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REVIEW

Ethics Committee Application Procedures in Clinical Trials

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Abstract

In Türkiye, legal regulations regarding clinical trials have been prepared in accordance with international standards and are updated when necessary. It is sometimes delayed for investigators to follow current regulations in addition to their routine work. With this purpose, this article aims to provide a brief overview of the current legislation and ethical committee procedures, especially as a guide for researchers and parties involved in clinical research.

Keywords: Clinical Trial; Ethics Committee; Medical Device; Pharmaceutical.

In Türkiye, legislation related to clinical research is being updated and conducted in accordance with international standards. Ethical principles in clinical research are a primary concern, and the rules that researchers must follow are specified in various documents. With the updating and detailing of the legislation, researchers can struggle to keep up with the rules they need to follow. This article, written to guide researchers who want to conduct clinical research, explains the legislation in our country, the structures and processes of ethical committees related to clinical research.

In the Contemporary Turkish Dictionary of the Turkish Language Association, science, defined as "a systematic knowledge or general validity and certainty characteristics showing methodical and systematic knowledge or a process of acquiring knowledge and methodical research, starting from the desire to know a certain subject and aimed at a certain purpose, based on methods and reality that choose a part of the universe or events as a subject, and trying to derive conclusions," fundamentally includes verification studies based on basic ethical principles[1].

It is necessary to prove and verify the safe and effective use of potential drugs, medical devices, treatment, or diagnostic methods on humans through studies conducted in scientific and ethical standards.

Clinical research or study describes research conducted with humans where researchers interact directly with individuals. Clinical research is of great importance as it directly affects human health. Legal regulations regarding clinical research to be conducted on humans in Türkiye are made by the Ministry of Health and its affiliated institutions.

Good Clinical Practices not only establish the scientific and ethical quality standards but also provide public assurance that patient safety and welfare are protected. In clinical research, the rights, safety, and well-being of volunteers (participants) are the most important points that need to be considered. These cannot be superseded by the interests of science and society[2].

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The structure, working procedures and principles, and standardization of ethical committees, formed to evaluate all aspects of research scientifically and ethically to enable clinical research to be conducted within the framework of scientific and basic ethical principles, and especially to protect the rights, safety, and well-being of healthy or ill volunteers participating in these studies, are of great significance. However, despite all activities and regulations since 1993, it is observed that this standardization has not yet been achieved in practice, and there are occasional problems and discussions between ethical committees and the decisions they make.

In Türkiye, legal regulations related to clinical research, initially focused on treatments, can be traced back to the "Law on the Practice of Medicine and its Branches" published in 1928, specifically articles 70 and 71, which stipulate that "physicians, dentists, and dental practitioners must obtain consent from the patient, or if the patient is a minor or legally incompetent, from the guardian or conservator before any kind of surgery." This implies that obtaining consent from participants in clinical research was considered even then[3]. Our Constitution, in Article 17, emphasizes the importance of obtaining consent in scientific research with the provision, "Everyone has the right to life, and to protect and develop their material and spiritual existence. Apart from medical necessities and cases prescribed by law, the integrity of a person's body cannot be violated; they cannot be subjected to scientific and medical experiments without their consent."[4] Numerous regulations have been made regarding clinical research. Although not all, a significant portion of these are provided in Table 1. Access to these regulations is possible through the Official Gazette's website (https://www.resmigazete.gov.tr/) or the websites of relevant health authorities.

In Türkiye, while there are existing regulations for interventional studies, there is no specific, comprehensive, and centralized legal regulation for non-interventional studies. Many universities and training-research hospitals try to manage and evaluate non-interventional studies through guidelines and regulations issued by their higher institutions as a result of decisions made within their own structures. However, the absence of any standard published by a higher authority on this subject often poses problems in evaluating such studies and even in researchers making applications within the correct and basic ethical framework.

This document aims to guide researchers in the process of applying to existing ethical committees and even to guide members serving on ethical committees in their evaluations from a correct, ethical, and scientific perspective.

