BASIC GUIDE ON RESEARCHES WITH HUMAN SUBJECTS

Updated according to Law No. 14,874/2024

What is **Human Research?**

Research that directly or indirectly involves the management of data, information or biological materials. It can be divided into three categories:

Scientific, technological or innovation research: Study that directly interacts with human beings (individually or collectively) without the purpose of regularizing or commercializing the product under researcht

Clinical research: A set of scientific procedures developed systematically with the aim of:

- Evaluating the action, safety, and efficacy of drugs, products, techniques, procedures, medical devices, or health care for preventive, diagnostic, or therapeutic purposes.
- Verifying the distribution of risk factors, diseases or conditions in the population.
- Assessing the effects of factors or states on health.

Clinical trial: clinical investigation trial with one or more human subjects, performed to evaluate the safety, clinical performance, or efficacy of a medical device, investigational drug, or advanced therapy.

Key Steps

PRECLINICAL
Manipulation of cells and/or animals to verify the feasibility of a substance or product as a new therapy, understand its mechanisms of action, and assess its potential for toxicity.

CLINIC
Carried out with human beings, it aims to progressively test the safety and efficacy of the investigational product.

The clinical stage is divided into 3 phases:

Phase 1

It evaluates the safety of therapy on a preliminary basis.

Group of 20 to 100 participants.

Phase 2

It analyzes the efficacy and possible adverse effects of the molecule, substance, or product.

Group of 100 to 300 participants with a certain disease and/or condition.

Phase 3

It evaluates the therapeutic advantage, establishes indications, contraindications, dosages and routes of administration, among others.

A group of 800 or more patients with a particular disease and/or condition.

In the case of products subject to pre-marketing authorization, the results of the research can be used to scientifically support the submission of applications to health agencies in each country (for example, the National Health Surveillance Agency – Anvisa). Such evidence can also contribute to health technology assessment (HTA) process, which also considers aspects of cost-effectiveness, necessity, and financial/budgetary striking, impact of a health system. In Brazil, incorporation can occur in the Unified Health System (SUS) or in the list of procedures of mandatory coverage by health plans established by the National Supplementary Health Agency (ANS).

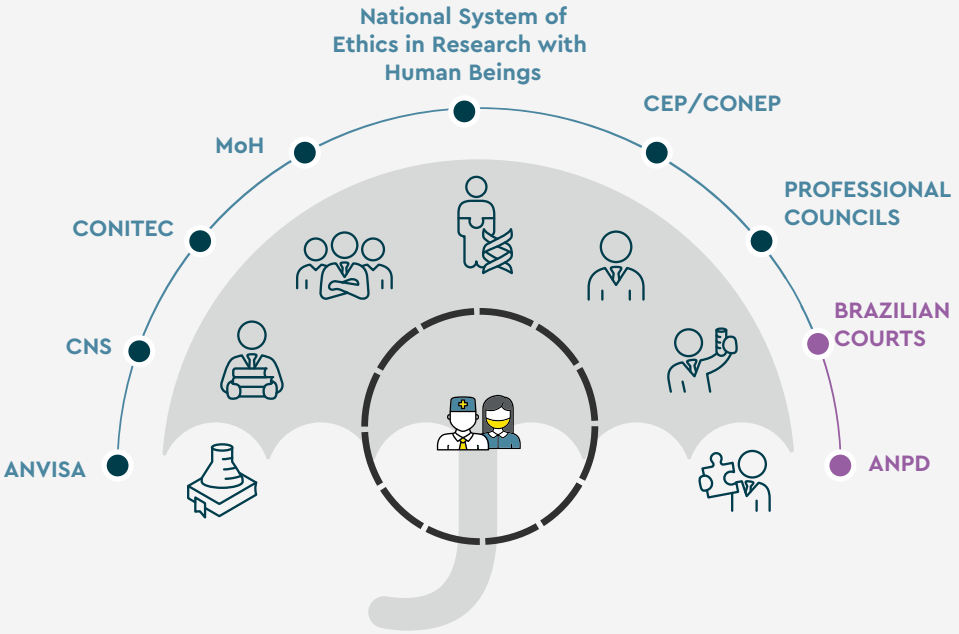
It is also possible to carry out a phase 4 of the research, already in the commercialization phase, when the product is already being used by hundreds or thousands of patients. The purpose is to collect and analyze Real World Data (RWD), develop Real World Evidence (RWE), and monitor pharmacovigilance actions, and search for new indications.

ANVISA

RWD and RWE expected regulations by Anvisa:
The agency has already published a guideline on real-life evidence and has an active working group to discuss the matter.

Key ***Players***

Research activities involve several stakeholders, which are subject to the regulation of authorities such as Anvisa,
the National Health Council (CNS), CONEP – which is now party of the Ministry of Health (MoH), Institutional Review Boards – IRBs (Comitês de Ética em Pesquisa – CEPs) and professional councils, in addition to the Brazilian Courts and ANPD.



National System of Ethics in Research with Human Participants (SNEP)

Institution: Entity to which the principal investigator is associated.

Research Center: Location where research-related activities are carried out.

Clinical Research Organization (CRO): Local entity contracted by the sponsor to accomplish part or all of the sponsor's responsibilities.

Participant: The individual who agrees to participate in the research in an informed, free, and voluntary way.

Sponsor: The individual or entity that is responsible for the research through financing, infrastructure, human resources, or institutional support.

Researcher or Investigator: Member responsible for conducting the research or being co-responsible for the integrity, and well-being of the research participants.

