Antibiotice

Clinical Trials Policy

2024

Contents

1. Scope

Clinical trials constitutes a fundamental component of research and innovation activities of Antibiotice SA, significantly contributing to protecting and improving public health by rigorously evaluating the safety and efficacy of new medicines. These trials collect data and evidence essential for making decisions about the approval and widespread use of medicines.

A medicine goes through a complex development process which includes four distinct phases of clinical trials, each with specific objectives:

- **Phase I trials**: Conducted on a small group of participants, these trials assess safety, identify possible adverse effects, and establish the optimal route of administration. They generally last several months.
- **Phase II trials:** These involve 100 - 300 participants and aim to collect data on safety and efficacy. The trials usually last several years.
- **Phase III trials:** These are estensive trials, involving thousands of participants, and compare the investigational medicine with a placebo or an existing treatment to determine whether it can be authorized. The authorization decision is based on the data collected.
- **Phase IV trials:** Conducted after the medicine is authorized, these trials complete safety data and evaluate the benefits of long-term use.

Bioequivalence clinical trials are a distinct category. They determine the equivalence between a generic and an innovator product, assessing bioavailability and safety of administration. They involve the participation of healthy subjects.

In order to conduct the phase I and biopequivalence clinical trials, Antibiotice SA established its own Clinical Trials Center in 2006, authorized by the National Agency for Medicines and Medical Devices of Romania (NAMMDR). The authorization is renewed every three years, following verification of compliance with the requirements related to location, facilities and personnel.

Animal testing is not involved in the process of obtaining the authorization to place Antibiotice products in the market. Generic products are authorized exclusively on the basis of clinical trials conducted on healthy human subjects, in compliance with the good clinical practice.

2. Regulations and ethical principles in clinical trials

The Clinical Trials Center of Antibiotice S.A. is authorized for conducting phase I and bioequivalence clinical trials in accordance with the national legislation in force:

• **DECISION No. 2/22.04.2014** issued by NAMMDR on approving the regulations for authorizing the units that may conduct clinical trials in the field of medicines for human use;

• **DECISION No. 24/03.07.2015** which approves the amendments to the annex of the Scientific Council Decision (SCD) No. 2/22.04.2014 on the regulations for authorizing the units that may conduct clinical trials in the field of medicinal products for human use.

• **ORDER No. 3390/08.11.2022,** on approving the Methodological Norms for applying the provisions of art. 3 para. (10), art. 4 para. (3) and art. 6 para. (2) of Government Emergency Ordinance no. 29/2022 on establishing the institutional framework and the necessary measures for implementing the Regulation (EU) no. 536/2014 of the European Parliament and of the Council of April 16, 2014 regarding the interventional clinical trials with medicinal products for human use and the repeal of the Directive 2001/20/EC, as well as for amending certain regulatory acts in the field of health*)

Clinical trials are conducted according to the European and international legislation and standards:

• **Regulation (EU) No. 536/2014** of the European Parliament and of the Council;

• ICH E6 Good Clinical Practice (GCP) along with other relevant requirements specific to the relevant National Medicines Agencies.

The ethical principles applicable to clinical trials conducted within the Clinical Trials Center are:

• **ICH Harmonized Guideline on Good Clinical Practice (Guideline for GCP),** adopted in June 2017;

• **The Declaration of Helsinki** of the World Medical Association on the ethical principles for medical research involving human subjects (Helsinki 1964, last amended in Brazil, 2013).

These regulations and principles ensures compliance with ethical and quality standards in all stages of clinical trials conducted by Antibiotice SA.

3. Recruitment of subjects and the database

The bioequivalence clinical trials conducted by Antibiotice SA involves the participation of healthy subjects, recruited mainly from the young population. The company periodically organizes information campaigns in the local and academic community, through specialized medical personnel (doctors employed in the company, collaborating doctors, family doctors). These campaigns:

- provide detailed information about the clinical trials conducted;
- presents the advantages and risks of participating in such trials;
- answer questions asked by potential participants.

The importance of participating in clinical trials is emphasized. They contribute to:

- developing medical research and discovering innovative treatments;
- authorizing affordable medicines with similar therapeutic benefits.