In Türkiye, in addition to the ethical committees formed as a result of legal regulations, it is also possible to encounter ethical committee structures with different names that unfortunately overlap in terms of their scope of work and even make decisions and evaluations for research that falls outside the scope of their working procedures and principles.

We can list the current types of ethical committees in Türkiye as follows:

1. Clinical Research Ethics Committee: These are ethics committees formed in accordance with the " Regulation on Clinical Research on Medicinal Products of Human Use" published in the Offical Gazette No.32203 on May 27, 2023.
2. Bioavailability/Bioequivalence Studies Ethics Committee: These committees are also established under the same regulation as the Clinical Research Ethics Committee, published in the Official Gazette No.32203 on May 27, 2023.
3. Cosmetic Clinical Research Ethics Committee: Formed in accordance with the "Regulation on Efficacy and Safety Studies and Clinical Research of Cosmetic Products or Raw Materials" published in the Official Gazette No. 29481 on September 20, 2015.
4. Traditional and Complementary Medicine (GETAT) Clinical Research Ethics Committee: Established under the "Regulation on Clinical Research of Traditional and Complementary Medicine Practices" published in the Official Gazette No. 30709 on March 9, 2019.
5. Other Ethics Committees: These are ethics committees operating under various names within universities (established by Senate decision) or Training-Research Hospitals (established with the approval of the Provincial Health Directorate or Chief Physician). Examples include Non-Interventional Studies Ethics Committee, Non-Interventional Research Ethics Committee, Non-Medicinal Studies Ethics Committee, Scientific Studies Ethics Committee, etc. However, to use clinical research terminology correctly and avoid overlaps in the structures or duties of ethics committees regulated by legislations, it is considered and recommended that the name of such planned ethics committees should be "Non-Interventional Studies Ethics Committee."

To understand which types of studies or research the ethical committees mentioned above will evaluate, it is best to look at the scope and exclusions of the legislation on

Table 1. Basic Legal Regulations Related to Clinical Trials

Category	Details
Law, International Treaty, Bylaw	• Constitution (Article 17)
	• Convention on Human Rights and Biomedicine
	• Law on the Practice of Medicine and Branches of Art (14/04/1928 - No. 863: Article 70)
	• Basic Law on Health Services, Supplementary Article 10
	• Turkish Penal Code (2004 / Amend: 2005 - No. 5237: Article 90)
	• Personal Data Protection Law (No. 6698) (07/04/2016 - Issue 29677)
	• Medical Deontology Regulation (19/02/1960 - No. 10436: Articles 10 and 11)
Regulation	• Regulation on Clinical Research on Medicinal Products of Human Use
	• Medical Device Clinical Trials Regulation
	• Medical Device Regulation
	• Regulation on Clinical Trials of Traditional and Complementary Medicine Practices (09/03/2019 -30709)
	• Regulation on Personal Health Data (21/09/2019-30808)
	• Regulation on Efficacy and Safety Studies and Clinical Trials of Cosmetic Products and Raw Materials
Guidelines	• Good Clinical Practice Guide
	• Observational Studies Guide for Medicinal Products of Human Use
	• Guide on the Application Method to the Ethics Committees for Clinical Research and Bioavailability-Bioequivalence Studies
	• Guide on Application Method to the Turkish Medicines and Medical Devices Agency Directorate of Clinical Trials in Clinical Research
	• Standard Operating Procedure Principles of the Ethics Committees for Clinical Research and Bioavailability-Bioequivalence Studies
	• Guide on Ethical Approaches in Clinical Research Conducted in Pediatric Population
	• Guideline on the Principles and Practices for Good Clinical Practices of Advanced Therapy Products
	• Biological Material Management in Clinical Research Guide
	• Insurance Coverage in Clinical Research Guide
	• Safety Notifications in Clinical Research Guide
	• Development Safety Update Report in Clinical Research Guide
	• Clinical Research Investigator Meeting Application Guide
	• Training Programming and Evaluation Principles in Clinical Research Guide
	• Central Organization Management Principles in Clinical Research Guide
	• Independent Data Monitoring Committees Guide
	• Bioethics Committee Structure and Operating Procedures and Principles Guide
	• Clinical Research Advisory Board Standard Operating Procedure Principles
	• Storage and Distribution of Research Products in Clinical Research Guide
	• Archiving Principles in Clinical Research Guide
	• Guide on Efficacy and Safety Studies of Cosmetic Products or Raw Materials to be Conducted on Volunteers
Guidance Documents	• Declaration of Helsinki
	• ISO 14155-1/2 Clinical Investigation of Medical Devices for Human Subjects
	• EN13612 Performance Evaluation of In vitro Diagnostic Medical Devices
	• Med-dev Documents
	• [http://ec.europa.eu/health/medical devices/documents/guidelines/index_en.htm] (http://ec.europa.eu/health/medical devices/documents/guidelines/index_en.htm)

