REGULATION ON CLINICAL TRIALS OF MEDICINAL PRODUCTS FOR HUMAN USE

PART ONE
Introductory Provisions

Purpose

ARTICLE 1- (1) The purpose of this Regulation is to regulate, within the framework of the international agreements to which Türkiye is a party, European Union standards and good clinical practices, the procedures and principles concerning the conduct of clinical trials performed with medicinal products for human use and the protection of the rights of volunteers, as well as the establishment, duties, and working procedures and principles of the Clinical Trials Advisory Board and ethics committees.

Scope

ARTICLE 2- (1) This Regulation covers the clinical trials of all medicinal products for human use, including bioavailability and bioequivalence studies, whether or not a marketing authorisation or permit has been obtained for them, the low-risk scientific studies, the trial sites, and the natural or legal persons that will conduct these trials.

(2) All non-interventional studies, including observational studies of medicinal products for human use, and retrospective studies are outside the scope of this Regulation.

Legal Basis

ARTICLE 3- (1) This Regulation has been prepared on the basis of the additional Article 10 of the Fundamental Law on Health Services No. 3359 dated 7/5/1987, and Articles 508 and 796 of the Presidential Decree No. 4 on the Organisation of Institutions and Organisations Affiliated to, Related to and Associated with Ministries and Other Institutions and Organisations.

Definitions

ARTICLE 4- (1) The following terms used in this Regulation shall mean:

a) Adaptive design clinical trial: a clinical trial design that allows one or more prospective changes to be made to the trial design based on the data obtained from volunteers,

b) Adverse event: all untoward medical occurrences that arise in a volunteer participating in a clinical trial, with or without a causal relationship to the treatment administered,

c) Adverse reaction: all unintended and unexpected responses to the investigational product that arise in a volunteer participating in a clinical trial,

ç) Trial protocol: the document that defines in detail the objective, design and methodology of the trial, the statistical methods to be applied and the arrangements pertaining to the trial,

d) Investigational product: a medicinal product for human use that is tested or used as a reference in a clinical trial, including placebo,

e) Investigational product dossier: the document containing information on the quality, manufacture and control of the investigational product, together with the data obtained from non-clinical studies and from clinical use, including clinical trials,

f) Investigator: a physician or dentist appointed by the principal investigator, under the supervision and oversight of the principal investigator, for the performance of critical trial-related methods or for the taking of important trial-related decisions,

g) Investigator's brochure: the documents containing the non-clinical and clinical data pertaining to the investigational product,

ğ) Commencement of a trial: unless otherwise defined in the protocol, the opening of the first centre of a specific clinical trial for the enrolment of volunteers,

h) Suspension of a trial: the suspension of the conduct of a clinical trial by the Agency or by the regulatory authorities of other countries,

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ı) Early termination of a trial: the termination of a clinical trial ahead of its time for any reason before the conditions specified in the protocol have been fulfilled,

i) Temporary halt of a trial: the interruption by the sponsor of the conduct of a clinical trial in a manner not foreseen in the protocol, with the intention of continuing the clinical trial,

j) Completion of a trial: the date on which the trial is completed in accordance with the protocol and all centres in Türkiye are closed,

k) Relative bioavailability: the bioavailability ratioed to the bioavailability obtained either by administration via a route allowing the highest bioavailability other than intravenous use, or with a pharmaceutical form administered via the same route but providing higher bioavailability,

l) Ministry: the Ministry of Health,

m) Unexpected serious adverse reaction: any serious adverse reaction whose nature, severity or outcome is not consistent with the reference safety information of the investigational product,

n) Medicinal product for human use (medicinal product):

1) any substance or combination of substances presented as having properties for treating or preventing disease in humans, or

2) any substance or combination of substances that may be used in or administered to humans with a view to restoring, correcting or modifying physiological functions by exerting a pharmacological, immunological or metabolic action, or to making a medical diagnosis,

o) Clinical trial of a medicinal product for human use (clinical study): the interventional study conducted in humans that aims at discovering or verifying the clinical, pharmacological and/or other pharmacodynamic effects of an investigational product or products, and/or identifying any adverse reactions to an investigational product or products, and/or determining the absorption, distribution, metabolism and excretion of an investigational product or products, for the purpose of determining the safety and/or efficacy of the investigational product or products,

ö) Observational study of medicinal products for human use: the epidemiological studies in which data on a medicinal product for human use prescribed spontaneously are collected from patients whose treatment continues in accordance with the indications for which the medicinal products for human use are licensed in Türkiye, their posology and modes of administration, and the Ministry's current diagnosis and treatment guidelines,

p) Informed consent form: the document that evidences in writing the consent obtained for the participation of the volunteer in the trial, after detailed and comprehensible information about the trial has been provided to the volunteer or to the volunteer's legal representative,

r) Scientific study: the low-risk scientific study,

s) Bioequivalence: the condition in which, following administration of two medicinal products for human use containing the same active substance, at the same molar dose and by the same route of administration, which are pharmaceutically equivalent or pharmaceutical alternatives of each other, their bioavailabilities (rate and extent) remain within predetermined acceptable limits,

ş) Bioavailability: the rate and extent to which the active substance, or the fraction responsible for the therapeutic effect, is absorbed from the pharmaceutical form into the systemic circulation and thus becomes present at the site of action in the body, or in biological fluids that reflect it (usually serum or plasma),

t) Serious adverse event or reaction: an adverse event or reaction that results in death, is life-threatening, requires hospitalisation or prolongation of the duration of hospitalisation, results in persistent or significant disability or incapacity, consists of a congenital anomaly or defect, requires medical or surgical intervention in order to prevent one of the outcomes listed, on the likelihood that it may endanger the volunteer, or leads to the development of dependence or drug abuse,

u) Serious breach: any deviation from the approved protocol, from good clinical practice or from the provisions of this Regulation that is likely to affect to a significant degree the safety of

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volunteers, their rights, or the reliability and quality of the data in a clinical trial,

ü) Conflict of interest: the situation in which the impartial and objective performance of persons' duties is, or appears to be, influenced by any kind of benefit provided to them, their relatives, their friends, or the persons or organisations with which they have relationships, by financial or other obligations relating to them, and by similar personal interests,

v) Child: a person who has not yet completed the age of eighteen,

y) Multicentre clinical trial: a clinical trial conducted at more than one centre in accordance with a single protocol, and which therefore involves more than one principal investigator,

z) Inspection: the activities whereby the activities and records relating to a clinical trial performed by the natural or legal persons involved in the clinical trial, the sites where the clinical trial is conducted, the sponsor, where applicable its legal representative and the other parties to which duties have been transferred, including service providers or trial centres, the quality assurance arrangements and the ethics committees related to the trial and other institutions, boards and organisations are examined by the Agency for compliance with this Regulation and the other relevant legislation,

aa) Sponsor: the person, institution or organisation responsible for the initiation, conduct and financing of a clinical trial,

bb) Low-risk scientific study: the scientific studies conducted for therapeutic purposes on a large number of patient volunteers in order to further investigate the safety and efficacy of the approved indications, posology and modes of administration of the medicinal products for human use licensed in Türkiye and, for products holding a permit, of their recommended uses, or in order to compare them with other established treatments, products and methods,

cc) Ethics committee: the independent clinical trial ethics committees or bioavailability and bioequivalence ethics committees that are established and approved by the Agency in order to give opinions from a scientific and ethical standpoint on the suitability of the natural or legal persons taking part in the clinical trial, of the sites where the clinical trial is conducted, of the information and documents required to be submitted in the clinical trial application dossier, and of the methods and materials to be used in obtaining and documenting informed consent from volunteers, for the purpose of protecting the rights, safety and well-being of volunteers,

çç) Vulnerable population: the groups of volunteers composed of persons with limited or diminished autonomy who are situated within a certain hierarchical structure, or in whom the capacity to protect themselves has not yet developed, has diminished or has been entirely lost for economic, social or medical reasons,

dd) Activity permit document: the permit document issued by the Agency to the centres in which the clinical or bioanalytical parts of Phase I clinical trials and bioavailability and bioequivalence studies are conducted,

ee) Phase I or first phase clinical trial: the clinical trial phase in which the investigational product is tested, in order to determine the clinical safety, pharmacokinetic properties and toxicity of the investigational product, its effects on body functions and the safe dose range, by administration to a sufficient number of healthy volunteers selected according to the nature and content of the trial or, in cases where it is not possible to work with healthy volunteers, by administration to patient volunteers,

ff) Phase II or second phase clinical trial: the clinical trial phase in which the investigational product is tested by administration to a sufficient number of patient volunteers, selected according to the nature and content of the trial, for the purpose of investigating the therapeutic dose range, clinical efficacy and safety of the investigational product,

gg) Phase III or third phase clinical trial: the clinical trial phase in which the investigational product, having sufficient and appropriate efficacy and safety data to commence a Phase III trial, is tested by administration to a sufficient number of patient volunteers selected according to the nature and content of the trial, with respect to efficacy, safety, the investigation of a new indication, different doses, new routes and methods of administration, a new patient population

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and new pharmaceutical forms,

ğğ) Volunteer: the patient or healthy person who participates in a clinical trial upon the written consent of himself/herself or of his/her legal representative, in accordance with the provisions of this Regulation and the relevant legislation,

hh) Administrative responsible person: in a multicentre trial, the person, preferably having completed specialty or doctoral training, who is responsible, where necessary during the conduct of the trial, for the coordination on administrative matters relating to the trial between the principal investigators of those centres and the ethics committee or the sponsor and, where necessary, between them and the Agency,

ıı) Good clinical practice: the rules, compliance with which is required by all parties taking part in the trial, covering arrangements on matters such as the design, conduct, monitoring, budgeting, evaluation and reporting of trials in accordance with international scientific and ethical standards, the protection of all the rights and the physical integrity of the volunteer, the assurance of the reliability of trial data and the maintenance of its confidentiality,

ii) Monitoring: the activity of overseeing the conduct of a clinical trial and of ensuring that the clinical trial is conducted, recorded and reported in compliance with the protocol, the standard operating procedures, good clinical practice and the relevant legislation,

jj) Legal representative: the person who, pursuant to the legislation in force, is authorised to give consent on behalf of a potential volunteer regarding the volunteer's participation in a clinical trial,

kk) Person under guardianship: the persons falling within the scope of the cases of guardianship defined in the Turkish Civil Code No. 4721 dated 22/11/2001,

ll) Clinical trial: the clinical trials of medicinal products for human use, the bioavailability studies and the bioequivalence studies,

mm) Clinical trial master file: the file, inspected by the Agency where necessary, that contains the essential documents and information relating to clinical trials, prepared in accordance with good clinical practice,

nn) Clinical trial pharmacist: the research pharmacist, appointed by the principal investigator, who is responsible for the receipt, record-keeping, storage, preparation and return of the medicinal products for human use used in the trial,

oo) Clinical trial nurse: the nurse appointed by the principal investigator or by the sponsor to perform the nursing services related to the trial under the supervision and oversight of the principal investigator,

