

Guidelines for organization, operation and evaluation of clinical trials pharmacies in Brazil: a scope review

Valeria Rita Teixeira Ribeiro (<https://orcid.org/0000-0002-2697-1695>)¹
Luana Monteiro Spindola Marins (<https://orcid.org/0000-0003-0045-6764>)¹
Ana Carolina Vitorino Vieira (<https://orcid.org/0000-0003-0984-9732>)¹
Debora Santana Geraldo (<https://orcid.org/0000-0003-4271-6341>)¹
Giovanna Giannini Costa (<https://orcid.org/0000-0001-8409-6043>)¹
Renata Bastos de Araujo (<https://orcid.org/0000-0002-5480-515X>)¹
Robson Pierre Nascimento da Silva (<https://orcid.org/0000-0003-3800-7569>)¹
Lusiele Guaraldo (<https://orcid.org/0000-0003-0047-6538>)¹
Thiago Silva Torres (<https://orcid.org/0000-0002-2557-601X>)¹

Abstract *The development of new drugs depends on several scientific steps, which culminate in clinical trials. The clinical trials pharmacy (CTP) is the place for receiving, preparing, storing and dispensing the investigational product or study drug. Therefore, it must have infrastructure and procedures that guarantee participant safety and quality of research data. This study aimed to systematize guidelines for CTP in Brazil. We conducted a scope review and organized the results using the Ishikawa Method (6Ms). In total, 51 publications were selected for each “M”, 39 laws, regulations or guidelines and 12 scientific articles: 25 publications for pharmaceutical services (pharmacy procedures to ensure participant safety from investigational product ordering to final disposition), 14 for Quality Indicators, 12 for Human Resources, 11 for Infrastructure, 11 for Material Resources and 5 for Investigational Product. Our results synthesize information for the organization, operation and evaluation of CTP in Brazil, emphasizes the inclusion of the pharmacist within the clinical trials context, and contributes to preparation for monitoring, auditing, and inspections conducted by regulatory agencies.*

Key words *Pharmacy, Clinical trial, Pharmaceutical services, Brazil*

¹ Instituto Nacional de Infectologia Evandro Chagas, Fundação Oswaldo Cruz. Av. Brasil 4365, Manguinhos. 21040-360 Rio de Janeiro RJ Brasil. thiago.torres@ini.fiocruz.br

Introduction

The development and registration of a new product or investigational product (IP) for use in humans, whether a drug, vaccine or medical device, takes several scientific steps until registration, from product development (pharmaceutical development) to clinical trials¹.

Clinical trials aim to (1) discover or confirm the clinical, pharmacological or pharmacodynamic effects of IPs; (2) identify any adverse reaction to IPs; and (3) study the absorption, distribution, metabolism and excretion of PI to assess its safety or efficacy². According to the website of the National Library of Medicine of the United States (clinicaltrials.gov), a total of 8,533 clinical trials with Brazilian participation have been registered, 70% of them in the past ten years, and an average of 586 new studies are registered each year³.

A clinical research site is a public, private or philanthropic organization legitimately constituted and registered in the National Registry of Health Establishments (CNES, for its Portuguese acronym), which must have a structure that allows the performance of clinical trials in accordance with Good Clinical Practices (GCPs), Brazilian legislation and international regulatory agencies, in case there is interest in registering the IP in other countries^{2,4,5}. These sites are usually located in hospitals or other health units, research institutions or independent clinical research centres. The sites must adhere to requirements, such as designated facilities for the reception, preparation, storage and dispensing of the IP, as recommended by national and international standards⁵. The clinical trials pharmacy (CTP) can be located inside the pharmacy of the health unit or in a separate area, which is common in large clinical research sites.

Pharmacies, including those belonging to hospital units^{6,7}, must maintain physical infrastructure, equipment, human resources and procedures that meet good dispensing practices⁸. Because it is a health establishment commonly linked to a hospital, the CTP can be understood, according to the provisions of Law 13.021/2014, as a service unit designed to provide pharmaceutical care, health care and individual and collective health guidance⁹. Pharmaceutical care is a set of actions aimed at health promotion, protection and recovery with access to and rational use of drugs, including in the research context¹⁰. In addition, pharmaceutical care includes a set of health education and promotion actions, such as clinical-care and technical-pedagogical activities¹¹.

The Brazilian Federal Pharmacy Council (Conselho Federal de Pharmacy, CFF) has the exclusive responsibility of monitoring pharmacists working in clinical trials to ensure compliance with sanitary requirements and other related laws and guiding any necessary adjustments to comply with the rules regarding the receipt, storage and dispensing of IPs¹².