The content of the information materials is evaluated in advance by the National Bioethics Committee for Medicinal Products and Medical Devices which certifies their accuracy, completeness and objectivity.

Access to Clinical Trials

Participation in the trials is open and non-discriminatory to anyone who meets the specific criteria. Individuals interested in participating may:

- contact the medical staff of the Clinical Trials Center;
- fill out a registration form available on the company's website https://www.antibiotice.ro/dezvoltare/centrul-de-studii-clinice/selectare-voluntari/.

By completing the form, participants agree to their personal data being entered into a secure database (eMed a+ application). This database:

- automatically generates a unique code for each participant;
- use this unique code to anonymize all the records (case report forms, informed consent forms, medical test reports, EKGs, training minutes, etc.).

Protecting Subjects

The Clinical Trials Center does not enroll vulnerable subjects. Strict measures are implemented to verify the criteria that define vulnerability status, according to the legislation. Vulnerable subjects are defined as individuals whose willingness to participate in a clinical trial may be influenced by:

- benefits associated with participation;
- pressure or retaliation from hierarchical superiors, in case of refusal to participate.

These measures guarantee the protection of participants' rights and compliance with ethical principles at all stages of clinical trials.

4. Selection of subjects for participation in a Bioequivalence Clinical Trial

Before a clinical trial begins, a detailed research plan is developed to ensure the protection of subjects throughout the trial. This document, called the Clinical Trial Protocol, includes:

- objectives and duration of the trial;
- working methodology;
- subject inclusion and exclusion criteria;
- legislative framework applicable to the trial.

The protocol is signed by the investigators and by the Antibiotice representatives, assuming respect for the rights of participants according to the ethical principles stipulated in the Declaration of Helsinki. The document is subject to the analysis made by regulatory authorities in Romania, and the study can only begin after obtaining the necessary authorizations from:

- **National Agency For Medicines and Medicale Devices of Romania (NAMMDR);**
- **National Bioethics Committee for Medicinal Products and Medical Devices (CNBMDM).**

Protection Measures for Subjects

To cover any damages associated with the subjects' participation, Antibiotice SA takes out a **professional liability insurance.**

Information and Informed Consent:

- Inclusion of subjects in the trial is conditional on obtaining the informed consent.
- The informed consent form contains detailed information about:
  - stages of conducting the study;
  - inclusion and exclusion criteria;
  - restrictions associated with participation;
  - possible adverse reactions;
  - financial benefits;
  - company policy on personal data protection.

The informed consent form is approved by the **National Bioethics Committee for Medicinal Products and Medical Devices** and includes:

- contact details of the committee for additional information or complaints;
- a clear statement informing subjects that they can withdraw at any time, without repercussions and without being required to justify the decision.

Subject's information process

The informed consent is obtained in the investigating physician's office, only after:

- the regulatory authorities (NAMMDR and CNBMDM) issued favorable opinions.
- Information sessions are organized individually, to ensure the confidentiality of the subjects.

Role of the clinical investigator:

- allows sufficient time for the subject to analyze the information about the trial;
- answers all the subject's questions;
- provides concise, clear and easy-to-understand explanations for non-specialists;
- verifies whether the subject has reviewed and understands the information provided;
- requests the subject's signature on each page of the informed consent form;
- hands the subject a copy of the form and requests a written confirmation of receipt.

These measures are implemented to guarantee an informed, voluntary and unconstrained participation, thus ensuring the protection of subjects' rights in clinical trials.

5. Participation in Clinical Trials

Participation of subjects in the clinical trials is strictly confidential, all personal data being anonymized through the use of unique identification codes automatically generated by the subject database application.

During participation in the trial, the subjects are constantly monitored by a complex medical team, consisting of:

- medical staff with medical practice license;
- emergency medical physicians;
- primary physicians;
- nurses.

The medical team collects exclusively the data specified in the Clinical Study Protocol, according to the detailed program included therein.

6. Post-Trial Follow-up

To assess the impact of participation in the trial on the subjects, a battery of medical tests is performed at the end of the trial to identify any changes in health status associated with the administration of the medicines or medical procedures involved.

