Söğütözü Mahallesi, 2176.Sokak No:5 06520

PRINCIPLES OF THE STANDARD OPERATING METHOD OF ETHICS COMMITTEES FOR CLINICAL TRIALS AND BIOAVAILABILITY/BIOEQUIVALENCE STUDIES

Çankaya/ANKARA Telephone No: (0 312) 218 30 00 Fax No: (0 312) 218 34 60 E-mail: halkla.iliskiler@titck.gov.tr Website: https://www.titck.gov.tr Kep Address: titck@hs01.kep.tr

PRINCIPLES OF THE STANDARD OPERATING METHOD OF ETHICS COMMITTEES FOR CLINICAL TRIALS AND BIOAVAILABILITY/BIOEQUIVALENCE STUDIES KAD-KLVZ-18

Initial Version Effective Date 05.09.2011 1st Revision Effective Date 06.12.2011 2nd Revision Effective Date 17.04.2013 3rd Revision Effective Date 03.06.2013 4th Revision Effective Date 06.08.2014 5th Revision Effective Date 13.11.2015 6th Revision Effective Date 14.05.2020 7th Revision Effective Date 22.03.2024 8th Revision Effective Date 23.01.2026

1. PURPOSE This document has been prepared for the purpose of determining the standard operating method principles of ethics committees for clinical trials and bioavailability/bioequivalence studies, and of providing complementary guidance and support in accordance with the current Declaration of Helsinki, the relevant legislation, and the principles of good clinical practice. 2. SCOPE It covers the ethics committees whose establishment has been approved by the Turkish Medicines and Medical Devices Agency (TİTCK) in accordance with the Regulation on Clinical Trials on Human Medicinal Products, which entered into force upon its publication in the Official Gazette No. 32203 dated 27 May 2023. 3. LEGAL BASIS It has been prepared on the basis of Article 23 of the Declaration of Helsinki, Article 10 of Annex to Law No. 3359 on the Basic Health Services dated 07.05.1987, and Chapter 18 of the Regulation on Clinical Trials on Human Medicinal Products, which entered into force upon its publication in the Official Gazette No. 32203 dated 27 May 2023. 4. DEFINITIONS 4.1. As used in this guideline; 4.1.1. Healthcare Professional: Physicians, dentists, pharmacists, nurses, midwives and opticians, as well as other professionals defined in Article 13 of the Annex to Law No. 1219 on the Practice of Medicine and its Branches dated 11/4/1928, 4.1.2. Institution: The university/training and research hospital/provincial health directorate within which the ethics committee is established, 4.1.3. TİTCK: The Turkish Medicines and Medical Devices Agency, shall be understood. 4.2. In this document, the term "ethics committee" refers to the "Ethics Committee for Clinical Trials" and the "Ethics Committee for Bioavailability/Bioequivalence Studies", and the term "trial" refers to both "trials" and "studies". 4.3. The definitions specified in the Good Clinical Practice Guideline and the relevant legislation shall apply. 5. METHOD TO BE FOLLOWED IN THE ESTABLISHMENT OF ETHICS COMMITTEES 5.1. Ethics committees shall be constituted in accordance with the relevant legislation and good clinical practice in order to ensure that applications are examined in an ethical and scientifically impartial and independent manner, free from all prejudice and influence. 5.2. The members of ethics committees are determined: in universities, by the board constituted by the board of trustees; in training and research hospitals, by the board constituted by the chief physician and all chief physician deputies; in city hospitals, by the board constituted by the coordinator chief physician, all coordinator chief physician deputies and all hospital chief physicians; and in provincial health directorates, by the provincial health director. 5.3. The establishment proposal of ethics committees is submitted to TİTCK by the rector in universities, by the chief physician in training and research hospitals, and by the provincial health director in provincial health directorates. The relevant proposal is evaluated by TİTCK. If the proposal is found appropriate, the ethics committee is established with TİTCK approval and commences its activities as of the date of such approval. 5.4. More than one ethics committee may be established within