which these committees are based. This approach ensures that research applications are reviewed according to certain standards, independently of institutional/personal opinions, and within scientific and ethical frameworks, to determine whether they are planned appropriately in accordance with the research design and intended objectives. The ethical committee can then make decisions within the scope of their authority.

For example, the scope of the " Regulation on Clinical Research on Medicinal Products of Human Use" " includes the procedures and principles for clinical research of all medicinal products which is used for human use , whether licensed or permitted, including bioavailability and bioequivalence studies. Therefore, the ethics committees established under this regulation can only evaluate research and studies related to these subjects. However, the "Medical Device Clinical Research Regulation (08.07.2022/31890)" and the "Medical Device Regulation (02.06.2021/31499)", which are formulated in reference to this regulation, also include all medical device clinical research, including observational medical device studies. Consequently, the "Clinical Research Ethics Committee" is also authorized to evaluate these types of studies.

1. Clinical Trials of Drugs and Biological Products

International norms and standards have been developed to enable countries to consistently regulate health products and technologies, ensuring economical access to safe, effective, and high-quality drugs and healthcare products worldwide. Drugs, vaccines, and biological products are still being developed today.

Biological products are used to diagnose, prevent, treat, and improve diseases and medical conditions. This category of products is diverse and usually comprises large, complex molecules. These products can be produced through biotechnology in a living system such as a microorganism, plant cell, or animal cell and are often more difficult to characterize compared to small molecule drugs. There are many types of approved biological products, including therapeutic proteins, monoclonal antibodies, and vaccines.

Under the " Regulation on Clinical Research on Medicinal Products of Human Use ", clinical trials on all medcinal products sucah as drugs, herbal products and biological products which is uzed on human use, including bioavailability and bioequivalence studies, must obtain permission from an ethics committee and the Turkish Medicines and Medical Devices Agency (TİTCK) before being conducted on humans, even if they have been authorized or licensed[5].

According to the principles set forth in the regulation, the Clinical Trials Ethics Committee, established for this purpose, is responsible for scientifically and ethically evaluating research studies, excluding bioavailability-bioequivalence studies. The "Bioavailability-Bioequivalence Studies Ethics Committee", established as a separate entity, is exclusively authorized to scientifically and ethically evaluate only bioavailability-bioequivalence studies.

2. Medical Devices and Clinical Trials

Understanding and interpreting the definition of research products within the scope of an ethics committee is crucial. A medical device, when used in humans, does not achieve its primary function through pharmacological, immunological, or metabolic effects but may be supported by these effects in its functioning. It is manufactured for use, alone or in combination, in the diagnosis, prevention, monitoring, treatment, or alleviation of disease or injury, diagnosis, monitoring, treatment, alleviation of, or compensation for, an injury or handicap, investigation, replacement, or modification of the anatomy or of a physiological process, or control of conception and includes any instrument, apparatus, implement, machine, appliance, implant, reagent for in vitro use, software, material, or other similar or related article, necessary for the medical device to achieve its intended purpose[6].