öö) Clinical trial site staff member (clinical trial site coordinator): the auxiliary clinical trial personnel appointed to work at the trial site under the supervision and oversight of the principal investigator, preferably trained in health sciences and science faculties, provided that they hold at least a bachelor's degree, for the performance of critical trial-related methods or for duties within the powers determined by the principal investigator in relation to the trial,

pp) Clinical trials advisory board: the board to be established in order to give opinions on matters relating to clinical trials,

rr) Clinical experiment: the prospective research conducted in humans for the purpose of investigating the effects of one or more health-related interventions on health outcomes in humans (human health, behaviour, structure and function of the body),

ss) Coordinator: the physician or dentist selected from among the principal investigators of a multicentre trial, who is responsible for ensuring the coordination between the principal investigators of those centres and the ethics committee, the sponsor, where applicable the legal representative, and, where necessary, with the Agency,

şş) Coordinating centre: the centre where the coordinator works in a multicentre trial,

tt) Agency: the Turkish Medicines and Medical Devices Agency,

uu) Absolute bioavailability: the bioavailability ratioed to the bioavailability measured following the intravenous administration of the same molar amount of the medicinal product,

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üü) Intervention: any physical or manipulative preventive, diagnostic or therapeutic product application, act or procedure, performed by a physician or dentist who is a specialist in his or her field, directed at the physical and/or mental integrity of a person for the purpose of protecting or restoring human health,

vv) Retrospective study: the studies in which data are obtained retrospectively from patient files,

yy) Healthcare professional: physicians, dentists, pharmacists, nurses, midwives and opticians, together with the other professionals defined in the additional Article 13 of the Law No. 1219 dated 11/4/1928 on the Practice of Medicine and its Branches,

zz) Principal investigator: the physician or dentist who has completed specialty or doctoral training in the field related to the trial and who is responsible for the conduct of the trial at the relevant centre,

aaa) Contract research organisation: the independent legal entities that carry out their activities in accordance with the principles of good clinical practice and to which the sponsor transfers all or part of its duties and powers relating to the clinical trial by means of a written contract,

bbb) Auxiliary medicinal product for human use: a medicinal product for human use licensed in Türkiye which, while not being a clinical trial product, is used in accordance with the requirements or needs arising under the clinical trial protocol,

ccc) Auxiliary clinical trial personnel: the member of the trial team, other than a physician or dentist, who takes part in a clinical trial and who is appointed by the principal investigator or by the sponsor in order to carry out the work and procedures relating to the clinical trial under the supervision and oversight of the principal investigator,

çççç) Legal representative (of the sponsor): in cases where the sponsor is not established in Türkiye, the natural or legal persons established in Türkiye who are responsible for ensuring compliance with the obligations of the sponsor under this Regulation and who are the addressee of all communications with the sponsor provided for in this Regulation.

PART TWO

General Principles and Rules for the Clinical Trial and the Scientific Study

General principle

ARTICLE 5- (1) In a clinical trial;

a) the protection of the rights, safety, dignity and well-being of volunteers and their being accorded precedence over all other interests,

b) the generation of reliable and robust data,

c) the conduct of the trial in a scientific and ethical manner,

are essential.

General rules

ARTICLE 6- (1) Clinical trials are designed, conducted, recorded and reported in line with the most current version of the World Medical Association Declaration of Helsinki on Ethical Principles for Medical Research Involving Human Subjects and of the relevant international standards.

(2) The following are required in order for research to be carried out on volunteers:

a) it is a condition that, for the trial to be conducted, the investigational product must first have been studied in a non-human experimental setting or on a sufficient number of experimental animals,

b) the scientific data obtained as a result of experiments conducted in non-human experimental settings or on animals must necessitate their being carried out also in humans in terms of reaching the intended objective,

c) the expected scientific benefits of the trial and the public interest may not be accorded precedence over the health of the volunteers who will participate in the trial, over the potential risks that may arise with respect to their health, or over the other personality rights,

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ç) no research may be conducted aimed at altering the genetic structure of the germ cells belonging to a volunteer.

d) decisions concerning the medical follow-up and treatment of the volunteer participating in the trial belong to the physician or dentist possessing the professional qualifications they require,

e) the application, during the trial, of methods that would cause the volunteer pain to an extent incompatible with human dignity is prohibited,

f) the trial is designed in such a way as to reduce to the lowest possible level pain, discomfort, fear, and any risk relating to the disease of the patient and to the stage of its development. Both the risk limit and the degree of discomfort must be specifically defined and continuously checked,

g) the objective sought to be attained by the trial must outweigh the burden it imposes on the person and the potential danger to the person's health,

ğ) it is a condition that the trial leaves no foreseeable harmful and permanent effect on human health,

h) where the ethics committee is satisfied that the benefits to be obtained are greater than the risks likely to arise from the trial, the trial may be commenced after ethics committee approval and Agency authorisation have been obtained,

ı) an informed consent form must be obtained from the volunteers who will participate in the trial, with due regard for their personality rights and in a duly manner.

(3) The trial may be conducted only for as long as the conditions specified in the second paragraph continue to exist.

PART THREE
General Rules on Applications for Clinical Trials and Scientific Studies

Persons evaluating the application

ARTICLE 7- (1) The persons who render an application valid, evaluate it and decide upon it at the Agency must be free from conflict of interest, and these persons must be independent of the sponsor, of the trial team, of the natural or legal persons financing the clinical trial, and of other improper influences.

(2) The evaluation is carried out by an appropriate number of persons possessing the necessary qualifications and experience.

Applications for the trial

ARTICLE 8- (1) Applications may be made simultaneously to the ethics committee and to the Agency for the clinical trials and scientific studies within the scope of this Regulation.

(2) Applications for the trial are made by the sponsor to the ethics committee and to the Agency.

(3) In multicentre clinical trials, the existence of a single ethics committee decision is sufficient. This ethics committee decision;

a) must be obtained from the ethics committee at the place where the coordinating centre is located, or from one of the ethics committees attached to the provincial health directorate of the province where the coordinating centre is located,

b) must be obtained, where there is no ethics committee at the places specified in subparagraph (a) of the third paragraph, from the ethics committee at the place where one of the centres included in the trial is located, or from an ethics committee attached to the provincial health directorate of that province,

c) must be obtained, where there is no ethics committee at any of the centres included in the trial or at the provincial health directorates of the provinces where those centres are located, from the ethics committee nearest to the coordinating centre,

is required.

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(4) In single-centre clinical trials, the decision must be obtained from the ethics committee at the place where the centre conducting the trial is located, or from an ethics committee attached to the provincial health directorate of the province where the centre is located; where there is no ethics committee, the decision must be obtained from the relevant ethics committee at the place nearest to the trial site.

(5) The nearest ethics committee referred to in the third and fourth paragraphs means an ethics committee in the province where the coordinating centre is located, where one exists; otherwise, an ethics committee in the nearest province.

(6) Except in cases deemed necessary by the Agency, force majeure or obligatory situations, the Agency accepts applications for a trial only electronically and conducts all correspondence with the applicants exclusively in the electronic environment.

(7) The Agency evaluates the applications for a trial in terms of whether they constitute a complete application with respect to the documents required to be submitted according to the nature of the application and the electronic application requirements, and in terms of the compliance of the trial with the provisions of this Regulation in line with good clinical practice.

(8) The ethics committee evaluates the applications for a trial in accordance with the matters specified in subparagraph (c) of the first paragraph of Article 63 and the guidelines published by the Agency pursuant to the first and second paragraphs of Article 69, with good clinical practice and with the relevant legislation.

(9) It is essential that applications for a trial which are duly made and in which there is no deficiency in the information and documents that must be contained in the application be examined by the ethics committee within twelve working days and by the Agency within twenty-two working days. It is essential that applications for bioavailability and bioequivalence studies which are duly made and in which there is no deficiency in the information and documents that must be contained in the application be examined by the ethics committee within seven working days and by the Agency within twelve working days.

(10) Where additional information and explanations are needed during the examination process of the ethics committee and of the Agency, all the necessary requests are communicated to the applicant in a single submission.

(11) A period of thirty working days may be added to the examination period determined for the ethics committee and the Agency in the trials set out below:

a) trials to be conducted using products carrying genetically modified organisms and products involving cell therapies or gene therapy;

b) trials in which the trials within the scope of this Regulation and the trials within the scope of the Regulation on Clinical Trials of Medical Devices published in the Official Gazette No. 31890 dated 8/7/2022 are conducted together so as to constitute the subject of a single trial.

(12) (Added: OG-29/12/2023-32414) Applicants are responsible for retaining the originals of all the documents they submit to the Agency and for submitting them to the Agency upon request.

Use of decisions and reports, and obtaining opinions

ARTICLE 9- (1) The Agency may, in the course of examining and evaluating trials and in exercising its powers, make use of the relevant decisions given and/or published reports of other medicines authorities possessing comparable standards, or of regional or international organisations.

(2) The Agency may, in the course of examining and evaluating trials and in exercising its powers, seek the opinions of the scientific advisory commissions established in accordance with the Regulation on the Establishment and Duties of the Scientific Advisory Commissions and Boards of the Turkish Medicines and Medical Devices Agency, published in the Official Gazette No. 30849 dated 1/8/2019, and of the members thereof.

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Special considerations for vulnerable populations

ARTICLE 10- (1) In cases where the volunteers are children, in order for the relevant group of volunteers to be included in the trial, the scientific and ethical suitability of the trial must be assessed by a specialist in pediatric health and diseases, and a positive opinion must be obtained.

(2) In cases where the volunteers are persons under guardianship, in the evaluation of the application made for the authorisation of the clinical trial, an expertise-based opinion may be obtained regarding the scientific and ethical suitability of including in the trial the relevant disease and the population represented by the relevant volunteer.

(3) In cases where the volunteer is a pregnant, postpartum or breastfeeding woman, in the evaluation of the application made for the authorisation of the clinical trial, an expertise-based opinion may be obtained regarding the scientific and ethical suitability of including in the trial the relevant disease and the population represented by the relevant volunteer.

(4) In the evaluation of the application made so that, together with the situations described above, the other vulnerable populations — such as persons performing compulsory military service, persons deprived of their liberty, persons who may not take part in clinical trials on account of a judicial decision, or persons residing in care homes — may be included in the clinical trial, an expertise-based opinion may be obtained concerning the population represented by the relevant volunteers; the Agency may take additional measures concerning the appropriate protection of these persons.

(5) Where deemed necessary, the opinion of a physician or dentist who holds a doctorate or a specialty in the branch of science related to the subject of the trial is obtained, and this opinion is taken into account in deciding whether the trial may be permitted.

PART FOUR
Authorisation Procedure for Clinical Trials and Scientific Studies

General principle

ARTICLE 11- (1) The clinical trials and scientific studies within the scope of this Regulation may be commenced after ethics committee approval and Agency authorisation have been obtained.

Initial eligibility application and Agency authorisation

ARTICLE 12- (1) The applicant makes an initial eligibility application to the ethics committee and to the Agency in order for clinical trials and scientific studies to be commenced.

(2) The guideline on the form and content of the initial eligibility application is published by the Agency.

Decision on the trial

ARTICLE 13- (1) The results of the evaluation of the applications made to the Agency and to the ethics committee are communicated to the applicant by official letter.