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

the same provincial health directorate, rectorate or chief physician's office, as needed and provided that the relevant request is deemed appropriate by TİTCK. 5.5. The application to be made for the establishment of an ethics committee shall be carried out in accordance with the information and documents regarding the application, published on the website of TİTCK. The documents to be submitted at minimum in the application are the following: 5.5.1. Cover letter,

5.5.2. The multi-signed board resolution obtained for the purpose of designating the ethics committee members (the board of directors at universities, the board formed by the chief physician and all chief physician deputies at training and research hospitals, the board formed by the coordinator chief physician, all coordinator chief physician deputies and all hospital chief physicians at city hospitals), 5.5.3. The member list prepared in accordance with the ethics committee member list format published on the TİTCK website, 5.5.4. Signed and current curriculum vitae documents of the ethics committee members and the personnel serving in the ethics committee secretariat, prepared in accordance with the format published on the TİTCK website, 5.5.5. Copies of diplomas of the ethics committee members and the personnel serving in the ethics committee secretariat (bachelor's degree diploma, specialty or doctoral certificate, if any), 5.5.6. Signed confidentiality agreements and conflict of interest declarations of the ethics committee members and the personnel serving in the ethics committee secretariat, prepared in accordance with the format published on the TİTCK website, 5.5.7. Copies of basic good clinical practice certificates of success, obtained within the last four years from a training organized or approved by TİTCK, of the ethics committee members, 5.5.8. The Ethics Committee Premises and Secretariat Inspection Form, approved by the provincial health directorate personnel who have been granted the authority to inspect ethics committee premises and secretariat as a result of training provided by TİTCK, 5.5.9. A sketch showing the layout plan indicating the sections of the premises where the ethics committee is located, such as archive, file acceptance area, meeting hall, and secretariat service, approved by the provincial health directorate personnel who have been granted the authority to inspect ethics committee premises and secretariat as a result of training provided by TİTCK, 5.6. TİTCK accepts applications of the ethics committee only electronically and conducts all correspondence with ethics committees exclusively in the electronic environment. Otherwise, the application is returned to the applicant without being evaluated by TİTCK. The originals of the documents shall be kept in the ethics committee archive for fourteen years to be submitted upon request by TİTCK. 5.7. Applications of the ethics committee may only be accepted through alternative application methods in cases of force majeure, necessity, or circumstances deemed necessary by TİTCK. 5.8. In all applications made to TİTCK, the ethics committee member list shall be submitted in Excel format as an attachment to the application, and all other documents shall be submitted in searchable PDF format. 5.9. The majority of the members must be healthcare professionals who have completed doctoral education or obtained a medical specialty. 5.10. 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, it is obligatory to designate at least one substitute member of the same qualification. Members other than the mandatory members may be selected from persons with different fields of specialty. 5.11. Principal and substitute members of the ethics committee must, before joining the ethics committee, have received and successfully completed basic training on good clinical practice and clinical trials. Certificates of success must be obtained from a training organized or approved by TİTCK in accordance with the requirements of the Regulation and must be renewed every four years. However, in the event of a legislative amendment, TİTCK may shorten the validity period of the certificate or require additional training to be received. 5.12. When establishing an ethics committee, it is essential that the members demonstrate a balanced distribution in terms of specialty, age, and gender. 5.13. An ethics committee member may not serve as a principal or substitute member in more than one ethics committee established within the scope of the Regulation on Clinical Trials on Human Medicinal Products. This situation does not prevent such person from serving in ethics committees with different structures established

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

outside the scope of the Regulation on Clinical Trials on Human Medicinal Products.