Researcher-coordinator or Investigator-coordinator: Member responsible for coordinating the research, the researchers from the different participating centers, and being co-responsible for the integrity and well-being of the research participants.

Product journey - from the research to the patient

I. Submission of research protocol (if conducted in Brazil)

II. Ethical approval of the research by the SNEP. — **30 working days**

III. Research approval by Anvisa (if applicable). — **~ 90 days**

IV. Product pre-rmarket authorization by Anvisa — **~ 365 days**

V. Drug price definition by the Medicines Market Regulation Chamber (CMED) (only for medicines and advanced therapies). — **~ 90 days**

VI. Product go-to-market

High-priority products may have different deadlines and procedures (e.g., for neglected or emergent diseases, serious or debilitating conditions, public health emergency).

KEY POINTS
LAW Nº 14.874/2024

In practical terms, Brazil already has a structured clinical research system, which includes the National Health Council (CNS), the National Research Ethics Commission (CONEP), and Institutional Review Boards – IRBs (Comitês de Ética em Pesquisa – CEPs) established in hospitals, survey centers, and academic institutions.

Law No. 14,874/2024 (in force as of August 2024), provides a more robust legal framework for the regulation and oversight of public and private institutions that carry out research with human participants in Brazil.

Ethical Approval

In the case of research with human participants, the research protocol will be subject to prior ethical approval by an Institutional Review Boards – IRB (Comitês de Ética em Pesquisa – CEPs), putting an end to the double review performed by Conep.

As in other countries, the study will continue to be previously evaluated by the IRB considering ethical principles, such as human dignity; risk-benefit relationship (individual and/or collective); voluntary participation; prevention of foreseeable harm; among others.

Post-Trial Access (PTA)

Before initiation of the clinical trial, the sponsor and the researcher must submit a post-trial access plan to the IRB, which should contain details on whether or not the investigated product should be offered to the research participant free of charge at the end of the study.

Said obligation will rest with the sponsor, provided that the product or therapy is the best option available and benefits the participant's clinical condition.

Differently from current ethical regulations, Law No. 14,874/2024 provides that PTA **can be interrupted** in the following situations:

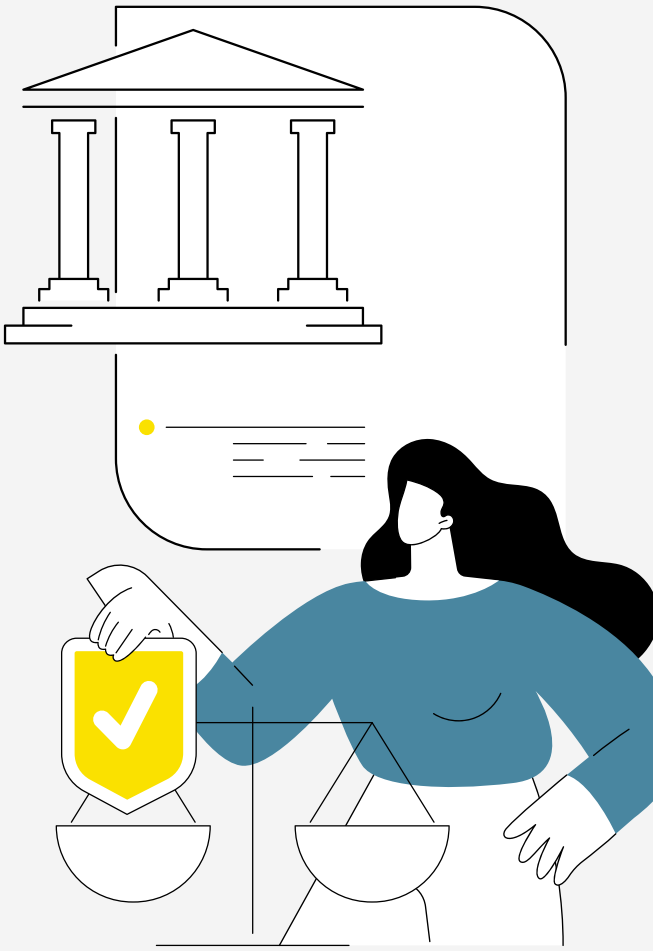
- Decision of the research participant or legal representative.
- Cure of the disease or introduction of satisfactory therapeutic alternative.
- No benefit to the human participant from continued use of the investigational drug, considering the benefit-risk outside the clinical trial setting or knowledge about new evidence on risks related to the safety profile of the product.
- An adverse reaction that precludes the use of the investigational drug.
- When obtaining or manufacturing of the investigational drug is impossible due to technical or safety reasons – provided that the sponsor offers an equivalent or superior therapeutic alternative available on the market.
- Availability of the experimental drug in the SUS.

- The provision dealing with the PTA interruption after 5 years counted from the availability of the experimental drug in Brazil was vetoed by the Brazilian President.

Open items subject to further regulations

Additional points that will be subject to further regulations by the SNEP include:

- Publicity of research protocols taking place in Brazil.
- Definition of operational standards and best practices.
- Rules for biobanks and biorepositories.
- Mandatory clauses under clinical research agreements.
- Definition of special groups.
- Procedures for suspension or termination of IRBs.
- Rules regarding monitoring of clinical studies.
- Procedures for execution of the ethical analysis by the IRBs.
- Creation of a national registry of volunteers in bioequivalence studies.
- Design and implementation requirements for PTAs or continuation of experimental treatment.
- Specificities of research in the humanities and social sciences.



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