(2) The deficiencies identified as a result of the examination of the initial eligibility application file by the Agency or the ethics committee, together with the additional information and explanations needed, are communicated to the applicant. The requested information and documents are submitted by the applicant to the Agency or to the ethics committee within thirty working days at the latest. Except in cases deemed necessary by the Agency, force majeure or obligatory situations, where the additional information and documents, or the necessary explanation that they cannot be submitted together with the information as to the date on which they will be submitted, are not provided to the Agency or to the ethics committee, the application is deemed withdrawn and is cancelled.

(3) Where the Agency or the ethics committee has given a negative decision on the conduct of the trial, it notifies the applicant thereof together with its reasons. The applicant may, on a single occasion, re-apply having made the necessary changes on the matters specified in the decision, or may appeal the decision with reasons within thirty working days. Where the requested

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changes are not implemented, or where no acceptable justification is provided in this respect, the Agency or the ethics committee may reject the trial.

(4) As a result of the examination and evaluation of the information and documents submitted to the Agency by the applicant, the Agency authorises the commencement of the clinical trials which have ethics committee approval and which are found to comply with the provisions of this Regulation, and the result is communicated to the applicant by official letter.

Withdrawal of the application

ARTICLE 14- (1) The applicant may withdraw its application at any time during the evaluation process. In order to withdraw the application, it applies to the Agency and to the ethics committee together with its reasons.

Re-application

ARTICLE 15- (1) Following the rejection, cancellation or withdrawal of an application, the relevant application may be re-submitted to the Agency as a new application; this must, however, be stated in the cover letter.

PART FIVE
Clinical Trials in Exceptional Circumstances

Application and authorisation

ARTICLE 16- (1) Clinical trials falling within the scope of at least one of the following are deemed to be trials in exceptional circumstances:

a) clinical trials to be conducted with investigational products intended for the treatment, prevention or medical diagnosis of life-threatening or seriously disabling diseases, which will address an unmet medical need;

b) clinical trials to be conducted with investigational products to be used in situations accepted by the World Health Organization or by our country as seriously threatening public health.

(2) In order to determine whether a trial is a trial in exceptional circumstances, an assessment application is made to the Agency by the sponsor with the information and documents that will prove that the trial bears the characteristics determined in the first paragraph.

(3) The Agency examines assessment applications within three working days and may request additional explanations and information from the applicant in cases it deems necessary. The requested explanations and information are submitted to the Agency within three working days. Together with the additional information and explanations, the application is re-examined by the Agency within three working days. The result of the evaluation of the assessment application is notified to the applicant as positive, or as negative together with its reasons.

(4) In trials in exceptional circumstances, the periods specified in the ninth and eleventh paragraphs of Article 8 are applied as seven working days.

(5) In trials in exceptional circumstances, the situation where the benefit of the trial to public health is greater than the risk created by the absence of data, notwithstanding that comprehensive data on efficacy and safety are not yet available, is taken into account in the examination to be carried out by the Agency and the ethics committee.

(6) The guideline on the application of this Article and on the form and content of the applications to be made for trials in exceptional circumstances is published by the Agency.

PART SIX
Conduct of the Clinical Trial and the Scientific Study

Applications and authorisations

ARTICLE 17- (1) The applicant submits amendment applications and notifications to the ethics committee and to the Agency with the appropriate application type and content.

(2) Amendments may be made during the conduct of clinical trials and scientific studies in compliance with the following:

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a) those of the amendments which are of an informative nature and those which require ethics committee approval and Agency authorisation are determined by the guidelines to be published by the Agency;

b) in amendments requiring approval and authorisation, the Agency may not authorise the implementation of amendments that do not have ethics committee approval. Such amendments may not be implemented without Agency authorisation. In amendments of an informative nature, the amendment may be implemented on the basis of the date of notification; however, the ethics committee or the Agency may request the correction of such amendments or may cancel them together with the reasons thereof.

(3) The interim report prepared concerning the evaluations made on the basis of the interim results of the trial and of the analyses carried out during the trial is notified to the ethics committee and to the Agency.

(4) Of the appointments relating to the trial, those of a notification nature and those requiring ethics committee approval and Agency authorisation are determined by the guideline to be published by the Agency. However, the Agency may, where necessary, cancel appointments of a notification nature together with its reasons.

(5) The progress report for the trial is prepared at least once a year, in accordance with the relevant guidelines and the forms published on the Agency's website, and is notified to the ethics committee and to the Agency. The Agency or the ethics committee may request a report within a shorter period where it deems necessary or in short-term trials.

(6) The sponsor is responsible for the regular communication to the ethics committee and to the Agency of all notifications within the scope of this Regulation.

PART SEVEN

Application Dossier for the Clinical Trial and the Scientific Study

Data submitted in the application dossier

ARTICLE 18- (1) Application dossiers are prepared using the cover letter samples, the application form and the other forms published on the Agency's website, within the framework of the Guideline on Good Clinical Practice and the guidelines published by the Agency on the form of application.

(2) The preclinical pharmacological and toxicological studies from which the non-clinical data submitted in the application dossiers are obtained are conducted in compliance with the provisions laid down in the Regulation on the Principles of Good Laboratory Practice, the Harmonisation of Testing Facilities, and the Inspection of Good Laboratory Practices and Studies, published in the Official Gazette No. 27516 dated 9/3/2010.

(3) Where the application dossiers refer to data obtained from clinical trials previously conducted outside Türkiye, those clinical trials must have been designed, implemented and reported on the basis of the good clinical practice and ethical principles determined in accordance with the rules laid down in this Regulation.

(4) At the time of application, the risk management plan, the pediatric investigation plan where applicable, and, where available, the letter of advice regarding the trial, the assessment report, or the information and documents evidencing the approval or authorisation obtained from the above-mentioned authorities for the conduct of the trial — granted by the competent authorities of which the International Council for Harmonisation (ICH) is a founding or standing member, by the Australian medicines authority (TGA) or by the medicines authority of the United Kingdom (MHRA) — are submitted.

Language requirements

ARTICLE 19- (1) It is essential that the cover letters and documents submitted in applications be prepared in Turkish. Nevertheless, the Agency may also accept documents in a foreign language prepared in accordance with the guideline it has published.

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PART EIGHT
Protection of Volunteers and Obtaining Volunteer Consent

General rules

ARTICLE 20- (1) The person wishing to be a volunteer in the trial, or his/her legal representative, shall, before being included in the trial, be informed adequately and in a manner that he/she can understand, by the principal investigator or by an investigator appointed by the principal investigator, of the objective of the trial, its methodology, its expected benefits, its foreseeable risks and difficulties, the aspects in which it is unsuitable with respect to the person's health and personal characteristics, and the conditions under which the trial will be conducted and continued, and of the fact that he/she has the right to withdraw from the trial at any time he/she wishes.

(2) The consent of the volunteer to the effect that he/she will join the trial entirely of his/her own free will, without any procurement of benefit in connection with his/her participation in the trial, is obtained, and this is documented by means of the Informed Consent Form covering the matters relating to the information referred to in the first paragraph.

(3) In cases where the volunteer is unable to give informed consent, the volunteer's legal representative shall be informed about all the relevant aspects of the trial.

(4) A principal investigator or one of the investigators is appointed so that the volunteer may, at any time, receive information on his/her own health and on the course of the trial and may make contact for that purpose.

(5) The treatment provided to the volunteers is under the responsibility of the principal investigator and the investigators.

(6) The volunteer may, with or without reason, of his/her own accord, leave the trial at any time he/she wishes, and may not suffer any loss of his/her existing rights in the course of his/her subsequent medical follow-up and treatment on that account.

(7) No persuasive inducement or financial offer may be made to the volunteer or to his/her legal representative in order to secure the volunteer's participation in the trial or its continuation; insurance coverage is outside this scope. However, the expenses that will arise from the participation of the volunteers in the trial, and the loss of income arising from the loss of working days of healthy volunteers, are stated in the trial budget and are covered from that budget.

(8) Where the information to be obtained as a result of the trial is published, the identity information of the volunteer may not be disclosed.

(9) Provided that the provisions of the Personal Data Protection Law No. 6698 dated 24/3/2016 are complied with, the data obtained from volunteers within the scope of the clinical trial protocol may be used in future scientific research. In order to collect data for such purposes, consent must be obtained from the volunteer for the use of his/her data also outside the clinical trial protocol, and he/she must have the right to withdraw that consent at any time. The withdrawal of consent does not affect the activities already carried out and the use of the data obtained on the basis of consent before its withdrawal. Since such scientific research is not covered by this Regulation, the Agency bears no responsibility.

(10) The physical and mental integrity of the volunteers, their confidentiality, and their rights concerning the protection of their relevant data under Law No. 6698 are safeguarded.

Obtaining volunteer consent

ARTICLE 21- (1) Informed volunteer consent shall be in writing.

a) After the volunteer or the legal representative has been duly informed by the principal investigator or by an investigator and has read the informed consent form, the date shall be entered on the informed consent form and the form shall be signed by the parties.

b) In obtaining informed volunteer consent, ample and sufficient time shall be allowed to the volunteer or to his/her legal representative to ask questions about the details of the trial and to decide whether or not to participate in the trial.

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c) Where the volunteer or the legal representative is unable to sign the consent form due to a medical or social reason such as illiteracy or visual impairment, the entire informed consent interview shall be conducted in the presence of an impartial witness who is not a member of the trial team. In this case, after the written informed consent form and the other written information to be given to the volunteer have been read out or explained to the volunteer or to his/her legal representative, after the volunteer or the legal representative has given oral approval to the volunteer's participation in the trial and, where possible, after these persons have signed and dated the approval form, an impartial witness shall sign and date the consent form. A copy of the consent form shall be given to the volunteer or to his/her legal representative. When the impartial witness signs the consent form, he/she has witnessed and attested that the information in the consent form and the other written information were accurately explained to the volunteer or to his/her legal representative, that they were understood by the volunteer or the legal representative, and that informed consent was given by the free will of the volunteer or of his/her legal representative.

ç) The minimum information to be provided in the implementation of this Article and in obtaining informed volunteer consent is published by the Agency.

Participation of persons under guardianship in trials

ARTICLE 22- (1) Where the subject of the trial directly concerns persons falling within the scope of the cases of guardianship, or where the condition is one that can be examined only in persons under guardianship, or in cases where the existing treatment options related to the disease of the person under guardianship have been entirely exhausted, where the trial carries no foreseeable risk for the health of the person under guardianship and there is a general medical opinion to the effect that the trial will provide a direct benefit to persons falling within the scope of the cases of guardianship, research on persons under guardianship may be permitted within the framework of the matters specified in Article 6, together with the following:

a) there must be a general medical opinion to the effect that the investigational product or the intervention has no known risk on persons under guardianship;

b) where the person under guardianship has the capacity to express his/her consent, his/her written consent, together with that of his/her guardian, is obtained after they have been informed in accordance with the first paragraph of Article 20;

c) where the person under guardianship has the capacity to form a judgement by evaluating the information given to him/her, he/she is immediately withdrawn from the trial in cases where he/she refuses to participate in the trial or wishes to withdraw from the trial at any stage thereof;

ç) the ethics committee is informed on the clinical, ethical, psychological and social problems relating to the trial by a physician who has obtained his/her specialty in the field related to the subject of the trial and by a physician who is a specialist in psychiatry, and the protocol is evaluated accordingly;

d) for clinical trials to be conducted on persons under guardianship, no persuasive inducement or financial offer may be made other than the covering of the necessary expenses that will arise from their participation in the trial.