In this context, and in view of the increase in clinical trials for new vaccines and drugs in Brazil, including those related to the COVID-19 pandemic¹³, it is necessary that clinical research sites have an CTP prepared to conduct these studies aiming to guarantee participants safety and GCP, to generate accurate data for the registration and use of medications¹⁴. However, to the best of our knowledge, no document that summarize national and international publications aimed at pharmacists and managers of clinical research sites is available. This study aimed to conduct a scope review to propose guidelines for the organization, operation and evaluation of an CTP in Brazil.

Methods

Study design

A scope review was conducted to map the main concepts related to the organization, operation and evaluation of pharmacies in the context of clinical trials, following the population, concept and context strategy (PCC) (P = not applicable, C = guidelines for operation pharmacies, C = clinical trials conducted in Brazil).^{15,16} This review was registered in the Open Science portal (<https://osf.io/a3f2k>) and adhered to the PRISMA scope review recommendations¹⁷.

Inclusion criteria

Scientific articles, documents of national and international laws, regulations and guidelines that were relevant to the areas of interest (pharmacy and clinical trials), with no restriction on the date of publication, and published in Portuguese, English and Spanish were eligible. Considering that the CTP and other pharmacies are intended to provide pharmaceutical care, health care and individual and collective health guidance⁹, publications related to the operation of pharmacies outside the context of clinical trials were also included in this review.

Databases

We conducted a systematic search of national laws and regulations by searching the website of Brazilian National Health Surveillance Agency (Agência Nacional de Vigilância Sanitária, Anvisa), and by using the PubMed, Virtual Health Library or VHL and Web of Science to access the databases MEDLINE, IBECs, LILACS, CUMED, LIPECS, medRxiv, LIS -Health Information Locator, SUS Collection, BIGG-GRADE, PAHO-IRIS, COCHRANE and SciELO Library guides. Complementary searches were performed on the CFF website and with the Google search engine.

Search strategies

At Anvisa website, we downloaded an Excel spreadsheet that listed all the laws and regulations published by the agency¹⁸. The following sequential Excel program (Microsoft) filters were applied to obtain the relevant documents: (1) “status”: we maintained documents “current,” “current with changes,” “to come into force” and “unidentified”; (2) “macrotema”: we excluded documents related to “pesticides,” “food,” “cosmetics,” “sanitizing,” “tobacco,” and “pharmaceutical ingredients”; (3) “grouping”: we excluded documents related to “customs,” “ports” and “airports”. For scientific articles, we used free terms combined by Boolean operators (Chart 1).

Selection

The selected documents were evaluated by two investigators independently (VRTR and LMSM) in two stages: title and content analysis. The results of each independent investigator were compared, and the differences were resolved by a third investigator (TST).

Data extraction and systematization using the Ishikawa method (6Ms)

The data extracted from the documents were structured into categories according to the Ishikawa diagram (Fishbone diagram or 6Ms method), in which the causes and effects of a problem are identified¹⁹. This method has been chosen so that the critical points of CTP functioning and management could be hierarchized and described in a practical, clear and systematized manner. To adapt to the reality of the CTP, the categories of the 6Ms were renamed as follows: (1) infrastructure (mother nature) included all parts of the ctp, including physical space and security; (2) material resources (machines) included furniture and equipment used in different clinical trials; (3) human resources (manpower) included aspects related to the pharmacy team, such as experience, training and certifications; (4) investigational product (materials) included aspects related to IPs, such as presentation and labelling; (5) pharmaceutical services (methods) included pharmacy procedures to ensure the safety of the participants, from IP ordering to IP final disposition; (6) quality indicators (measurements) included all standards used to evaluate the processes.

Data extraction was performed by one investigator (VRTR) using a standardized spreadsheet in the Excel program (Microsoft) divided according to the six proposed categories (6M Method). Data initially included were reviewed by a group of eight pharmacists with experience in clinical trials (VRTR, LMSM, TST, RPS, RB, GG, ACV, DS), and disagreements were resolved by consensus.

Chart 1. Search keys.

(1) BVS: (((ti:pharmacy)) OR (ab:pharmacy))) OR ((ti(pharmacist)) OR (ab:(pharmacist)))) AND ((ti:(clinical trial*)) OR (ti(clinical research)) OR (ti:(regulatory)) OR (ti:(infrastructure)) OR (ti:(pharmacy legislation)))
(2) PUBMED: ((pharmacy[Title/Abstract]) OR (pharmacist[Title/Abstract])) AND ((clinical trial*[Title]) OR (clinical research[Title]) OR (regulatory[Title]) OR (infrastructure[Title]) OR (pharmacy legislation[Title]))
(3) Web of Science: TI=(pharmacy OR pharmacist) AND T=(clinical trial* OR clinical research OR regulatory OR infrastructure OR pharmacy legislation)

Source: Authors.