5.14. At least three of the principal members and at least three of the substitute members of the ethics committee must be from outside the university/training and research hospital/provincial health directorate within which the ethics committee is established. 5.15. Senior executives of universities, training and research hospitals, and provincial health directorates (the rector and deputies, the dean and deputy deans of the faculty of medicine and the faculty of dentistry, the chief physician and deputies, the provincial health director and the presidents reporting to the provincial health director) may not serve in ethics committees. 5.16. In the member structure of the ethics committee, the number of substitute members may be greater than the number of principal members. 5.17. An ethics committee member may not be an owner, shareholder, or employee of any pharmaceutical or medical device company. 5.18. The ethics committees for clinical trials shall include, as a minimum, members with the following qualifications: 5.18.1. A person who has obtained a specialty in the internal sciences of medicine or completed a doctorate, and who has participated as a coordinating investigator or investigator in at least one international or at least three national clinical trials conducted in accordance with good clinical practice rules, 5.18.2. A person who has obtained a specialty in the surgical sciences of medicine and who has participated as a coordinating investigator or investigator in at least one international or at least three national clinical trials conducted in accordance with good clinical practice rules, 5.18.3. A person who has obtained a specialty in the basic sciences of medicine or completed a doctorate, 5.18.4. A medical doctor or pharmacist with a doctorate in the field of pharmacology, or a medical doctor who has completed medical specialty training in this field, 5.18.5. A legal professional, 5.18.6. A person who is not a healthcare professional, does not work in a health-related institution or organization, and has no involvement in clinical trials. 5.18.6.1. The member who is not a healthcare professional is expected to represent the general view of society with respect to clinical trials, and it is essential that the educational level of the relevant member be determined accordingly. It is preferable that the relevant member be selected, where possible, from among persons without postgraduate education or an academic background. 5.18.6.2. A health-related institution or organization shall be regarded as places providing healthcare services, such as hospitals and healthcare centers. Requests for the appointment as a non-healthcare-professional member of persons working in organizations that do not provide healthcare services, such as associations, are taken into evaluation by TİTCK. 5.18.6.3. Considering the undergraduate education received by certain professional groups such as veterinary medicine, requesting such persons as non-healthcare-professional members would not be appropriate, as they cannot fully represent the general view of society with respect to clinical trials. 5.19. In order to demonstrate that the member possesses the qualification specified in 5.18.1 and 5.18.2, the Ministry codes of the trials in which the member served shall be indicated on the curriculum vitae form and the member list, or where the Ministry code cannot be indicated, the trial protocol code shall be indicated. 5.20. The ethics committees for bioavailability/bioequivalence studies shall include, as a minimum, members with the following qualifications: 5.20.1. A medical doctor or pharmacist with a doctorate in the field of pharmacology, or a medical doctor who has completed medical specialty training in this field, 5.20.2. A person with a doctorate in the field of biostatistics, or a public health specialist who has completed medical specialty training, or a person who has completed a doctorate in the field of public health, 5.20.3. A pharmacist with a doctorate in the field of biopharmaceutics, pharmacokinetics, pharmaceutical biotechnology, or pharmaceutical technology, 5.20.4. A pharmacist with a doctorate in the field of pharmaceutical chemistry or analytical chemistry, or a chemist or chemical engineer with a doctorate in these fields, 5.20.5. A legal professional.

5.20.6. A person who is not a healthcare professional, does not work in a health-related institution or organization, and has no involvement in clinical trials. 5.21. In addition to the mandatory members, it is essential that a sufficient number of physicians or dentists who have completed their doctorate or specialty training in the relevant field be appointed, depending on