All medical tests performed during the selection and post-study follow-up stages are performed by RENAR-accredited laboratories.

If changes in the analyzed parameters are identified, the medical team may:

- request additional analyses;
- refer the subject to the family physicians or a specialist for detailed investigations.

7. Incentives for trial participants

Participation in bioequivalence clinical trials does not imply direct therapeutic benefits for the subjects. They are rewarded depending on the complexity of the trial, according to an amount approved by the **National Bioethics Committee for Medicinal Products and Medical Devices.**

- The amount and method of payment are approved to prevent any form of undue influence or coercion on participants.
- Payments are proportional to the subject's participation in the trial and are not conditional on its completion.

Details of the amount, payment methods, and payment schedule are included in the informed consent form. As an additional benefit, participants receive clinical examinations (including EKG) and laboratory tests, performed before and at the completion of the trial.

8. Personal data protection

Antibiotice SA complies with the legislation on the personal data protection. The informed consent form includes the following information:

- data collection method;
- data processing and archiving;
- the company's confidentiality policies.

9. Responsibilities and Quality Assurance

The Clinical Trials Center has an internal quality assurance unit made up of trained monitors and auditors, who ensure that clinical trials comply with:

- European harmonized legislation (ICH);
- Integrated management system;
- Good Clinical Practice (GCP) and Good Laboratory Practice (GLP) Guidelines;
- Declaration of Helsinki.

The specialists of Clinical Trials Center prepared a set of **standard operating procedures (SOP)**, periodically updated, in order to:

- increase the quality and efficiency;
- reduce the costs;
- improve the capacity of reaction and correcting any issues.

The **clinical monitor**, a specialist physician with experience in the field of clinical trials, plays a central role, ensuring:

- communication with the sponsor's site;
- coordination with the Project Manager, Data Management and Pharmacovigilance Department;
- prompt resolution of issues related to the conduct of clinical trials within Antibiotice SA.

10. Policy on the Clinical Trials conducted by Third Parties

Antibiotice SA collaborates with third-party partners to conduct clinical trials, ensuring that these collaborations comply with the highest ethical, legal and quality standards. This policy defines the general framework and guidelines regarding the collaboration with the third parties for developing clinical trials.

All the clinical trials conducted by third parties are aligned with relevant legislation and regulations in Romania and the European Union, including:

- Law no. 95/2006 on healthcare reform;
- Order of the Ministry of Health no. 904/2006;
- Order of the Ministry of Health no. 903/2006;
- Decisions of the Scientific Council of NAMMDR no.39/2006 and no. 2/2014;
- Government Decision no. 734/2010;
- Declaration of Helsinki;
- Good Clinical Practice (GCP) Guidelines.

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Third-party partners involved in clinical trials are responsible for:

- implementing safe and compliant practices at all locations where trial activities are carried out;
- maintaining and updating the authorizations necessary to carry out the activities;
- adopting appropriate measures to prevent risks and minimize the impact on health, safety and environment.

Antibiotice SA promotes an approach based on transparency and effective collaboration in partnerships with third parties. The guidelines include:

- alignment with the objectives established for each clinical trial;
- efficient and prompt communication regarding the conduct of activities;
- compliance with the Antibiotice's policies and ensuring the quality of services.

Professional ethics and Integrity

All activities related to clinical trials must be carried out in compliance with the principles of professional ethics and integrity. These activities of third-party partners are essential to : avoid the conflicts of interest; comply with anti-corruption legislation, maintain a safe and regulatory working environment.

Performance Monitoring and Evaluation - Antibiotice SA is committed to constantly monitoring collaborations with third-party partners to ensure: compliance with quality standards, compliance with contractual requirements.

11. Reporting violations

Any violation of this policy may be reported to contact.cem@antibiotice.ro or by following the instructions in the Procedure for receiving, examining and resolving reports on violations of the law, drawn up in accordance with the provisions of Law No. 361/2022, on the protection of whistleblowers of public interest, guaranteeing the confidentiality and protection of whistleblowers - https://www.antibiotice.ro/wp-content/uploads/2023/03/Procedura-raportari-avertizori-in-interes-public-.pdf.

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