic effects.

Thus, the selected set of outcomes should allow for a comprehensive assessment of the efficacy and safety of the combination, reflecting its potential clinical impact and therapeutic relevance in the overall management of the disease.

6.4.8 Is a 24-week efficacy assessment sufficient for the clinical development of antidiabetic drugs?

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Efficacy assessment at 24 weeks, usually based on HbA1c change, is widely accepted as a primary endpoint in confirmatory studies of antidiabetic drugs. However, clinical development should also include assessment of the maintenance of the therapeutic effect.

In line with international clinical development guidelines, such as the *Guideline on clinical investigation of medicinal products in the treatment or prevention of diabetes mellitus* (EMA, 2023), it is recommended that the development program include at least one study demonstrating the maintenance of the glycemic effect over a longer period, typically 12 months. Whenever possible, this assessment should be conducted in controlled studies, preferably with an active comparator, in order to allow for more robust inferences about the maintenance of the effect over time.

This aspect is particularly relevant considering the chronic and progressive nature of type 2 diabetes, in which loss of effectiveness can occur over time.

In the case of ADF, the maintenance of the effect should be evaluated in the context of the combination itself. Extrapolating efficacy maintenance data from studies conducted with single drugs is not considered appropriate, since the combination may present pharmacodynamic and pharmacokinetic interactions, as well as additive or non-linear effects, which can influence both the magnitude and the persistence of the therapeutic effect.

Therefore, demonstrating the maintenance of efficacy and safety over time must be based on direct evidence obtained from the proposed combination, over a period compatible with applicable regulatory requirements. This approach is essential to ensure an adequate characterization of the benefit-risk profile of the combination over time.

6.4.9 What aspects should be considered in the assessment of hypoglycemia?

Hypoglycemia is a critical safety outcome in clinical trials with antidiabetic drugs and should be systematically evaluated and characterized throughout clinical development.

The analysis should consider the frequency, severity, and timing of events, and may include standardized classifications (e.g., symptomatic events, events confirmed by blood glucose, or severe events requiring assistance) to allow for comparability between treatments.

In addition to its role as an adverse event, hypoglycemia represents a relevant factor in assessing the benefit-risk ratio, since it can impact treatment adherence, quality of life, and the occurrence of adverse clinical events. Therefore, the risk of hypoglycemia should be considered when defining therapeutic strategies and glycemic targets.

In certain contexts, especially when comparators present a differential risk of hypoglycemia, this outcome can contribute to the evaluation of the clinical benefit of the intervention, not only as a safety outcome, but also as...

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A relevant component of the overall assessment of efficacy and safety, provided it is interpreted in conjunction with the glycemic control achieved.

Thus, reductions in the incidence of hypoglycemia should be evaluated in conjunction with the glycemic control achieved, in order to ensure that observed differences are not due to less effective glycemic control. The interpretation of this outcome should therefore consider the balance between glycemic control and safety, within the context of the overall assessment of the clinical benefit of the intervention.

7.0 Security Monitoring

7.1 How to notify SUSARs to COPEC?

Upon becoming aware of an adverse event, the investigator must classify it according to causality, severity, intensity, and expected/unexpected nature. If the adverse event is considered serious and unexpected, considering the provisions of the Reference Safety Information (RSI) in the Investigator's Brochure or the drug's package insert, if registered; and there is also a reasonable possibility of a causal relationship (i.e., suspicion) with the investigational drug, the event becomes a SUSAR (Sustainable *Adverse Event* Report). Therefore, it must be reported to COPEC (Commission for the Evaluation of Research and Combating of Adverse Events) through the VigiMed system.

We recommend consulting the Manual for Reporting Suspected Adverse Reactions.
Serious and Unexpected Events – SUSARs and Safety Monitoring in Clinical Trials, available at

https://www.gov.br/anvisa/pt-br/assuntos/medicamentos/pesquisaclinica/notificacoes/guias-e-manuais-1

7.2 What are the minimum requirements for using and including SUSAR notifications in the VigiMed system?

We recommend consulting the VigiMed Empresas – Clinical Research user manual, which describes all the technical and operational requirements necessary for submitting SUSARs.

Furthermore, the Manual for reporting Suspected Serious and Unexpected Adverse Reactions – SUSARs and safety monitoring in clinical trials describes the minimum information that must be included in each report to allow for evaluation by the COPEC team.

We remind you that as of March 21, 2026, RDC No. 967/2025 came into effect, making the use of the WHODrug Dictionary mandatory for the coding of medicines and active ingredients.

The use of the MedDRA dictionary will now also be mandatory in SUSAR notifications.

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7.3 How do I gain access to the VigiMed system?

To request access to VigiMed Empresas, a form is required, available on the VigiMed-Pesquisa page, or by email at vigimed.pesquisa@anvisa.gov.br.

Both sponsors and Clinical Research Organizations (CROs) can request access to VigiMed.

7.4 How do I access VigiMed?

Access to VigiMed must be done through the link sent in the email response to the registration request: vigiflow.who-umc.org.

7.5 Considering that the MedDRA license has global scope, while the WHODrug license may have geographical restrictions according to the contract established by each entity, and considering a local CRO representing a sponsor without operations in the country, should both the sponsor and the CRO have licenses covering Brazil?

Regarding MedDRA and WHODrug licenses, both the sponsor and the ORPC must have their respective licenses. Therefore, both licenses will be considered for enabling the VigiMed system.