Results

Scope review

The searches were performed on August 31, 2021. A total of 2,059 publications were identified on the Anvisa website, and 21 were selected after exclusion. For scientific articles, 823 publications were identified, and after the exclusions, 12 documents were selected. Six publications were selected from the 711 publications on the CFF website. Through Google, we found the Brazilian Pharmacopoeia and a guideline published by Anvisa, three publications by the Ministry of Health, and seven other guidelines and standards. In total, 51 publications were included in our study (Figure 1).

Following the Ishikawa method, 11 documents were included in Infrastructure (Anvisa

4, other laws/regulations 4, and articles 3), 11 in Material Resources (Anvisa 8, other laws/regulations 2, articles 1), 12 in Human Resources (Anvisa 1, CFF 6, MS 1, other laws/regulations 2, articles 2), 5 in Investigational Product (Anvisa 3, other laws/regulations 2), 25 in Pharmaceutical Services (Anvisa 11, CFF 1, MS 2, other laws/regulations 5, articles 6), 14 in Quality Indicators (Anvisa 8, MS 1, other laws/regulations 4, articles 1) (Chart 2). The items described below summarize the main findings of the scope review related to the 6Ms.

Infrastructure

To minimize errors and ensure the safety of study participants, it is essential that the CTP infrastructure for the organization of IPs, study documents and equipment is in accordance with

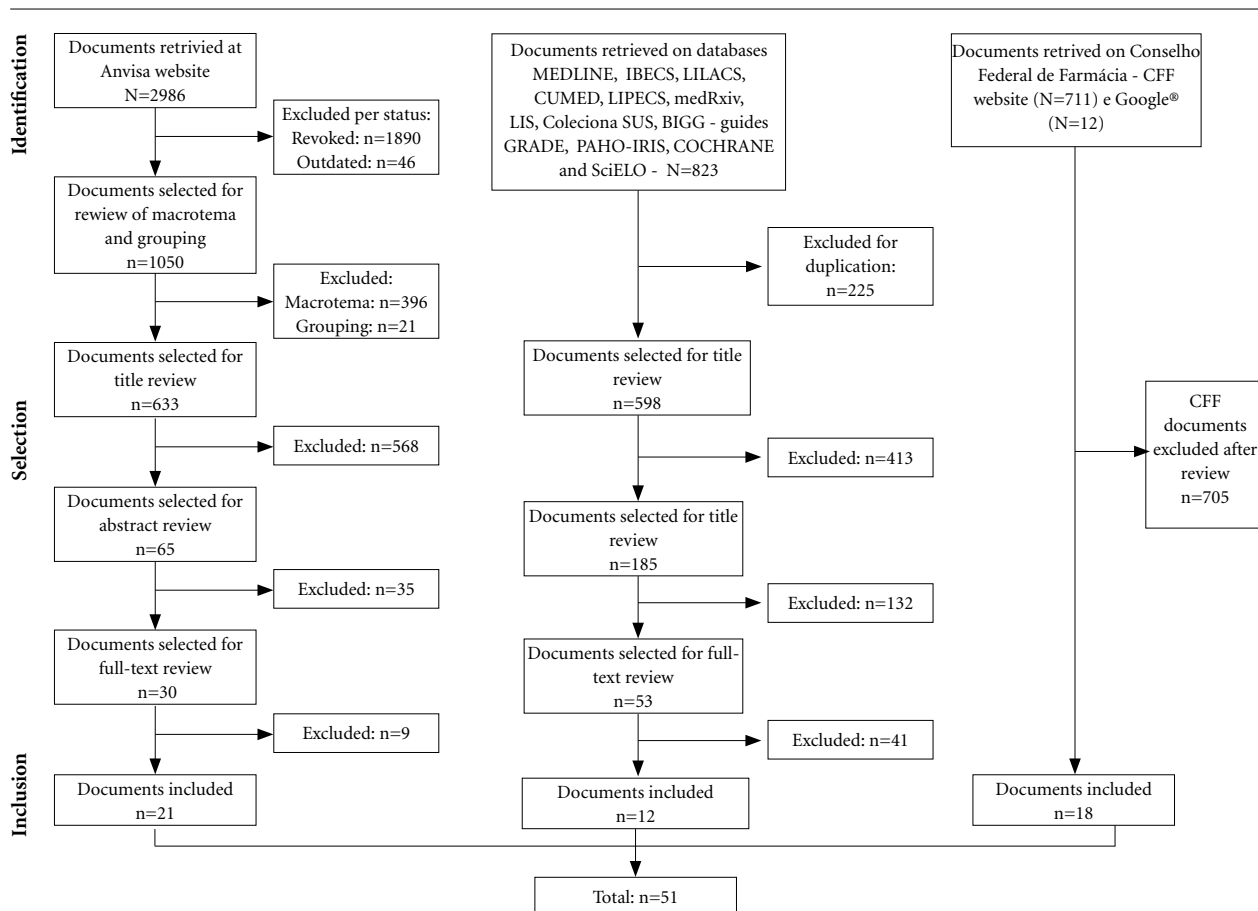


Figure 1. Flowchart for document selection.

national and international regulatory standards and is a safe and clean space, adequate for daily activities^{4,5,14,20}.