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

the volume of trial applications submitted to the ethics committee. 5.22. Establishment approval is granted by TİTCK to ethics committees that meet the requirements regarding the member structure of the ethics committee set forth above, and the ethics committee may continue its activities as long as it satisfies the specified requirements. 6. CONDITIONS FOR THE APPOINTMENT OF ETHICS COMMITTEE MEMBERS AND MATTERS TO BE COMPLIED WITH 6.1. Members are appointed, in universities, upon the proposal of the rector; in training and research hospitals, upon the proposal of the chief physician; and in provincial health directorates, upon the proposal of the provincial health director, with the approval of TİTCK, and assume office as of the date of approval. 6.2. The term of office of ethics committee members is two years, and members whose term has expired may be reappointed. However, just as the involvement of experienced members who have served on ethics committees is important, the inclusion of new members who will bring new ideas and approaches in the member structure will also make a significant contribution to the application evaluation process. This should also be taken into consideration in cases of member changes. 6.3. Ethics committee members are determined, in universities, by the board of trustees; in training and research hospitals, by the board formed by the chief physician and all deputy chief physicians; in city hospitals, by the board formed by the coordinator chief physician, all deputy coordinator chief physicians, and all hospital chief physicians; and in provincial health directorates, by the provincial health director. 6.4. The selection of ethics committee members shall be carried out impartially, in a manner that does not compromise the independence of the ethics committee. 6.5. Requests for the appointment of a new member to the ethics committee shall be made in accordance with the provisions above (Articles 6.1, 6.2, 6.3, and 6.4). The membership request is submitted to TİTCK. The person for whom a membership request has been submitted may not attend meetings, and their name may not be included in decision forms, until their membership is approved. 6.6. Requests for the reappointment of ethics committee members whose two-year term of office has expired shall be made in accordance with the provisions above (Articles 6.1, 6.2, 6.3, and 6.4). Requests for the reappointment of ethics committee members must be submitted no later than 15 business days prior to the date on which the member's term of office expires. Applications submitted earlier than 15 business days are returned to the applicant without being evaluated by TİTCK. However, where requests for the reappointment of ethics committee members are submitted after the date on which the member's term of office has expired, the decisions taken at the meetings attended by that member shall be deemed invalid. 6.6.1. Where no application is made to TİTCK for the extension of the member's term of office within the specified period, the member's membership lapses; the member may not attend meetings and may not sign decisions. If the person in question is a mandatory member, the decisions taken by the ethics committee shall be deemed invalid. 6.7. The term of office of an ethics committee member ends only in the following circumstances: 6.7.1. Completion of the term of office, 6.7.2. Written statement of resignation, 6.7.3. Determination and/or declaration that the member will be unable to attend four consecutive meetings due to excuses such as an assignment abroad or a health problem, 6.7.4. Expiration of the validity period of the member's training certificate, 6.7.5. Failure to attend three consecutive meetings or five non-consecutive meetings without excuse during the term of membership, 6.7.6. Establishment of a violation of ethical rules. 6.8. In cases where the membership of an ethics committee member has ended in accordance with Article 6.7 or where it has been determined to have ended, notification shall be made to TİTCK by the rectorate, chief physician's office, or provincial health directorate, together with the justification and relevant documents, within at most five business days. The relevant documents must clearly indicate the date on which the membership ended.

6.9. Where the membership of a principal member who is mandatory in the ethics committee member structure ends, a substitute member who possesses the same qualifications and has already been approved by TİTCK shall be appointed as a principal member, and the ethics committee continues its activities without interruption. The information that the substitute member has been appointed as a principal member shall be notified to TİTCK within five business