At the time of submission, the license of the company that will share the information with Anvisa through the VigiMed system will be used.

7.6 Regarding the access of CROs to Vigimed, what model does ANVISA expect for the system's operation, especially in cases where the same CRO acts for different sponsors: Single access for the CRO, without specific identification by sponsor; or creation of sub-profiles/specific accesses segregated by sponsor linked to the CRO user?

Regarding registration, access is granted through sub-profiles, using the sponsor's XML credentials.

We understand that the model must preserve adequate traceability of the notification sender, according to the identifiers defined in the registration and the E2B(R3) standard.

The system allows the same user/email to be associated with more than one company or account, including distinct accounts, and it is possible to select the desired account before submission.

7.7 Is there a specific workflow for requesting access to the test environment for validating XML submissions?

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The applicant must follow the same procedure described for requesting access to VigMed.

It is necessary to fill out a form, available on the VigiMed-Pesquisa page, and send it to the email vigimed.pesquisa@anvisa.gov.br.

After access is granted, COPEC will reply to the email with instructions on how to exit the test environment.

7.8 In cases where the ORPC only has an XML file extracted from a global database, without the case narrative in Portuguese, how can the narrative be supplemented in Portuguese?

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In this case, it is necessary to modify the XML file, including the translation of the narrative, before submitting it.

Another possibility is to manually enter the data.

8.0 General Questions

8.1 - 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).

8.2 - In accordance with Article 6 of IN No. 457/2026, which, pursuant to RDC No. 945/2024, establishes the criteria for filing the documents that comprise the Investigational *Medicinal Product* Dossier (DPI).

(IMPD) of the Drug Clinical Development Dossier (DDCM) process or the petition for substantial modification to the product under investigation, the pending documents must be added to the corresponding petition with a specific subject code defined by Anvisa. What is the number of the specific subject code mentioned?

The “REQUEST FOR FILING BY PROCEDURE OF
"CONTINUOUS SUBMISSION" must be attached to the DDCM or substantial modification petition for the investigational medicinal product, and any pending documents must be added to the corresponding petition using subject code 1363 – CLINICAL TRIALS.
– Addendum.

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The technical team will continue to monitor the situation and, if necessary, may create a specific subject code.

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9.0 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.

9.1. 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.

9.2. 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.

9.3. Compliance with requirements

ÿ Send the answers in Portuguese.

10. BIBLIOGRAPHIC REFERENCES

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ANVISA. Technical Note No. 1/2026/SEI/GGBIO/DIRE2/ANVISA, dated June 26, 2026. Evaluation of comparative pharmacokinetic studies of biosimilars submitted as supporting documentation for the registration and approval of DDCMs.

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

ANVISA. Collegiate Board Resolution – RDC No. 753, of September 28, 2022.
This law regulates the registration of medicines for human use with synthetic and semi-synthetic active ingredients, classified as new, innovative, generic, and similar.

ANVISA. Collegiate Board Resolution - RDC No. 735, of July 13, 2022.
This law regulates the control of the substance lenalidomide and medications containing it, and provides other measures. Official Gazette of the Union, September 15, 2022.

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ANVISA. 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 in list C3 of Annex I of Ordinance SVS/MS No. 344/1998, as well as medicines containing them, except thalidomide.

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10. 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 Drug Efficacy and Safety Assessment Management	Changes made to reflect current management and membership.

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	• Update of full/alternate members	
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 in subsequent versions.
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 large number of questions related to the investigator-sponsor relationship, a new section has been created to facilitate the search.
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.

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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
v.4	Inclusion of clarifications regarding the submission of petitions related to Fixed-Dose Associations (FDA). – Item 5.3.4	Further clarifications regarding the submission and analysis of pharmacokinetic interaction studies and pharmacokinetic studies for biosimilar drugs, as per Technical Note No. 1/2026/GPBIO.
v.4	Update on subject codes for petitioning through the SOLICITA system – 5.3.10	Migration of clinical research subject codes to the SOLICITA system.
v.4	Update on the submission of stability studies according to IN No. 457/2026 regarding continuous submission – Item 5.6.1	Submission of pending documents via rolling submission.
v.4	Update on submission and analysis of pharmacokinetic interaction studies and FC studies for biosimilar products, as per NT No. 1/2026 – Item 5.13.1	Analysis of pharmacokinetic studies for biosimilar products by GPBIO.
v.4	Importing 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 – item 5.19.3	Importation and distribution of lab kits to clinical research centers.
v.4	Inclusion of section 6.0 - Clinical Development of Fixed-Dose Combinations (FDCs)	6.1 Main points of attention related to ADF 6.2 ADF for the Treatment of Arterial Hypertension 6.3 ADF for the Treatment of Flu and Common Cold 6.4 ADF for the Treatment of Type 2 Diabetes Mellitus (DM2)
v.4	Update on subject code for submission of pending documents – Continuous submission – IN No. 457/2026.	Submission of pending documents by Addendum (Subject Code 1363)
v.5	Inclusion of additional guidelines on DICD submission – item 5.3.3	Follow the guidelines of the specific standard regarding risk classifications and the need to submit the DICD (Diagnosis of Risk Classification and Disability).
v.5	Inclusion of additional guidelines on submitting studies for biosimilar products – item 5.13	Additional guidance to clarify whether or not DDCM submission is required. Guidance on procedures to be followed
v.5	Inclusion of the topic on security monitoring. of clinical trials - Item 7.0	for reporting SUSARs.