The CTP should be built in a location that facilitates the maintenance, cleaning and operationalization of activities²¹. The internal surfaces (floor, walls and ceiling) should be smooth, coated with resistant material and impervious with rounded corners, in perfect condition, resistant

to sanitizing agents and easily washed (biodegradable material and cleaning performed by trained staff)^{8,22,23}.

The CTP should be composed of areas or rooms that allow administrative activities; IP storage, preparation, dispensing and quarantine; changing room and toilets; cleaning area; deposit of cleaning materials; quality control activities^{22,24}. Additionally, there should be a pri-

Chart 2. Documents used to prepare the guidelines for the organization, operation and evaluation of clinical trial pharmacies in Brazil according to the Ishikawa Method.

	Infrastructure	Material resources	Human resources	Investigational product	Pharmaceutical care cycle	Quality indicators
Anvisa						
Farmacopeia Brasileira, 2019 ³⁷						x
Guia N°35/2015 ⁴	x	x				x
IN 20/2017 ⁵⁵						x
IN 45/2019 ⁴⁰				x	x	
RDC 007/2010 ³¹		x				
RDC 009/2015 ²				x	x	x
RDC 010/2011 ⁴⁴					x	
RDC 509/2021 ³⁰		x				x
RDC 044/20098	x				x	
RDC 050/2002 ²⁴	x					
RDC 067/2007 ²²	x	x			x	
RDC 071/2009 ⁴¹				x		
RDC 172/2017 ⁴³					x	
RDC 204/2006 ³³		x			x	x
RDC 214/2006 ²⁷		x			x	
RDC 220/2004 ²⁹		x				
RDC 222/2018 ²⁸		x				
RDC 301/2019 ³⁷			x			
RDC 360/2019 ⁴⁵					x	
RDC 430/2020 ⁴⁶					x	
RDC 449/2020 ⁵⁹						x
RDC 548/2021 ⁴²					x	
RES 009/2003 ⁵⁸						x
Federal Council of Pharmacy						
Lei 5991/1973 ⁶			x			
Lei 13021/2014 ⁹			x		x	
Portaria 1017/2002 ³⁵			x			
RDC 585/2013 ³⁶			x			
RDC 509/2009 ¹²			x			
RES 711/2021 ³⁴			x			
Ministry of Health						
Portaria N°4283 ⁷			x			
RES 338/2004 ¹⁰					x	x
RES 466/2012 ⁴⁸					x	

it continues

Chart 2. Documents used to prepare the guidelines for the organization, operation and evaluation of clinical trial pharmacies in Brazil according to the Ishikawa Method.

	Infrastructure	Material resources	Human resources	Investigational product	Pharmaceutical care cycle	Quality indicators
Other guidelines and regulations						
ALCOA-C ⁵⁴						x
INEA 79/2019 ⁵³					x	
MERCOSUL RES 49/2002 ²¹	x	x			x	
NIH, 2021 ¹⁴	x	x	x	x	x	x
OPAS, 2005 ³⁸			x	x	x	x
SBRAFH, 2017 ²³	x					
Scientific articles						
Barberato, 2019 ¹¹			x			
Barbosa, 2017 ²⁶	x				x	
Barbosa, 2011 ⁵⁶						x
Cardoso, 2019 ⁵²					x	
Costa, 2018 ⁴⁹					x	
Hoagland, 2021 ⁵¹					x	
Khandoobhai, 2017 ⁴⁷					x	
La, 2011 ³²		x				
Leite, 2017 ²⁵	x					
Littauer, 2017 ⁵⁰					x	
Mehta, 2015 ²⁰	x					
Santos, 2006 ³⁹			x			

Source: Authors.

vate area for management and a waiting room for study participants^{23,25,26}.

Access to the CTP should be limited to the pharmacy team, and in the absence of the pharmacist the CTP should remain locked. A security system should be implemented with cameras and doors with padlocks or passcodes. It is recommended the implementation of a record of visitors (e.g., auditors, maintenance)¹⁴. Fire safety must be ensured and include access to fire extinguishers²².

Resource materials

The equipment and furniture should meet the needs of the studies conducted and be for the exclusive use of the CTP¹⁴. They should be organized to allow free movement of employees, participants and visitors^{22,27}. The equipment should ideally have an exclusive connection to a power source to avoid electricity overload and dedicated technical support for prompt service²¹.

The cabinets, refrigerators and freezers should allow storage that preserves the integrity,

stability and efficacy of the IP^{4,14}. When appropriate, they should be identified with an international symbol of the risks related to IPs, such as biological, chemical or radiological risk²⁸. A temperature-controlled system with air conditioning, thermometers and hygrometers is essential, in addition to a power generator in the case of blackouts or electrical failure²².