Participation of children in trials

ARTICLE 23- (1) Where the subject of the trial directly concerns children, or where there is a clinical condition that can be examined only in children, or in cases where it is mandatory to demonstrate the validity in children of the data obtained from research conducted on adults, where the trial carries no foreseeable risk for the health of the volunteers and there is a general medical opinion to the effect that the trial will provide a direct benefit to the volunteers, research on children may be permitted within the framework of the matters specified in Article 6, together with the following:

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a) there must be a general medical opinion to the effect that the investigational product or the intervention has no known risk on children;

b) where the child has the capacity to express his/her consent, his/her own written consent is obtained, as well as that of his/her mother and father or, if he/she is under guardianship, of his/her guardian, after they have been informed in accordance with the first paragraph of Article 20;

c) where the child refuses to participate in the trial or wishes to withdraw from the trial at any stage thereof, the child is withdrawn from the trial;

ç) where the child is capable of evaluating the information given to him/her and of forming a judgement thereon, all the necessary information relating to the trial is explained to the child in an appropriate manner;

d) the ethics committee is informed on the clinical, ethical, psychological and social problems relating to the trial by a physician who is a specialist in pediatric health and diseases, and the protocol is evaluated accordingly;

e) the ethics committee may not approve any clinical trial to be conducted on children without a positive opinion of a physician who is a specialist in pediatric health and diseases on the conduct of that trial on children. Where deemed necessary for such trials, the opinion of a physician or dentist who holds a doctorate or a specialty in the branch of science related to the subject of the trial is obtained, and whether the trial may be permitted is assessed on the basis of the outcome of that opinion;

f) for clinical trials to be conducted on children, no persuasive inducement or financial offer may be made other than the covering of the necessary expenses that will arise from their participation in the trial;

g) where a child participating in the trial reaches the age of consent during the conduct of the trial, informed volunteer consent is obtained from the child.

Participation of pregnant, postpartum and breastfeeding women in trials

ARTICLE 24- (1) Where the subject of the trial directly concerns pregnant, postpartum or breastfeeding women, or where there is a clinical condition that can be examined only in pregnant, postpartum or breastfeeding women, where the trial carries no foreseeable risk for the health of the volunteer and of the foetus or the baby, and where there is a general medical opinion to the effect that the trial will provide a direct benefit to the volunteers, research on pregnant, postpartum and breastfeeding women may be permitted within the framework of the matters specified in Article 6, together with the following:

a) there must be a general medical opinion to the effect that the investigational product and the intervention have no known risk on pregnant, postpartum and breastfeeding women and on the foetus or the baby;

b) the written consent of pregnant, postpartum or breastfeeding women is obtained after they have been informed in accordance with the first paragraph of Article 20;

c) where pregnant, postpartum or breastfeeding women refuse to participate in the trial or wish to withdraw from the trial at any stage thereof, they are withdrawn from the trial;

ç) the ethics committee is informed, in particular with respect to the health of the foetus or the baby, on the clinical, ethical, psychological and social problems relating to the trial by a physician who has obtained his/her specialty in the field related to the subject of the trial, and the protocol is evaluated accordingly;

d) for clinical trials to be conducted on pregnant, postpartum or breastfeeding women, no persuasive inducement or financial offer may be made other than the covering of the necessary expenses that will arise from their participation in the trial.

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Participation of persons in intensive care and of unconscious persons in trials

ARTICLE 25- (1) Where the subject of the trial directly concerns persons in intensive care and unconscious persons, or where the condition is one that can be examined only in persons in intensive care and unconscious persons, or in cases where the existing treatment options related to the disease of the persons in intensive care and the unconscious persons have been entirely exhausted, where the trial carries no foreseeable risk for the health of the persons in intensive care and the unconscious persons and there is a general medical opinion to the effect that the trial will provide a direct benefit to persons in intensive care and to unconscious persons, research on persons in intensive care and on unconscious persons may be permitted within the framework of the matters specified in Article 6, together with the following:

a) there must be a general medical opinion to the effect that the investigational product or the intervention has no known risk on persons in intensive care and on unconscious persons;

b) where the persons in intensive care and the unconscious persons have legal representatives, the written consent of those representatives is obtained, and where they do not, that of their relatives, after they have been informed in accordance with the first paragraph of Article 20;

c) where the persons in intensive care and the unconscious persons regain the capacity to evaluate the information given to them and to form a judgement thereon, they are immediately withdrawn from the trial in cases where they refuse to participate in the trial or wish to withdraw from the trial at any stage thereof;

ç) the ethics committee is informed on the clinical, ethical, psychological and social problems relating to the trial by a physician who has obtained his/her specialty in the field related to the subject of the trial, and the protocol is evaluated accordingly;

d) for clinical trials to be conducted on persons in intensive care and on unconscious persons, no persuasive inducement or financial offer may be made other than the covering of the necessary expenses that will arise from their participation in the trial.

(2) Where the legal representatives or the relatives of the persons in intensive care and of the unconscious persons cannot be reached and their written consent cannot be obtained, the persons in intensive care and the unconscious persons may be included in the trial under the responsibility of the principal investigator or of an investigator, provided that the following conditions exist together with the provisions of the first paragraph:

a) the ethics committee has assessed in advance whether the proposed trial protocol or the other documents sufficiently address the ethical issues in the trial concerned;

b) in situations that develop suddenly and require the physician to intervene immediately, such as cardiac arrest, head trauma, central nervous system infections and intracerebral haemorrhages, and in which the existing treatment options have been entirely exhausted, there is a general medical opinion to the effect that the trial will provide a direct benefit to the persons in intensive care and to the unconscious persons.

PART NINE

Commencement, Completion, Temporary Halt and Early Termination of the Clinical Trial and the Scientific Study

Notification of the commencement of the trial and of the end of volunteer enrolment

ARTICLE 26- (1) Clinical trials and scientific studies may not be commenced without the authorisation of the Agency. Before the initial eligibility application, these trials are registered by the sponsor in a publicly accessible database, with due observance of the confidentiality of personal data.

(2) The dates of commencement, of the first visit of the first volunteer and of the end of volunteer enrolment of the trial authorised by the Agency, and of the re-commencement of volunteer enrolment, are notified to the ethics committee and to the Agency within fifteen days of the date on which they occur.

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(3) Where no volunteer has been included in the clinical trial in our country within two years of the date of notification of the authorisation, the authorisation given by the Agency is cancelled unless an extension is approved upon the request of the applicant.

Completion, temporary halt and early termination of the trial and the submission of its results

ARTICLE 27- (1) Where the trial protocol foresees a date for interim data analysis before the completion of the trial and the relevant results of the trial are available, a summary of those results is submitted to the Agency and to the ethics committee within 1 year of the date of the interim data analysis.

(2) The sponsor notifies the Agency and the ethics committee that the trial has been completed within fifteen days of the completion of the trial in our country.

(3) The trial is notified to the Agency and to the ethics committee within thirty days following its completion in all the countries in which it is conducted. Within one year, a summary of the clinical trial results report and a version of that summary prepared in a manner that the volunteers can understand are submitted to the ethics committee and to the Agency. Where the content of those documents is updated, the necessary notifications are made to the ethics committee and to the Agency. However, where it is not possible to submit the summary of the results within one year for the scientific reasons detailed in the protocol, that summary is submitted as soon as it is ready. In this case, when the results will be submitted is stated in the protocol, where possible together with the reason thereof.

(4) Information on the trials and the trial results are published by the Agency in a publicly accessible database, prepared in a manner that the volunteers can understand, with due observance of commercial confidentiality and of the confidentiality of personal data.

(5) Where a trial has been temporarily halted or early terminated by the sponsor after its commencement, the decision to halt or to terminate it, together with its reasons, is notified to the Agency and to the ethics committee within fifteen days, with the addition of a letter of information containing the measures for the continuation of the treatment of the volunteers enrolled in the trial. The trial may not be recommenced unless the Agency authorises its recommencement.

(6) In order for the trial to be recommenced, an application is made together with the justification for recommencement, including the risk-benefit assessment and the measures taken following the temporary halt and their outcomes.

(7) Where a clinical trial that has been temporarily halted is not recommenced within two years, whichever is earlier of the date on which that period ends or the date on which the sponsor decides not to recommence the clinical trial is accepted as the date of termination of the clinical trial. Where the clinical trial is early terminated, the date of early termination is accepted as the date of termination of the clinical trial.

PART TEN

Notification of Adverse Events and Serious Adverse Reactions, Other Notifications

Database for safety notifications

ARTICLE 28- (1) The safety notifications submitted to the Agency are retained on a database established and operated by the Agency. This database may be operated as a stand-alone database or as a sub-module of the Clinical Trials Module referred to in Article 56.

Notification of adverse events and serious adverse events to the sponsor

ARTICLE 29- (1) The principal investigator or an investigator to be appointed by him/her records and documents all adverse events, unless otherwise foreseen in the protocol. The adverse events or laboratory findings defined as critical for safety evaluations are reported to the sponsor within the period and in the manner specified in the protocol.

(2) The principal investigator or an investigator to be appointed by him/her shall report to the sponsor all serious adverse events occurring in the volunteers whom he/she treats in the

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clinical trial, unless otherwise specified in the protocol.

(3) Except for those serious adverse events which the protocol states are not required to be reported immediately, the principal investigator or an investigator to be appointed by him/her shall report serious adverse events to the sponsor without undue delay, at the latest within 24 hours of becoming aware of the events.

(4) Where relevant, the principal investigator or an investigator to be appointed by him/her shall send a follow-up report to the sponsor in order to enable the sponsor to assess whether the serious adverse event has an impact on the benefit-risk balance of the clinical trial.

(5) In the event of the death of one of the volunteers participating in the trial, the principal investigator or an investigator to be appointed by him/her submits to the sponsor, to the ethics committee and to the Agency every kind of additional information requested.

(6) The records of all adverse events reported by the principal investigator or by an investigator appointed by him/her to the sponsor are kept in detail by the sponsor. These records are submitted to the Agency and to the ethics committee upon request.

(7) Where the principal investigator or an investigator appointed by him/her becomes aware of a serious adverse event occurring in a volunteer whom he/she has treated after the completion of the clinical trial and suspected of having a causal relationship with the investigational product, he/she shall notify the serious adverse event to the sponsor without delay.

Notification of suspected unexpected serious adverse reactions to the ethics committee and the Agency

ARTICLE 30- (1) The sponsor, indicating the open title of the trial and the coordinating centre, shall report, together with all the relevant required information:

a) all suspected unexpected serious adverse reactions (SUSARs) identified at the trial sites in Türkiye or in other countries;

b) the SUSARs arising in the clinical trials which the sponsor is conducting, whether in our country or in other countries, with the same investigational product, regardless of the pharmaceutical form, potency or indication; the spontaneous notifications; the SUSARs described in a scientific publication; or the SUSARs communicated to the sponsor by the regulatory authorities;

c) all suspected unexpected serious adverse reactions identified in relation to the investigational product, seen in any of the clinical trial volunteers and determined or noticed by the sponsor after the end of the clinical trial.