Therefore, all kinds of research products, such as dialysis machines, endoscopy sets, hospital motorized beds, stents, catheters, pacemakers, prosthetic sockets, should be considered as medical device clinical trials within this definition. However, determining whether a product is a medical device can often be challenging. An algorithm that can be utilized for this purpose is presented in Figure 1.

Clinical trials related to any medical device under investigation can be conducted to assess the safety, effectiveness, or performance of the medical device. Research can be carried out with the approval of the Clinical Trials Ethics Committee and subsequent permission from the Ministry.

Performance evaluation studies can also be conducted to validate the performance claims of in vitro diagnostic medical devices under their expected conditions of use.

Guidelines and documents regarding clinical trials with medical devices are published on the TİTCK webpage, but one of the main points of attention is the presence of the CE mark, which indicates conformity with the European Union. The CE mark, a health and safety mark applied under the "New Approach" framework established by the European Union in 1985, signifies that a product adheres

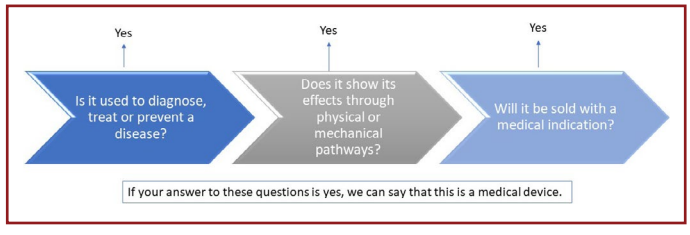

Figure 1. Medical device identification algorithm.

to EU's New Approach Directives and is safe and healthy for humans, animals, and the environment[7,8]. The purpose and validity of the CE certificate must always be checked.

3. Cosmetic Products and Clinical Trials

The definition of a cosmetic product, as published by the Turkish Medicines and Medical Devices Agency in the "Guide to Cosmetic Products and Borderline Products," is as follows: Substances or mixtures prepared to be applied to the external parts of the human body; the epidermis, nails, hairs, scalp, lips, and external genital organs, or to the teeth and oral mucosa, primarily intended to clean, perfume, change their appearance, protect, keep in good condition, or correct body odors[9].

Under cosmetic legislation, products should not be intended to treat or prevent any disease, diagnose, or alter, modify, or regulate a physiological function through pharmacological, immunological, or metabolic effects, nor should they claim or imply that they renew, correct, or change physiological functions, refer to the effect of a medicinal product, or contain health claims.

For example, dandruff shampoos containing corticosteroids, skin lightening products containing hydroquinone, are not considered cosmetic products. Furthermore, substances or mixtures intended to be ingested, inhaled, injected, or implanted into the human body are not evaluated as cosmetic products. For instance, slimming tablets or drinks, preparations marketed with cosmetic claims and under names like nutri/nutraceutical cosmetics, botox applications are not considered within this scope.

For cosmetic product studies, applications must be made according to the "Regulation on the Efficacy and Safety Studies and Clinical Trials of Cosmetic Products or Raw Materials". Approval from the "Cosmetic Clinical Trials Ethics Committee" established under the same regulation and permission from TİTCK are required[10].

Article 10 of the relevant legislation states, "Applications are evaluated by the Agency. Those requiring ethics committee permission are referred to the ethics committee. Studies or research may commence after obtaining the permission of the Agency." This provision contradicts many regulations requiring ethics committee approval for scientific research, and therefore, it is considered more appropriate to obtain ethics committee approval before applying to TİTCK.

4. Traditional and Complementary Medicine (GETAT) and Clinical Trials

The practices of traditional and complementary medicine are determined according to the "Regulation on Traditional and Complementary Medicine Practices" by the Ministry of Health. According to the regulation, research on humans can be conducted to discover or validate the clinical or pharmacological effects of one or more products and/or methods within the field of traditional and complementary medicine, to identify adverse events or reactions, and to investigate their safety and effectiveness. Practices such as acupuncture, apitherapy, phytotherapy, hypnosis, and homeopathy are evaluated within this scope. Research, prioritizing volunteer safety according to the principles of the Regulation, can be conducted in Ministry-affiliated training and research hospitals, university hospitals, or university-affiliated and approved research and development centers designed for conducting clinical research, with suitable personnel, equipment, and laboratory facilities for the healthy conduct, monitoring, and, if necessary, emergency intervention of the study. Approval from an ethics committee and the General Directorate of Health Services is required. Applications for research within this scope should be made to the "Ethics Committee for Clinical Trials of Traditional and Complementary Medicine Practices."[11]