Biosafety cabinets are essential for the preparation of injectable PIs, such as vaccines. The class II type B2 vertical laminar flow cabinet is recommended for most IPs because it provides an aseptic area for preparation and protection for the pharmacist and the environment¹⁴. The cabinets should be turned on at least 30 minutes before the start of preparation, and it is recommended that the air filtration system remain on for 30 minutes after completion, i.e., cleaning and disinfecting the cabinet^{27,29}.

Personal protective equipment (PPE) should be made available according to the procedures performed in the CTP. For the preparation of injectables, gloves, safety masks, goggles, caps and lab coats are needed. For the care of patients

with respiratory diseases, such as tuberculosis or COVID-19, biological protection with the use of respirators is necessary^{30,31}.

Computerized systems for inclusion or randomization of participants, drug dispensing, communication with the team, and form filling are commonly used in clinical trials and should be considered by the CTP³². These systems should have sufficient controls to prevent access, unauthorized changes, data omissions, and a data recovery system³³.

Human resources

The CTP must have a pharmacist registered with the State Pharmacy Council (Conselho Regional de Farmácia, CRF)^{12,34,35} and at least one pharmacist during all working hours^{6,9}. Pharmacists must follow the rules established by the CFF and the national and international health legislation¹⁴. Whenever necessary, the pharmacist must provide information and perform care and technical-scientific assistance related to medications to the clinical team and study participants^{7,36}. In addition, they should be trained in GCPs, protection of human subjects and research protocols, including amendments and new versions approved by the local Institutional Review Boards (Comitê de Ética em Pesquisa, CEP), in addition to specific procedures, such as chain of custody, preparation of injectable drugs and biosafety^{14,37,38}. The pharmacist must perform professional education¹¹ since clinical trials classes are usually not included in university curricula³⁹. In addition to the pharmacist, other members of the team may include pharmacy technicians, research assistants and receptionists. The IP management is considered the exclusive responsibility of the pharmacist according to some international guidelines¹⁴, but it can be performed by other professionals under the supervision of the principal investigator, as recommended by the International Conference on Harmonisation (ICH)⁵.

Investigational product

The IP must be manufactured according to the Good Manufacturing Practices (GMP), with quality control assured by the certificate of analysis (CoA) and certificate of conformity (CoC)^{2,40}. The manufacturer's instructions or the study protocol contain all the technical information about the IP and are essential documents for the CTP.

IPs should be labelled with information that meets the applicable regulatory requirements before they are dispensed to participants³⁸. According to Anvisa, the labels should contain information in Portuguese, such as name of the IP, pharmaceutical form, number of dispensed units, lot number and expiration date^{40,41}. In case of extension of the IP expiration time, the pharmacist should immediately relabel the vials as soon as notified by the sponsor¹⁴.

Pharmaceutical services

The pharmaceutical services in a clinical trial corresponds to the management of the IP from ordering to the sponsor or manufacturer to the final disposition (Figure 3).

The IP ordering and import activities can be performed by the sponsor or by the clinical research site. In the second case, it is recommended that the pharmacist lead these activities, making the order based on the available IP on site and the predicted inclusion of participants in a study. The import must follow the Anvisa standards, and it is necessary to obtain an import license for each shipment^{2,42,43}. The transport of the IP to the CTP is usually performed by a courier specialized in the transport of medicines and vaccines under controlled temperature and humidity, which should be continuously recorded by calibrated equipment⁴⁴⁻⁴⁶.

Upon IP receipt, the pharmacist must inspect IP physical integrity, the temperature during transport, and whether the documents referring to the shipment are in accordance with the material received before updating the inventory¹⁴. The sponsor or manufacturer must be notified after inspection.

The IP storage should be performed under appropriate conditions of temperature, humidity and lighting, according to the manufacturer's instructions, to avoid affecting its quality^{22,26,33,38}. Access should be restricted to the CTP team to ensure product safety and avoid unblinding in double-blind studies in which the pharmacist is the nonblind member of the study team.

Pharmaceutical assistance is a key step within the pharmaceutical services. In the context of clinical trials, it occurs whenever IP is dispensed. The service includes four main steps: checking the signature on the informed consent form, screening the medical prescription, dispensing the IP and other medications, and pharmaceutical care^{9,26,38,47}. All procedures performed by the pharmacist during the visit should be recorded