The sponsor shall notify the ethics committee and the Agency without delay.

(2) However, SUSARs identified during the use of the investigational product in different clinical trials abroad shall be presented to the principal investigator in the form of a ranking list. The Agency may request this list in cases it deems necessary.

(3) The periods for the notification by the sponsor of SUSARs to the ethics committee and to the Agency are as follows:

a) The sponsor informs the ethics committee and the Agency of SUSARs arising during the trial which were fatal or life-threatening, no later than seven days from the date on which the said information reached him/her. He/she communicates to the ethics committee and to the Agency the follow-up reports containing the additional information on those cases, within eight days of their reaching him/her.

b) SUSARs that are not fatal or life-threatening in nature are notified by the sponsor to the ethics committee and to the Agency within at the latest fifteen days following the acquisition of the initial information.

c) SUSARs assessed at the time of the initial notification as not being fatal or life-threatening in nature, but revealed during the follow-up period to be fatal or life-threatening, are notified within at the latest seven days.

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(4) In cases necessary to ensure that notification is made in a timely manner, the sponsor may submit an incomplete initial report and, following that report, a completed report. In addition, he/she communicates to the ethics committee and to the Agency the follow-up reports containing the additional information on the notifications, within eight days of their reaching him/her.

(5) The sponsor shall also inform the principal investigator and the investigators of the reports specified in the third paragraph.

Notification of the development safety update report

ARTICLE 31- (1) In relation to investigational products other than placebo, the sponsor submits annually to the ethics committee and to the Agency, through the database referred to in Article 28, the development safety update report (DSUR) concerning the safety of each investigational product used in a clinical trial of which he/she is the sponsor.

(2) In the case of a clinical trial requiring the use of more than one investigational product, the sponsor may, where this is foreseen in the protocol, submit a single safety report on all the investigational products used in that clinical trial.

(3) The annual report referred to in the first paragraph contains aggregated and anonymised data.

(4) The obligation referred to in the first paragraph starts as of the date of the authorisation given for the clinical trial under this Regulation. It ends with the termination of the last clinical trial conducted with the relevant investigational product by the sponsor.

Notification concerning auxiliary medicinal products for human use

ARTICLE 32- (1) All safety notifications relating to the auxiliary medicinal products for human use used in clinical trials must be made in accordance with this Regulation.

PART ELEVEN

Suitability of the Trial Sites and of the Trial Team

Compliance with the protocol and good clinical practice

ARTICLE 33- (1) The sponsor, the other parties to which duties have been transferred, the principal investigator, the members of the trial team and all other parties taking part in the clinical trial are responsible for conducting the trials in compliance with the trial protocol, good clinical practice and the provisions of the relevant legislation.

(2) Without prejudice to the provisions of the relevant legislation, the sponsor and the trial team also take into account, in preparing and implementing the protocol, the relevant guideline principles on quality standards and good clinical practice published by the International Council for Harmonisation (ICH), together with this Regulation.

(3) The Agency publishes on its website the list of the relevant International Council for Harmonisation (ICH) guidelines on the quality standards and good clinical practice referred to in the second paragraph.

Monitoring

ARTICLE 34- (1) The sponsor is responsible for monitoring activities in order to ensure the protection of the rights, safety and well-being of the volunteers, that the reported trial data are accurate, complete and verifiable from source documents, and that the trial is conducted in accordance with the currently approved trial protocol, good clinical practice and the relevant legislation.

(2) The scope of the monitoring is determined by the sponsor on the basis of an assessment that takes into account all the characteristics of the clinical trial, including its objective and design.

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Suitability of the trial team

ARTICLE 35- (1) The clinical trials within the scope of this Regulation are conducted under the chairmanship of the principal investigator, with a team appropriate to the nature of the trial. Under the supervision of the principal investigator, a sufficient number of investigators, clinical trial nurses and site staff members possessing the appropriate qualifications and, preferably, a clinical trial pharmacist, together with other auxiliary trial personnel, are appointed.

(2) The persons taking part in the conduct of a clinical trial must possess qualifications appropriate, in terms of training, education and experience, to the performance of their duties.

(3) In Phase I clinical trials and in bioavailability and bioequivalence studies, it is mandatory for the trial team to include a pharmacologist holding a degree in medicine who has completed his/her specialty or doctorate.

(4) (Amended: OG-5/6/2025-32921) Before appointments are made to the trial team, the information relating to the investigators is notified to the ethics committee and to the Agency, and the information relating to the auxiliary clinical trial personnel is notified to the ethics committee. The information relating to the auxiliary clinical trial personnel is also submitted to the Agency where the Agency so requests.

Suitability of the trial sites

ARTICLE 36- (1) (Amended: OG-5/6/2025-32921) Clinical trials may be conducted in healthcare institutions and organisations and in research and development centres which possess the standards determined by the Agency and which, at a minimum, have the qualifications laid down in the third paragraph so as to ensure the safety of the trial volunteers and the sound conduct and follow-up of the trial.

(2) Phase I clinical trials and bioavailability and bioequivalence studies are conducted in healthcare institutions and organisations and in research and development centres approved by the Agency, possessing facilities suitable for the provision of emergency medical treatment and standards determined separately for each. (Repealed phrase: OG-5/6/2025-32921) Where, as a result of the inspections carried out by the Agency in those centres and of the assessments to be made, it is understood that the provisions of the relevant legislation are fulfilled, an Activity Permit Document is issued. Exceptions may be created in line with the relevant current international practices for the centres in which Phase I clinical trials foreseeing the inclusion of patient volunteers only are to be conducted.

(3) Taking the Guideline on Good Clinical Practice as the basis, the places where clinical trials are to be conducted must, at a minimum, possess:

a) the personnel and equipment necessary and sufficient according to the nature of the trial;

b) the premises and facilities necessary for the storage and distribution of the product according to the nature of the investigational product;

c) the facilities and equipment to provide appropriate care for the volunteer, including situations that may require emergency medical treatment;

ç) sufficient facilities and equipment to make it possible, where necessary, for the volunteer to be transferred to a more advanced healthcare institution or organisation;

d) sufficient facilities and equipment to be able to retain the information and documents relating to the clinical trial and to the volunteers after the completion of the trial.

Traceability, storage, return and destruction of investigational products

ARTICLE 37- (1) The investigational products and the auxiliary medicinal products for human use to be used in the trial must be tracked, stored, and returned and/or destroyed in accordance with good distribution practices.

(2) It is the obligation of the sponsor to apply, after the manufacture or the import of the investigational product, the procedures and instructions for its storage in accordance with the characteristics of the product, its distribution and its delivery to the trial site and for the

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maintenance of those conditions at the trial site, or to verify their existence at the relevant places; to ensure that the unused products are collected from the trial site and returned, or destroyed in an appropriate manner; and to keep the records of that entire process. In the destruction of investigational products, the provisions laid down in the Waste Management Regulation published in the Official Gazette No. 29314 dated 2/4/2015 and the other relevant provisions of legislation are applied.

(3) The receipt and safekeeping of the investigational products, their distribution in accordance with the written request or the trial protocol, stock control, the actions to be taken for the surplus portion and the keeping of their records are the obligations of the principal investigator at each centre where the trial is conducted. It is essential that the principal investigator appoint a clinical trial pharmacist for these operations. However, in trials where a clinical trial pharmacist cannot be appointed, the principal investigator is obliged to take the necessary measures concerning the work and procedures relating to the products.

Notification of serious breaches

ARTICLE 38- (1) A breach of the provisions of this Regulation and of the approved trial protocol affecting the safety and the rights of the volunteers or the reliability and quality of the data obtained in the clinical trial shall be notified by the sponsor to the ethics committee and to the Agency at the latest within seven days of the breach being noticed.

Other notification obligations relating to volunteer safety

ARTICLE 39- (1) The sponsor shall notify the ethics committee and the Agency of all unexpected events, other than the SUSARs referred to in Article 30, which affect the benefit-risk balance of the clinical trial. This notification shall be made at the earliest opportunity, but at the latest within fifteen days of the date on which the sponsor became aware of the event.

(2) The sponsor shall notify the ethics committee and the Agency of all inspection reports concerning the clinical trial conducted in our country by the competent authorities of other countries, and of the translations of those reports. This notification is made at the latest within thirty days of the date on which the report was communicated to the sponsor.

Urgent safety measures

ARTICLE 40- (1) Without prejudice to the matters specified in the second paragraph of Article 17 and in Part Ten, the sponsor, the principal investigator or an investigator shall, where a new situation arises during the conduct of the trial or in connection with the development of the investigational product that may affect volunteer safety, take the necessary urgent safety measures to protect the volunteers against those hazards.

(2) The principal investigator or the sponsor shall notify the ethics committee and the Agency of the information concerning this new situation and the measures taken, at the latest within seven days of the date on which the measures were taken. Otherwise, the Agency halts the trial.

Investigator's brochure

ARTICLE 41- (1) The sponsor provides the investigator's brochure to the principal investigator and to the investigators.

(2) The investigator's brochure shall be updated as significant new information, including information relating to safety, is obtained.

(3) The sponsor shall review the investigator's brochure at least once a year.

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Recording, processing, management and retention of information

ARTICLE 42- (1) All clinical trial information shall be recorded, processed, handled and retained in such a way that it can be accurately reported, interpreted and verified by the sponsor or the trial team. The confidentiality of the records and the personal data of the volunteers shall be protected in accordance with the legislation in force concerning the protection of personal data.

(2) Appropriate technical and administrative measures shall be taken by the sponsor and the trial team in order to prevent the unauthorised or unlawful access to the clinical trial information and to the personal data, their disclosure, distribution, alteration or destruction, or their accidental loss, in particular in cases where the processing involves transmission over a network.

Clinical trial master file

ARTICLE 43- (1) Trial master files with appropriate content are prepared for the principal investigator and for the sponsor. The relevant file is held by the principal investigator and by the sponsor. The clinical trial master file always contains the essential documents relating to the clinical trial in question, enabling the conduct of the clinical trial and the verification of the quality of the data generated, taking into account all the characteristics of the clinical trial. At the end of the trial, the monitor, after reviewing the files of both the principal investigator and the sponsor and after ensuring that all the required documents are in the appropriate files, performs a close-out.

(2) The clinical trial master file kept by the principal investigator and the file kept by the sponsor may have different contents where the principal investigator and the sponsor have responsibilities of a different nature.

(3) The trial master files must be easily and directly accessible upon request of the ethics committee and of the Agency.

Confidentiality, archiving and transfer of the clinical trial master file and of the trial records

ARTICLE 44- (1) The trial master file and all the records relating to the trial are kept regularly by the sponsor and by the principal investigator, and are retained for a period of at least fourteen years after the termination of the trial at all its centres.