One important aspect to consider in studies on GETAT practices is that if medical devices are used during these practices, permission must also be obtained from the Clinical Trials Ethics Committee and TİTCK.

5. Bioavailability/Bioequivalence Studies

Bioequivalence is defined as the extent to which two pharmaceutical equivalent preparations, when administered at the same molar dose, have similar bioavailabilities and thus, in terms of both efficacy and safety, essentially the same effects, while bioavailability is the rate and extent to which the active ingredient or its therapeutic moiety is absorbed from the pharmaceutical form into the systemic circulation, thereby being present in the body's effect site or reflected in biological fluids, typically serum or plasma[5].

Bioavailability-bioequivalence studies can be conducted in centers approved by TİTCK through system audits, and often the Bioavailability/Bioequivalence Studies Ethics Committees are located in the institutions/organizations where these centers are situated.

Researchers often face difficulties in determining which ethics committee to apply to in their submissions. To assist researchers in this regard, an algorithm outlining the pathways to be followed for ethics committee approvals for drug and medical device clinical trials, including phase study definitions, has been published[12]. Particularly with the

increase in the variety of clinical trial types, the evaluation of studies by different ethics committees depending on the nature of the product under investigation, and the increasing number of such studies, the previously prepared algorithm for drugs and medical devices has been updated to serve as a guide (Fig. 2).

Many studies and research activities require not only ethics committee approval but also permission from the Ministry of Health according to the Supplementary Article 10 of the Basic Law on Health Services. These include:

1. Licensed or unlicensed drugs, medical and biological products
2. Licensed/permitted or unlicensed/unpermitted herbal products
3. Cosmetic products or raw materials
4. Non-drug clinical trials (such as medical device clinical trials) where a treatment or application will be directly administered to a volunteer
5. Any treatment method
6. Stem cells
7. Traditional and complementary medicine practices

Important considerations in the ethics committee application process are outlined below:

1. Legislation Knowledge: It is crucial to correctly determine whether the research product and type of study fall under or outside the scope of specific legislation.
2. Purpose, Scope, Method, and Sample Size of the Research: Accurate determination and explanation of all these parameters are important. The purpose of the research is the main criterion determining to which ethics committee we should apply.
3. Evaluation of Previous Studies (Preclinical, etc.): Detailed information in this regard is highly valuable for decision-making by the members of ethics committees.
4. Risk-Benefit Balance: Should be detailed and thoroughly explained.
5. Consistency in Study Plan/Protocol and Other Documents (e.g., ICF [inform consent form], CRF [case report form]): Using the current application forms for the ethics committee we are applying to and ensuring consistency across all documents is crucial.
6. Biological Material Management: Must be detailed and relevant forms should be completed.
7. Insurance/Budget: Should conform to legislation and the purpose, inclusion, and exclusion criteria of the research.