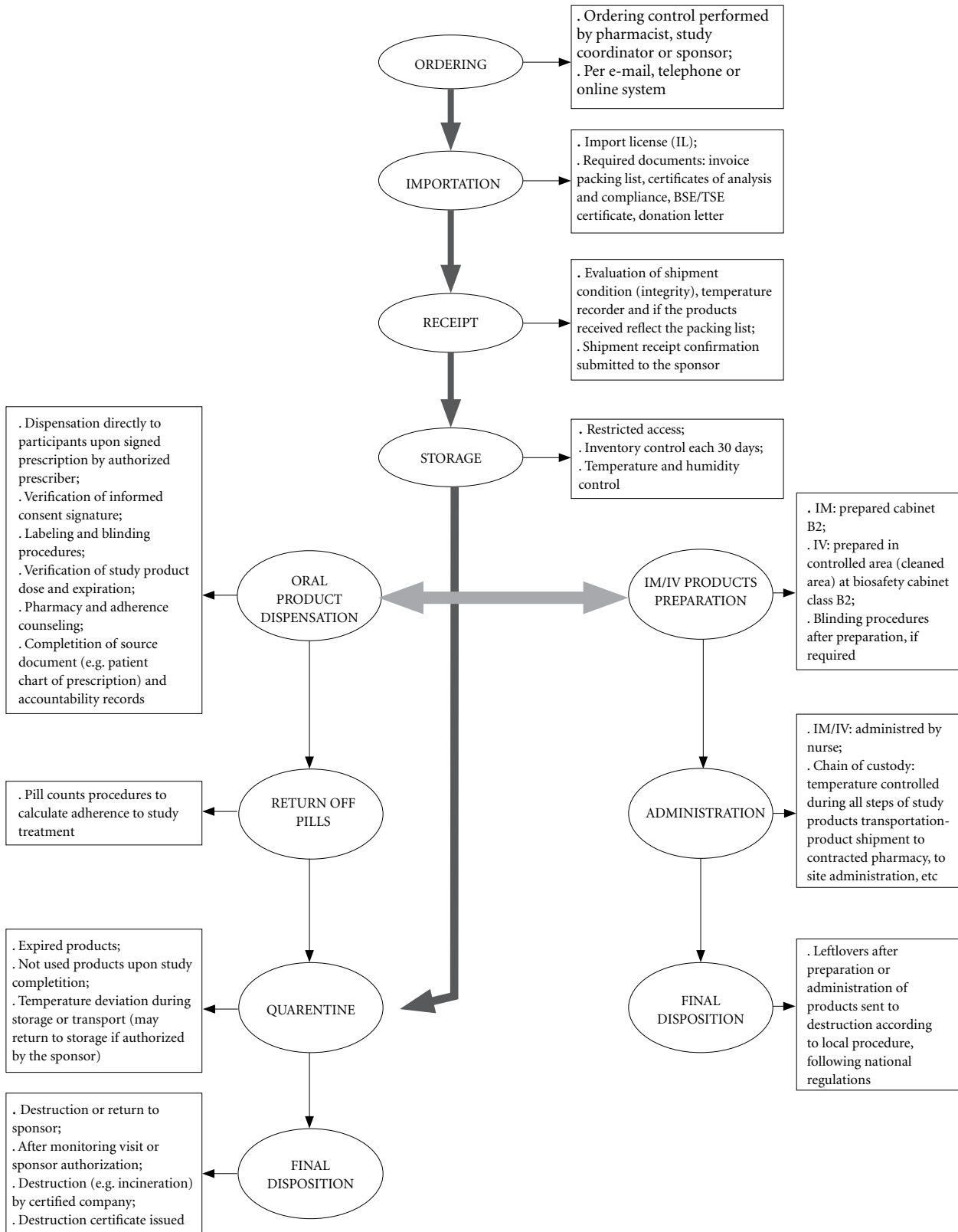


Figure 2. Pharmaceutical services for clinical trials.

Source: Authors.

in the source document (participant's medical records and accounting records).

The participant must sign the informed consent form before any study procedure, including PI dispensing⁴⁸. Thus, the pharmacist must create mechanisms for this verification, such as dispensing by upon a copy of the signed informed consent form. The importance of effective communication between the pharmacist and the clinical site staff is emphasized here, as the participant must consent and sign new versions of the informed consent form approved by the IRB.

The pharmacist can dispense the PI directly to the participant or to a member of the study team through a prescription signed by a prescriber authorized by the principal investigator¹⁴. The pharmacist should check if other drugs dispensed (concomitant drugs) are in accordance with the study protocol to ensure no drug interactions, and verify drug doses.

The pharmaceutical care provided in clinical trials includes adherence counselling. Adherence can be measured by direct (drug concentration) and indirect (self-report, pill count or medication possession rate) measures⁴⁹. The pharmacist must follow the adherence procedures recommended by the study. However, it is recommended that the pill count be performed as a standard of care unless it is not allowed by the protocol, and low adherence should be discussed with the principal investigator. In addition to adherence, the pharmacist should instruct the participant on the IP use or administration to ensure the efficacy and safety of the therapy and the success of the clinical trial^{18,10,47}. The use of telemedicine procedures has had a positive impact on pharmaceutical care in recent clinical trials and should be considered in periods of social distancing^{50,51}.