(2) Where the trial is transferred by the sponsor for any reason, the situation is notified to the ethics committee and to the Agency. Where the Agency deems it appropriate, it grants approval for the transfer. In the event of the transfer of ownership of the trial master file, the new owner of the data or documents is responsible for the retention and archiving of all of them.

(3) The information and documents relating to the trial must be archived in accordance with the guideline published by the Agency.

(4) The confidentiality of the documents relating to the trial is essential. These documents are provided only to authorised persons, upon the request of persons or authorities legally authorised.

(5) The sponsor appoints archiving officers within its own organisation and takes measures to ensure that access to the archive remains limited to those persons.

(6) The medium used to archive the clinical trial master file must be such as to ensure that the content remains complete and legible throughout the period referred to in the first paragraph.

(7) Every kind of change made in the content of the clinical trial master file must be traceable.

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PART TWELVE

Import of Investigational Products and Auxiliary Medicinal Products for Human Use

Import of investigational products

ARTICLE 45- (1) It is ensured that the investigational products are manufactured in compliance with the rules laid down in the Regulation on Manufacturing Facilities for Medicinal Products for Human Use and in the Guideline on Good Manufacturing Practice, published in the Official Gazette No. 30217 dated 21/10/2017.

(2) An authorisation is obtained from the Agency for the import of the investigational products to be used in the trials.

(3) In relation to the investigational product, the sponsor fulfils the matters set out below:

a) In the application to be made to the Agency, each batch of the investigational product to be manufactured or imported must have been manufactured under conditions complying with good manufacturing practice standards and in accordance with the product specifications stated in its dossier.

b) The samples of each batch of the products manufactured or imported for the purpose of conducting research, together with the information and documents pertaining to them, are retained for a period of at least fourteen years.

Import of auxiliary medicinal products for human use

ARTICLE 46- (1) An authorisation may be obtained from the Agency, where necessary, for the import of the auxiliary medicinal products for human use to be used in the trials.

Withdrawal of the products used in the trial

ARTICLE 47- (1) In the event of the suspension of the trial, all the products remaining with the principal investigator are immediately withdrawn by the sponsor from the places of distribution. This situation is notified to the ethics committee and to the Agency within fifteen days, together with its documents and in the form of a report.

(2) The withdrawal of the products and the procedures to be carried out and the measures to be taken concerning the withdrawn products are specified in detail in the report notified to the ethics committee and to the Agency.

Labelling of investigational products and auxiliary medicinal products for human use

ARTICLE 48- (1) The labelling, on the outer packaging of the investigational products and auxiliary medicinal products for human use to be used within the scope of the clinical trial or, where there is no outer packaging, on the outermost immediate packaging, is prepared in Turkish and in accordance with the Guideline on Good Manufacturing Practice.

PART THIRTEEN

The Sponsor, the Sponsor's Legal Representative and the Principal Investigator

Sponsor

ARTICLE 49- (1) A clinical trial may have one or more sponsors.

(2) In cases where a clinical trial has more than one sponsor, unless the sponsors decide otherwise by means of a written contract determining the responsibilities falling to them, all the sponsors bear the sponsor responsibilities specified in this Regulation.

(3) A single sponsor selected from among the sponsors must be responsible for the application processes to be made to the Agency.

(4) The principal investigator and the sponsor may be the same person.

The sponsor's legal representative

ARTICLE 50- (1) In cases where the sponsor is not established in Türkiye, the sponsor in question ensures that a natural or legal person established in Türkiye becomes its legal representative.

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(2) This legal representative becomes responsible for ensuring compliance with the obligations of the sponsor under this Regulation, and becomes the addressee of all the communications provided for in this Regulation to be made with the sponsor.

(3) Every kind of communication made with this legal representative is deemed to be communication made with the sponsor.

Transfer and sharing of duties

ARTICLE 51- (1) The sponsor may transfer any or all of its duties by means of a written contract to a person, company, institution or organisation. The said transfer does not remove the sponsor's responsibility, above all with regard to the safety of the volunteers and the reliability and quality of the data generated in the clinical trial. The sponsor and the party to which duties have been transferred are jointly responsible for the consequences of the work and procedures that are the subject of the contract.

(2) The references made in this Regulation to the sponsor are also deemed to be made, where applicable, to the sponsor's legal representative or, to the extent of the duties transferred, to the party to which duties have been transferred in accordance with the first paragraph.

(3) The written contracts specified in the first paragraph and the written contract made between the sponsor and its legal representative are submitted to the ethics committee and to the Agency as part of the trial applications.

(4) Of the making of all applications and notifications to the ethics committee and to the Agency:

a) for sponsors established in Türkiye, the sponsor itself, or a contract research organisation established in Türkiye to which duties have been transferred;

b) for sponsors not established in Türkiye, the sponsor's legal representative, or a contract research organisation established in Türkiye to which duties have been transferred,

is authorised and responsible.

Principal investigator

ARTICLE 52- (1) The principal investigator is responsible for the conduct of the relevant trial at the clinical trial centre in accordance with the requirements of this Regulation, of good clinical practice and of the trial protocol.

(2) The principal investigator shall distribute the duties among the members of the trial team at the clinical trial centre so as to ensure the safety of the volunteers and the reliability and quality of the data generated in the clinical trial.

(3) The principal investigator selects the trial team from among persons possessing qualifications appropriate in terms of training, education and experience.

(4) The principal investigator may include in the trial team investigators possessing the appropriate qualifications from other institutions.

(5) The principal investigator must be present at the trial site for a sufficient amount of time in order to be able to fulfil his/her responsibilities and to follow the trial team.

Responsibility

ARTICLE 53- (1) Every kind of financial responsibility for the trials within the scope of this Regulation belongs to the sponsor and, where present, to its legal representative and to the other parties to which duties have been transferred. (Amended phrase: OG-5/6/2025-32921)

(2) No fee may be requested from the volunteer for every kind of investigational product used in the trial, for all the materials allocated to the use of the products, and for the examinations, tests, analyses and treatments.

(3) It is mandatory to state in the application dossier how the financing of the trial will be provided.

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PART FOURTEEN
Compensation of Damage

Compensation of damage

ARTICLE 54- (1) In order to ensure that the volunteers are secured against damage that may arise from the clinical trial, it is mandatory, except for the volunteers who will participate in low-risk scientific studies, to take out insurance for the volunteers who will participate in the clinical trials, in accordance with the relevant legislation.

(2) The fact that the informed consent form has been obtained from the volunteer participating in the trial does not remove the volunteer's right to compensation for the damage he/she has suffered on account of the trial.

PART FIFTEEN
Powers of the Agency and Inspection

Powers of the Agency and inspection

ARTICLE 55- (1) Pursuant to this Regulation:

a) The Agency inspects, with prior notice or without notice, the trials conducted domestically or abroad, the principal investigators and the investigators, the places where the trials are conducted, the sponsor, the legal representative and the other parties to which duties have been transferred, the facilities where the investigational products are manufactured, the places where they are stored, the laboratories where the analyses relating to the trial are carried out, the ethics committees and all the persons and places relating to the trial, in terms of their compliance with this Regulation and with the other relevant provisions of legislation.

b) The data obtained from the clinical trials authorised by the competent authorities of which the International Council for Harmonisation (ICH) is a founding or standing member, by the Australian medicines authority (TGA) or by the medicines authority of the United Kingdom (MHRA), and the good clinical practice inspections arranged specifically for the trial by those authorities or the trial authorisations, are accepted by the Agency so long as no situation contrary to the legislation of our country is identified. Where the good clinical practice inspection report carried out by the competent authorities of which the International Council for Harmonisation (ICH) is a founding or standing member, by the Australian medicines authority (TGA) or by the medicines authority of the United Kingdom (MHRA) cannot be submitted in respect of the trials authorised by other health authorities outside those and of the data obtained from the trials, good clinical practice inspections are carried out by the Agency in accordance with the relevant guideline requirements.

(2) The inspections in terms of compliance with this Regulation and with the other relevant provisions of legislation are carried out by the inspectors of the Agency. The inspectors must be persons who have received education at licence level, who possess sufficient training and experience in good clinical practice and who are preferably educated in the fields of medicine and pharmacy.

(3) The inspectors, during the inspections they conduct, are authorised to request from the public or private institutions and organisations and the relevant persons which they inspect, unless there is a legal impediment, the files and documents they deem necessary; to examine them; to take, where deemed necessary, copies approved by the competent authorities; to carry out counting and research; to take samples and, where necessary, to seal them; to take products into custody, to collect them or to have them collected; to request every kind of assistance and information from the authorised and relevant persons at every level on these matters; and to carry out the necessary correspondence. The inspectors are obliged to protect the confidentiality of the information they obtain during the inspection.

(4) Physical-space-related changes concerning a Phase I clinical trial centre or bioavailability and bioequivalence centres — such as the relocation of the centre, the inclusion of a new physical space and/or the closure or relocation of an existing space — and organisational/managerial changes must be notified to the Agency as soon as possible, together with their reasons. Whether

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the relevant change requires a new inspection of the centre is notified to the centre at the latest within fifteen days of the application's reaching the Agency. In cases where the change or changes require the re-inspection of the centre, an inspection is planned again for the centre.

(5) Where the Agency identifies at least one of the following, it may cancel the authorisation for the trial and terminate the trial, halt the trial, or request that changes be made to the trial:

a) The safety or health of the volunteers being at risk.

b) The trial not being conducted in accordance with the approved documents.

c) The disappearance of one of the existing conditions at the time authorisation was granted for the trial.

ç) The reliability and quality of the data obtained in the trial adversely affecting the conduct of the trial.

d) The non-fulfilment of the application and notification requirements.

(6) The decision of termination, of halting or of requesting a change given by the Agency is notified, together with its reasons, to the sponsor and to the ethics committee.

(7) In the event that the safety and the health of the volunteers in the trial are endangered, the Agency may directly terminate the trial.

(8) In the event of the halting of the trial, where the reasons for the halt are eliminated within the period determined, the Agency may authorise the recommencement of the trial. In cases where the reasons for the halt are not eliminated within the period determined, where it is understood that their elimination is not possible, or where the health of the volunteers is endangered during that period, the trial may be directly terminated.

(9) Where a change to the trial is requested, in cases where the necessary changes are not made within the period determined or where it is understood that making them is not possible, the trial may be halted or directly terminated.

(10) In situations that do not involve a direct risk for the volunteers, before the measures specified in the fifth paragraph are taken, the views of the sponsor or of the relevant principal investigator on the matter may be sought. In this case, the sponsor or the relevant principal investigator sends its views on the matter to the Agency within fifteen days.

(11) In multicentre trials, the measures specified in the fourth paragraph may also be applied at the level of the trial site.

PART SIXTEEN
Database, Portal and Digitalisation

Clinical trials database

ARTICLE 56- (1) The Agency establishes and operates the Clinical Trials Module in order to receive the applications and notifications relating to the clinical trials within the scope of this Regulation, to archive and analyse electronically the data relating to the trials, and for use in the performance of its duties and powers.

(2) The Clinical Trials Module will identify each clinical trial with a unique trial code. The sponsor will refer to that trial code in all subsequent applications and notifications relating to, or referring to, the clinical trial in question.