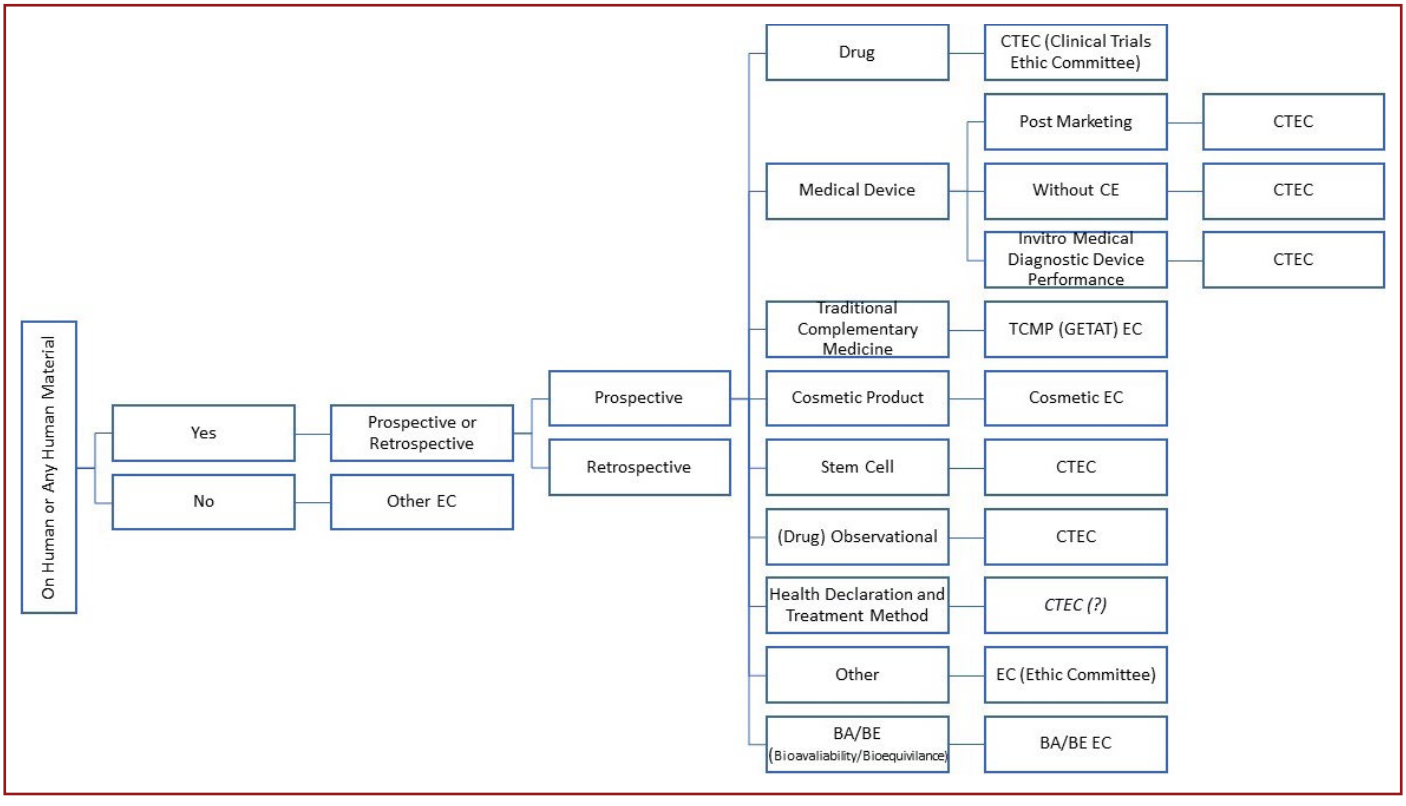

Figure 2. Ethics committe application algorithm.

8. Transparency: This is important not only for the applicant but also for the ethics committees.
9. Ethics Committee Secretariat: Should be communicative and knowledgeable. Additionally, it should be ensured that mandatory members' signatures (like a pediatrician for studies on children, a lay member for medical device clinical trials) are present in the ethics committee's decision.

Conclusion

In conclusion, using current application forms and reviewing the prevailing legislation during the ethics committee application process will be beneficial. There are many guidebooks of a guiding nature for researchers. The correct and rational selection of ethics committee members and the provision of training by experienced educators are also of significant importance.

The increasing number of ethics committees complicates standardization and the lack of specialized, experienced secretariat and dedicated working areas for ethics committees, as well as the absence of transparent and user-friendly websites, can sometimes create challenges for applicants.

In addition to all these regulations, it is crucial for journal editors and those involved in committees like conference abstract acceptance to be knowledgeable about ethics committee processes, especially regarding which type of study or research requires permission from which ethics committee.

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