The pharmacist must keep accounting records of all PIs received, dispensed to participants and returned to CTP. An inventory should be performed at least once a month, and this procedure should be documented in the study specific forms^{5,14,38}.

If preparation of injectable IP is necessary, the pharmacist should use aseptic techniques, following written and validated procedures, according to the laws and the clinical trial manual of procedures (MOP)^{22,27}. The use of checklists to facilitate, standardize procedures and prevent errors is recommended⁵².

All returned and expired IPs should be quarantined until final destination (return to sponsor or destruction), i.e., they should be separated from the active stock and identified. In case of

temperature deviation, the PI should be kept in quarantine and returned to the active stock if the sponsor authorizes it¹⁴.

To prevent the use of IP by others, the pharmacist should instruct the participant to return the unused IP to the CTP. In case of death, relatives, friends or other health professionals may return the IP. IPs returned, expired or not used during the clinical trial must be returned to the sponsor or destroyed by a specialized company⁴⁰. These companies must comply with local environmental legislation¹⁴ and provide documents that prove the destruction⁵³.

Quality indicators

The CTP must have a quality control plan to ensure the GCP and thus ensure the safety of the participant and adequate use of the IPs^{10,14}.

Documentation is an essential part of the quality system and should be easily available³³. The management activities of the CTP should be defined in its organization chart³⁰, and all documentation must be safely stored and accessible only to the pharmacy team, principal investigator, monitors, auditors and inspectors of regulatory agencies¹⁴. The documents should be updated periodically and retained for up to two years after the last approval of regulatory agencies or at least two years since the formal discontinuation of the IP clinical development³⁸. Physical documents should not be erased, and any changes should be made according to the acronym ALCOA-C (attributable, responsible for data entry easily identified; legible, data without erasures; contemporaneous, events documented at the time they occurred; original, source document is the first place of information recording; accurate, consistent data; complete), which advocates the quality and integrity of data collected in clinical studies⁵⁴.

The Standard Operating Procedures (SOPs) provides detailed and written instructions to ensure uniformity in the execution of a specific function and are essential documents according to the GCP and Anvisa standards^{4,5,38,55}. The establishment of SOPs for conducting clinical trials is essential to standardize the processes, serving as a basis for training, traceability and quality⁵⁶. The CTP should develop SOPs that describe the general pharmacy procedures (pharmaceutical services) or specific SOPs per study.

Ideally, temperature control should be performed by two different systems: electronic devices for continuous data recording and daily

manual control of the maximum and minimum temperature. Depending on the country, there are different regulatory definitions for “room temperature” and “cold chain.” According to the Brazilian Pharmacopoeia, the temperature conditions are defined as follows: freezer (-20°C to 0°C), refrigerator (2°C to 8°C) and room temperature (15°C to 30°C).⁵⁷ Regardless of the definition, the storage area must follow the temperature conditions determined for each IP.

The CTP must be equipped with a remote access alarm system to detect temperatures outside the allowed range. This system allows monitoring when the pharmacy is closed, alerting to cases of power failure or equipment malfunction¹⁴.

The humidity control should follow the same periodicity as the temperature control. According to Brazilian standards, the humidity of a storage room should be maintained between 40% and 65%. The maximum operation value should be 65%, with the exception of access areas that may operate up to 70%⁵⁸.

The CTP may be inspected by regulatory agencies, in addition to monitoring and audits promoted by the sponsor^{2,55}. Nonconforming findings should be addressed and corrective actions taken³⁸. Due to the COVID-19 pandemic, Anvisa adopted remote inspection mechanisms, replacing face-to-face sanitary inspections for the purpose of GCP compliance⁵⁹.

Discussion

In this scope review, we summarized guidelines for the organization, operation and evaluation of an CTP in Brazil. Few national documents referring to CTPs were found, indicating a gap in this area of knowledge. However, documents referring to other areas of pharmacy, especially Anvisa laws and regulations and the international regulations, enabled us to propose these guidelines that, to the best of our knowledge, are novel and may serve as reference for clinical trial research sites in Brazil. In addition, the systematization of the results using the Ishikawa method was innovative and identified critical points for CTPs.

In Brazil, the guidelines and regulatory standards for clinical trials, established by the National Commission of Ethics in Research (CONEP: Comissão Nacional de Ética em Pesquisa) and Anvisa, are based on the main international documents on research involving human subjects, such as the Nuremberg Code, the Declaration of Human Rights and the Declaration of Helsinki

(in all its versions), and the International Covenant on Civil and Political Rights of the United Nations (UN), which was approved by the Brazilian National Congress in 1992⁴⁸. It is also noteworthy that Brazil is a signatory of the Document of the Americas of the Pan American Health Organization (PAHO), and therefore Brazilian clinical research sites that participate in international multicentre studies must follow the guidelines of the GCP of the ICH⁵.