(3) The necessary work is carried out by the Agency in order to establish and operate the links connecting the relevant data and documents held in the Clinical Trials Module and in the other databases managed by the Agency.

(4) The sponsor is responsible for keeping all the information relating to the clinical trial up to date in the Clinical Trials Module.

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Clinical trials portal

ARTICLE 57- (1) The Agency establishes and operates the Clinical Trials Portal for the purpose of disclosing, in a transparent manner and with due observance of commercial confidentiality and of the confidentiality of personal data, the information on the trials contained in the Clinical Trials Module and the trial results and, in cases the Agency deems necessary, the Agency's summary assessment reports on the trials.

(2) The statistical information on the numbers of clinical trials for which applications and evaluations have been made to the Agency, and the summary grounds of the rejection decisions given by the Agency on the applications, are published annually, in the form of a report, on the website of the Clinical Trials Portal.

(3) So long as there is no public interest in their publication, the information on the clinical trials for which a rejection decision has been given, which have been cancelled or withdrawn, and the information relating to bioavailability and bioequivalence studies are not published in the database of the Clinical Trials Portal.

(4) The content of the information to be published on the Clinical Trials Portal is announced on the Agency's website.

(5) The necessary work is carried out by the Agency so that all the data published on the Clinical Trials Portal are in an easily searchable format.

Digitalisation practices in clinical trials

ARTICLE 58- (1) Digitalisation practices may be included in the conduct and organisation of clinical trials in order to ensure adaptation to the evolving nature of the technology and informatics infrastructure and to the changes in clinical trial organisation.

(2) The matters relating to clinical trial organisation and to the practices and processes of digitalisation are determined by the guideline to be published by the Agency.

PART SEVENTEEN
Fees

Fees charged by the Agency

ARTICLE 59- (1) In order for the applications published on the Agency's website, for which the requirement to pay an application fee is stated, to be evaluated, the application fee must be paid to the Agency.

(2) The Agency may apply charging for other activities, above all the inspection activities within the scope of this Regulation, provided that this is stated in the price tariff published on its website.

(3) For the fees specified in the first and second paragraphs, a discount may be applied in the charging for non-commercial trials and non-commercial sponsors, or those fees may be waived.

Ethics committee application fee

ARTICLE 60- (1) The ethics committee may determine an application fee in such a way that it does not exceed the application fees determined by the Agency. The application fee determined is paid to the university, the training and research hospital or the provincial health directorate to which the ethics committee is attached.

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PART EIGHTEEN

Structure of the Ethics Committees, their Working Procedures and Principles, and their Duties

Structure of the ethics committees

ARTICLE 61- (1) The ethics committees are established in order to evaluate, from a scientific and ethical standpoint, the natural or legal persons taking part in the clinical trial, the places where the clinical trial is conducted, the information and documents required to be submitted in the clinical trial application dossier and, together with these, the methods and materials to be used in informing the volunteers, for the purpose of protecting the rights, safety and well-being of the volunteers.

(2) The majority of their members must be healthcare professionals educated at doctorate or medical specialty level.

(3) All members must possess a certificate of achievement obtained from the basic good clinical practice training organised or approved by the Agency.

(4) The ethics committee must have at least seven and at most fifteen principal members, and at least as many substitute members as the number of principal members. For each mandatory member specified in the seventeenth and eighteenth paragraphs, it is mandatory to determine at least one substitute member of the same qualification.

(5) The ethics committees are constituted in the form of a Clinical Trials Ethics Committee or a Bioavailability and Bioequivalence Studies Ethics Committee.

(6) The ethics committees may be established within a university, a training and research hospital and a provincial health directorate.

(7) The members of the ethics committees are determined, in universities, by the board of directors; in training and research hospitals, by the chief physician's office; and, for the ethics committees constituted within a provincial health directorate, by the provincial health director.

(8) The proposal for the establishment of the ethics committees is communicated to the Agency, in universities, by the rector; in training and research hospitals, by the chief physician; and in provincial health directorates, by the provincial health director. The relevant proposal is evaluated by the Agency. Where the proposal is found appropriate, the ethics committee is established with the approval of the Agency and commences its activities as of that date of approval.

(9) More than one ethics committee may be established, as required, within the same provincial health directorate, rectorate or chief physician's office, provided that the relevant request is deemed appropriate by the Agency.

(10) For changes to the members and to the secretary of the ethics committee, the procedures specified in the seventh and eighth paragraphs apply. A person whose membership has not been approved by the Agency may not take part in the discussions at the meetings of the ethics committee and may not sign the decisions taken.

(11) The Clinical Trials Ethics Committee is established in order to evaluate, from a scientific and ethical standpoint, the clinical trials and scientific studies of medicinal products for human use within the scope of this Regulation, the post-market studies and the medical device clinical trials within the scope of the Regulation on Clinical Trials of Medical Devices published in the Official Gazette No. 31890 dated 8/7/2022, the clinical trials conducted with stem cells within the scope of Circular No. 2018/10 published by the General Directorate of Health Services on 5/4/2018, and the observational studies conducted with medicinal products for human use. It may not evaluate the trials and studies other than those specified in this paragraph.

(12) The Bioavailability and Bioequivalence Studies Ethics Committee is established in order to evaluate, from a scientific and ethical standpoint, only bioavailability and bioequivalence studies.

(13) In constituting the ethics committee, it is essential that the number of members shows a balanced distribution in terms of specialty, age and gender.

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(14) A member of an ethics committee may not be a member of more than one ethics committee established under this Regulation.

(15) The senior executives of the university, of the training and research hospital and of the provincial health directorate may not take part in the ethics committees.

(16) At least three each of the principal and the substitute members of the ethics committee are determined from outside the institution where the secretariat of the ethics committee is located.

(17) In the clinical trials ethics committee, at a minimum, there are members of the qualifications set out below:

a) (Amended: OG-5/6/2025-32921) one person each, from the internal and the surgical sciences of medicine, who has obtained his/her specialty or completed his/her doctorate and who has participated, as principal investigator or investigator, in at least one international or at least three national clinical trials conducted in accordance with the rules of good clinical practice;

b) a physician or a pharmacist who has completed a doctorate in the field of pharmacology, or a physician who has received medical specialty training in that field;

c) a lawyer;

ç) a person who is not a healthcare professional, who does not work in a health-related institution or organisation and who has no involvement in clinical trials;

d) (Added: OG-5/6/2025-32921) a person who has obtained his/her specialty or completed his/her doctorate in the basic sciences of medicine.

(18) In the bioavailability and bioequivalence ethics committee, at a minimum, there are members of the qualifications set out below:

a) a physician or a pharmacist who has completed a doctorate in the field of pharmacology, or a physician who has received medical specialty training in that field;

b) a person who has completed a doctorate in the field of biostatistics, or a public health specialist who has received medical specialty training, or a person who has completed his/her doctorate in the field of public health;

c) a pharmacist who has completed a doctorate in the field of biopharmaceutics, pharmacokinetics, pharmaceutical biotechnology or pharmaceutical technology;

ç) a pharmacist who has completed a doctorate in the field of pharmaceutical chemistry or analytical chemistry, or a chemist or a chemical engineer who has completed a doctorate in those fields;

d) a lawyer;

e) a person who is not a healthcare professional, who does not work in a health-related institution or organisation and who has no involvement in clinical trials.

(19) In addition to the mandatory members, it is essential that a sufficient number of physicians or dentists who have completed their doctorate or specialty in the relevant field be appointed, depending on the intensity of the trial applications made to the ethics committee.

(20) In order for the work of the ethics committees to be conducted, it is essential that at least one person be appointed, by the university, the training and research hospital or the provincial health directorate within which the ethics committee has been established, as secretary of the ethics committee, solely to perform that duty.

(21) The provision of the premises, secretariat, archive and other equipment indispensable for the conduct of the work of the ethics committee and of the financing for that purpose, and the continuity of these conditions, are ensured by the university, the training and research hospital or the provincial health directorate within which the ethics committee has been established. The application fees referred to in the first paragraph of Article 60 are administered by the university, the training and research hospital or the provincial health directorate within which the ethics committee has been established. The relevant directorate or health facility takes the necessary measures in order to prevent any situation that could influence the independent and impartial work of the members of the ethics committee, depending on the application fees received.

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Working procedures and principles of the ethics committees

ARTICLE 62- (1) The working procedures and principles of the ethics committees are as follows:

a) The ethics committees are independent in evaluating clinical trial applications from a scientific and ethical standpoint and in deciding upon them.

b) The members of the ethics committees are obliged to comply with the principle of confidentiality for every kind of information reaching them and to exercise due care concerning conflict of interest.

c) The members and the secretaries of the ethics committees commence their duties by signing the confidentiality agreement and the conflict of interest undertaking prepared by the Agency. The confidentiality agreement and the conflict of interest undertaking are renewed in January of every year and in cases where there is a change in the declaration given.

ç) A member of the ethics committee who has a connection with the trial under examination or who has a duty in the trial may not take part in the discussions and the voting on that trial at the ethics committee and may not sign the decision of the ethics committee.

d) The members of the ethics committee convene with a two-thirds majority of the total number of members and decide with an absolute majority of the total number of members. In cases where a two-thirds majority cannot be achieved with the principal members, a majority is achieved by inviting the substitute members to the meeting.

e) The members whose presence is mandatory in the composition of the ethics committee must take part in every meeting of the ethics committee and must give an opinion on all the trials. In cases where a mandatory principal member cannot attend, a substitute member possessing the same qualifications should be invited to the meeting and should give an opinion on the trial.

f) The term of office of the members of the ethics committee is two years, and members whose term of office has expired may be re-elected as required. For the re-appointment of the members who will continue in their duties, the procedure specified in the seventh and eighth paragraphs of Article 61 applies.

g) The membership of members who, during their term of membership, fail to attend three consecutive meetings or five non-consecutive meetings without excuse lapses.

ğ) The ethics committees, where necessary, obtain the written opinion of expert persons from the relevant branch or from a subsidiary branch and may invite those persons to the meeting as advisors.

h) In necessary cases, in clinical trial applications made in the field of dentistry, the scientific and ethical suitability of the trial must be assessed by a dentist who is a specialist in the relevant field, and his/her positive opinion must be obtained.

ı) The working methods of the ethics committees are determined by the Agency and published on the Agency's website. The ethics committees conduct their work within the framework of these determined standards.

i) Where the term of office of a principal member whose presence is, at a minimum, mandatory in the composition of the ethics committee expires, or his/her membership lapses, a substitute member possessing the same qualifications and already approved by the Agency is appointed as principal member, and the committee continues its activity. In cases where the requirements specified in the seventeenth and eighteenth paragraphs of Article 61 cannot be met even with substitute members, the ethics committee may not operate and the decisions taken are deemed invalid.

j) The meeting may be cancelled in cases where the required number of members cannot be achieved or there is no meeting agenda.

k) Where the meeting is postponed or cancelled, a new meeting date is determined so that the applications on the agenda are evaluated within the period specified in the legislation.

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Duties and powers of the ethics committees

ARTICLE 63- (1) The duties and powers of the ethics committees are as follows:

a) The applications within the scope of this Regulation are evaluated by the ethics committees constituted in accordance with Article 61. The ethics committees must take into evaluation the applications made in compliance with the matters specified in Article 8.

b) For the purpose of evaluating the matters falling within the scope of this Regulation, a separate board or structure that will perform the functions of an ethics committee may not be created by other institutions or organisations.

c) The ethics committees, in forming an opinion on the trial application, evaluate, at a minimum:

1) the analysis of the expected benefit, harm and risks of the trial;

2) the risk management plan relating to the trial;

3) whether the trial is based on scientific data and on a new hypothesis;

4) in trials to be conducted on humans for the first time, the necessity that the trial first have been carried out in a non-human experimental setting or on a sufficient number of animals;

5) whether, in terms of reaching the objective sought to be attained, the trial has reached the maturity to be conducted on humans on the basis of the scientific data obtained as a result of the experiments conducted in non-human experimental settings or on animals, and whether this necessitates its being conducted also on humans;

6) the trial protocol;

7) the evaluation of the content of the investigator's brochure and whether it has been prepared in a duly manner;

8) the investigational product dossier;

9) the written information given in relation to the trial, the method followed in order to obtain the consents of the volunteers, and the sufficiency of the justification for the trials to be conducted on persons under guardianship, on children, on pregnant, postpartum and breastfeeding women, and on persons in intensive care and unconscious persons;

10) in cases of injury or death, including the permanent health problems likely to arise on account of the trial, the responsibility of the principal investigator, of the investigators and of the sponsor;

11) the provision of compensation in the event of an injury or death that can be attributed to the trial;

12) the arrangements concerning the enrolment of the volunteers in the trial;

13) the suitability of the trial team taking part in the trial according to the nature of the trial.

ç) The ethics committee may, where necessary, monitor during the trial and on site the applications which it has approved. The ethics committee is also responsible for the evaluation of the applications made during the conduct of the trials. As a result of these evaluations it makes, and of the new information and developments arising in connection with the scope of the trial, it reviews the approval it has given to the trial. In cases where a risk that cannot be disregarded arises in the trial, or where the safety, well-being and health of the volunteers are adversely affected, it may request that the measures specified in the fifth paragraph of Article 55 be taken by the Agency.

PART NINETEEN
Clinical Trials Advisory Board

Structure of the Clinical Trials Advisory Board

ARTICLE 64- (1) The Clinical Trials Advisory Board is composed of the Deputy Minister of Health as chair; three persons each, selected by the Agency from the surgical, internal and basic sciences of medicine, who have obtained their specialty or completed their doctorate; one clinical psychologist and one theologian; and the First Legal Adviser of the Agency or a legal adviser to be appointed by it.

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Duties, working procedures and principles of the Clinical Trials Advisory Board

ARTICLE 65- (1) The Clinical Trials Advisory Board performs the following duties:

a) to give opinions from a scientific and technical standpoint on matters on which the ethics committees are in doubt in relation to clinical trials and which are communicated in writing to the Agency alone for the purpose of obtaining an opinion;

b) to give opinions on matters on which the volunteers and the parties to the trial are in doubt in relation to clinical trials and which are communicated in writing to the Agency alone for the purpose of obtaining an opinion;

c) to give opinions to the Ministry to serve as a basis for clinical trial policies;

ç) to evaluate, where necessary, the decisions taken by the clinical trial ethics committees on trial applications.

(2) The working procedures and principles of the Clinical Trials Advisory Board are as follows:

a) The Clinical Trials Advisory Board elects a deputy chair from among its own members at its first meeting.

b) The term of office of the members elected to the Clinical Trials Advisory Board is two years, and members whose term of office has expired may be re-elected.

c) The membership of members who fail to attend three consecutive meetings or five non-consecutive meetings without excuse lapses. In place of the member whose membership has lapsed, a member possessing the same qualifications is elected.

ç) The Clinical Trials Advisory Board convenes with a two-thirds majority of the total number of members and takes decisions with an absolute majority of the total number of members.

d) Where necessary, the Clinical Trials Advisory Board may seek the opinions of the relevant experts or may hear those experts by inviting them.

e) The standard working method principles of the Clinical Trials Advisory Board are prepared by the Agency.

f) The secretariat of the Clinical Trials Advisory Board is conducted by the Agency.

PART TWENTY
Clinical Trials Training

Training

ARTICLE 66- (1) The Agency may organise training, courses or seminars on good clinical practice or on clinical trial subjects for the purpose of training qualified principal investigators or investigators, health personnel and the other persons working in that field, may support the training organised by other public institutions or non-profit associations, or grants organisation approval to institutions or organisations wishing to organise training in accordance with the guideline to be published by the Agency.

(2) The period of validity of the documents given to the participants at the end of the training is four years. However, in the event of a change in the legislation, the period of validity of the document may be shortened by the Agency or additional training may be requested.

PART TWENTY-ONE
Sanctions

Administrative sanctions

ARTICLE 67- (1) In the event of a breach of the provisions relating to clinical trials, where the relevant trial is an international multicentre clinical trial, the part of the trial conducted in Türkiye may be halted or terminated by the Agency. In this case, the relevant authorities are also notified. Where the reasons for the halt are eliminated, the relevant situation is notified to the Agency by the sponsor and, where the Agency deems it appropriate, the trial is continued.

(2) The Agency issues a warning to an ethics committee which does not work in compliance with the ethical principles or which fails to fulfil the Ethics Committee Standard Working Method principles published by the Agency. Where the reason for the warning is not eliminated within the period determined, or where the ethics committee is warned more than twice within a one-year period, the approval given pursuant to the eighth paragraph of Article 61 is cancelled by the

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Agency. The chair of that ethics committee may not become the chair of an ethics committee within the scope of this Regulation again. All the members of that ethics committee, including its chair, may not take part in the ethics committees within the scope of this Regulation for a period of one year; in case of repetition, that period is applied as two years.

(3) The Agency issues a warning to an ethics committee in which deficiencies are identified, as a result of an inspection carried out, with respect to the premises, secretariat, archive and other equipment indispensable for the conduct of the work of the ethics committee. Where the reason for the warning is not eliminated within the period determined, the approval given pursuant to the eighth paragraph of Article 61 is cancelled by the Agency. At the relevant centre, ethics committees within the scope of this Regulation may not be constituted again for a period of six months; in case of repetition, that period is applied as one year.

(4) The provisions of the Turkish Penal Code No. 5237 dated 26/9/2004 and of the other relevant legislation are applied, according to the nature of their acts, to those who act contrary to, and engage in activity contrary to, the provisions laid down in this Regulation.

(5) Where it is determined that the ethics committee has not been active for a period of six months, the approval concerning the establishment of the ethics committee given by the Agency is cancelled. The establishment of an ethics committee at the same place may not be requested for a period of one year.

(6) In the centres where Phase I clinical trials and the clinical or bioanalytical parts of bioavailability and bioequivalence studies are conducted, a period is given to the centres, appropriate to the nature of the deficiencies, in order for the deficiencies identified in the inspections carried out by the Agency to be remedied. Where deficiencies that have not been remedied remain at the end of the period given, the activity permit document may be suspended or cancelled. As a result of the examination to be conducted upon the request of the centres for a determination that their deficiencies or non-conformities have been remedied, where it is understood that those deficiencies or non-conformities have been remedied, the centre is permitted to resume its activity.

(7) The activity permit documents of Phase I clinical trial and bioavailability and bioequivalence centres determined by the Agency to be operating contrary to the legislative provisions relating to clinical trials may be suspended partly or entirely, or cancelled.

(8) In the event of the cancellation of the activity permit document, the Phase I clinical trial centre or the bioavailability and bioequivalence centre must send its activity permit document to the Agency within five working days following the date on which the said decision was officially notified to it.

(9) Objections to the decision to suspend or to cancel the activity permit document are made to the Agency within sixty days following the notification of the said decision to the centre.

Prohibitions

ARTICLE 68- (1) It is prohibited to conduct the trials falling within the scope of this Regulation in a manner contrary to this Regulation or to the procedures and principles determined in the other relevant legislation.

PART TWENTY-TWO
Miscellaneous and Final Provisions

Guidelines

ARTICLE 69- (1) Guiding and explanatory guidelines for the implementation of this Regulation are published by the Agency.

(2) In cases where there are no guidelines published by the Agency for the implementation of this Regulation, the Agency may accept, provided that it announces this on its official website, the guidelines published by the official health authorities of other countries or by international organisations.

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Cases where there is no provision

ARTICLE 70- (1) In cases where this Regulation contains no provision, the Convention for the Protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine, the Medical Deontology Regulation put into effect by Council of Ministers Decision No. 4/12578 dated 13/1/1960, the provisions specified in the Patient Rights Regulation published in the Official Gazette No. 23420 dated 1/8/1998 concerning the rights of the volunteers participating in the trial, and the other relevant provisions of legislation are applied.

Alignment with the legislation of the European Union

ARTICLE 71- (1) This Regulation has been prepared within the framework of alignment with the legislation of the European Union, taking into consideration the Regulation (EU) No 536/2014 of the European Parliament and of the Council of 16 April 2014 on clinical trials on medicinal products for human use and the Commission Directive 2005/28/EC of 8 April 2005 laying down principles and detailed guidelines for good clinical practice as regards investigational medicinal products for human use, as well as the requirements for authorisation of the manufacturing or importation of such products.

Regulation repealed

ARTICLE 72- (1) The Regulation on Clinical Trials on Medicinal Products and Biological Products published in the Official Gazette No. 28617 dated 13/4/2013 has been repealed.

(2) References to the Regulation on Clinical Trials on Medicinal Products and Biological Products repealed by the first paragraph are deemed to be references made to this Regulation.

Transitional provision

PROVISIONAL ARTICLE 1- (Amended: OG-29/12/2023-32414)

(1) The Phase I centres and the bioavailability and bioequivalence centres for which a certificate of conformity was issued before 27/5/2023 are required to apply to the Agency as of 1/1/2024 in order to make their permit documents compliant with this Regulation.

(2) The clinical trial ethics committees and the bioavailability and bioequivalence ethics committees established under the Regulation on Clinical Trials on Medicinal Products and Biological Products repealed by Article 72 are required to re-arrange their ethics committee member structures in compliance with the requirements of this Regulation and to apply to the Agency by 1/1/2024. The ethics committees that do not apply may continue their activities with their existing ethics committee structures until 1/1/2024.

Entry into force

ARTICLE 73- (1) This Regulation;

a) subparagraph (b) of the first paragraph of its Article 55, on 1/1/2025,

b) its other provisions, on the date of its publication,

enters into force.

Execution

ARTICLE 74- (1) The provisions of this Regulation are executed by the President of the Turkish Medicines and Medical Devices Agency.

Official Gazette in which the Regulation was published

Date	Issue No
27/5/2023	32203

Unofficial English translation for information purposes only. In the event of any discrepancy, the Turkish original text (mevzuat.gov.tr) shall prevail.

Official Gazettes in which the amending Regulations were published

No	Date	Issue No
1.	29/12/2023	32414
2.	5/6/2025	32921

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