For the infrastructure and material resources, 11 documents were selected to summarize the requirements for CTP. The infrastructure and material resources of an CTP must meet the specificities of the clinical trials conducted. Many clinical research sites in Brazil are located in public institutions, where there are often budgetary and physical space restrictions, and CTPs must provide sufficient space for receiving, storing and dispensing IPs. More complex studies in which IP is an injectable drug or vaccine require extensive investment in the purchase and maintenance of equipment, in addition to qualified human resources. In these cases, the cost-benefit of outsourcing these services by specialized pharmacies that adhere to the GCP should be considered. Computerized remote access systems, such as file sharing platforms and temperature control by online applications, in addition to facilitating the work of the pharmacist, have become increasingly essential in the context of the COVID-19 pandemic.

Regarding human resources, 12 documents were considered relevant. In an CTP, the pharmacist is the team lead, according to the CFF¹². More broadly, the pharmacist plays a key role in clinical trials, collaborating directly in pharmaceutical services, which includes ensuring the processes of managing ordering, storage and dispensing of IPs, and ensuring pharmaceutical care, adherence to IP and the safety of participants. However, there is no national standard that clearly establishes the pharmacist's obligation to manage IP. The Document of the Americas includes the pharmacist as one of the professionals responsible for this procedure, which can be delegated to another health professional by the principal investigator^{5,38}. In some clinical research sites, IP management is not performed by the pharmacist but by other professionals responsible for coordinating the study, such as nurses and biologists or the principal investigator himself/herself. It is justified that, like the dispensaries, the sites use IP exclusively for investigational use. As IPs are dispensed on prescription to research partici-

pants with no commercial or outpatient purpose, there would be no obligation for the assistance of a pharmacist. In clinical trials conducted by the National Institutes of Health (NIH), the presence of a pharmacist is mandatory, and we recommend this should be followed in Brazil.

The IP is central to a clinical trial, especially in studies for the purpose of registration, and the pharmacist should have knowledge about the IP's characteristics from previous studies, such as dose, stability, adverse events and drug interactions. This allows planning regarding the storage area, temperature and humidity control, preparation and dispensing of the product. Only five documents included in this review addressed these issues. This may reflect the consolidation of knowledge in the pharmaceutical field, which includes the IP quality assurance throughout its useful life, from manufacturing in laboratories to its use by clinical trial participants. In addition, each IP has particularities that often cannot be generalized into guidelines, and it is necessary to follow the provisions of the study protocol, the study protocol or the manufacturer's package insert.

Pharmaceutical service in clinical trials is a key point in the functioning of the CTP, being addressed in half of the selected publications ($n = 25$). All procedures related to IP management, from ordering to the final disposition, have as their main objective the assurance of the participants' safety and confidentiality, considering the main ethical milestones in human research, such as the Nuremberg Code, the Declaration of Helsinki and the Belmont Report.⁴⁸ The importance of reliable data collection is also emphasized, as the results of clinical trials will serve as subsidies for the registration of a new drug or change of ex-

isting registration. In this context, errors in the IP preparation and dispensation or low adherence due to inadequate pharmaceutical counselling can have an impact the effectiveness and safety of the study.

The CTP's quality assurance is essential for the functioning and credibility of a clinical research site. Because it is one of the most critical sectors, the CTP is periodically monitored, audited and inspected. It is essential that periodic quality control procedures be performed, including the development of quality indicators that prevent errors, ensure the IP quality, following GCP, ethical standards, and study protocols. For this item, 14 publications were selected, mostly national guidelines and regulations.

This study has several limitations. The information systematized here was obtained by extensive search in 12 databases, in addition to websites of national and international regulatory or public health agencies. However, few documents referring to CTP were found, indicating a gap in this area of knowledge. The inclusion of documents related to other areas of pharmacy and international regulations allowed us to propose these guidelines. This study was based only on documents found in the literature, and research clinical sites were not consulted regarding the CTP's internal operational protocols and procedures.

Our results summarize information for the functioning, organization and evaluation of CTP in Brazil and corroborate the need for the inclusion of the pharmacist in the pharmaceutical services in the context of clinical trials. In addition, these results may assist in the creation of SOPs for the operation of the CTP and instruments that facilitate quality control and preparation for monitoring, audits and inspections.

Collaborations

VRT Ribeiro, LMS Marins and TS Torres were responsible for the study design, search and selection of documents. VRT Ribeiro, LMS Marins, TS Torres, RPN Silva, RB Araujo, GG Costa, ACV Vieira and DS Geraldo performed the data extraction. VRT Ribeiro, LMS Marins, L Guaraldo and TS Torres draft the initial version of the manuscript. All authors reviewed and approved the final manuscript.

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