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

days. A new substitute member shall be designated in place of the substitute member appointed as a principal member and submitted for the approval of TİTCK within 22 business days. Otherwise, the ethics committee may not continue its activities, and in the event the ethics committee holds a meeting, the decisions taken shall be deemed invalid. 6.10. Where the memberships of both the principal and the substitute member with the same qualifications, among the mandatory members of the ethics committee, end at the same time, and the member structure fails to meet the requirements of the Guideline, the ethics committee may not operate. This situation must be notified to TİTCK within five business days. In order to continue its activities, a member structure compliant with the legislative requirements must be established and the approval of TİTCK must be obtained. 6.11. Where the membership of a principal member who does not hold mandatory member status in the ethics committee member structure ends: 6.11.1. Where the minimum number of principal members is met, the appointment of a substitute member as a principal member is not mandatory. 6.11.2. Where the minimum number of principal members is not sufficient, one of the substitute members shall be appointed as a principal member, and the ethics committee continues its activities without interruption. The information that the substitute member has been appointed as a principal member shall be notified to TİTCK within five business days. Where there are fewer substitute members than the minimum number of principal members, a new substitute member shall be designated in place of the substitute member appointed as a principal member and submitted for the approval of TİTCK within 22 business days. 6.12. Ethics committees may request the appointment of a person who is not a substitute member as a principal member in the event a principal member's term of office ends. The relevant request is made in accordance with Article 6.1. 6.13. Where the membership of a substitute member in the ethics committee member structure ends: 6.13.1. If the member whose term has ended is one of the mandatory substitute members and there is no other member with the same qualifications in the current substitute member structure, a new substitute member shall be designated in their place, and this appointment shall be submitted for the approval of TİTCK within 22 business days. 6.13.2. If the member whose term has ended is one of the mandatory substitute members but there is another member with the same qualifications in the substitute member structure, and, as a result of the end of the membership, the requirement of having at least as many substitute members as principal members is met, the Agency shall evaluate whether a new member will be appointed. 6.13.3. Where, as a result of the end of membership of a principal member who does not hold mandatory member status in the ethics committee member structure, the substitute member structure fails to satisfy the requirement of having at least as many substitute members as principal members, a new substitute member shall be designated in their place, and this appointment shall be submitted for the approval of TİTCK within 22 business days. However, where the substitute member structure satisfies the requirement of having at least as many substitute members as principal members, the Agency shall decide whether a new substitute member will be appointed. 6.14. Ethics committee members must act in accordance with the conflict of interest policy set out in Section 7. 6.15. Ethics committee members are obligated to observe the principle of confidentiality with respect to all information received by them, and assume their duties by signing the confidentiality agreement and conflict of interest declaration document published on the TİTCK website. The said documents shall be renewed every year in January and in the event of any change in the declaration made, and submitted to TİTCK within at most five business days. 6.16. An ethics committee member may not be the owner, shareholder, or employee of any pharmaceutical or medical device company; if this is the case, the ethics committee membership must be terminated. This situation must be notified to TİTCK within at most five business days.

6.17. Ethics committee members shall follow the current legislation concerning clinical trials. 6.18. The training records of ethics committee members concerning clinical trials shall be kept in the ethics committee archive. 7. CONFLICT OF INTEREST 7.1. A conflict of interest exists where ethics committee members possess any kind of benefit provided to themselves, their relatives,

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

their friends, or persons or organizations with which they have relationships, financial or other obligations related to them, and similar personal interests, which affect, or appear to affect, the performance of their duties in an impartial and objective manner. 7.2. Situations that may lead ethics committee members into a conflict concerning the decision to be taken, that may compromise their objectivity, or that may provide an advantage based on unfair competition in favor of any person or organization shall be assessed within the scope of conflict of interest. 7.3. The main matters that may give rise to a conflict of interest include, but are not limited to, the ethics committee member's: 7.3.1. Serving as coordinator, principal investigator, investigator, auxiliary clinical trial personnel, independent data monitoring committee member, or in any other position in the trial under evaluation, 7.3.2. Providing consultancy services to the sponsor company, 7.3.3. Having kinship by blood or affinity up to the second degree with any person connected to the trial under evaluation, 7.3.4. Being in any material or immaterial situation that may affect his/her independent decision-making. 7.4. Before the ethics committee meeting commences, the members shall be questioned by the ethics committee chairperson regarding conflicts of interest concerning the trials to be evaluated at the meeting. 7.5. In the event of a conflict of interest concerning a trial, the ethics committee member is obliged to declare this situation. This declaration may be made orally before the trial is evaluated at the meeting, or in writing addressed to the ethics committee chairperson. 7.6. In cases where a conflict of interest is declared by an ethics committee member, the member concerned may not participate in the discussions and voting of the ethics committee regarding the trial and may not sign the ethics committee decision. Where the ethics committee deems necessary, information regarding the trial may be requested from the member concerned. 7.6.1. Where the member with a conflict of interest declaration is one of the principal members required to be present in the ethics committee member structure, a substitute member with the same qualifications shall be invited to the relevant meeting. The substitute member participates in the discussions and voting of the ethics committee regarding the trial in question. 7.6.2. In cases where both the principal member and the substitute member have a conflict of interest declaration concerning the relevant trial and there is no other member with the same qualifications among the ethics committee members, the trial in question shall be evaluated by a different ethics committee in accordance with the provisions of the Regulation. 7.7. The signature of the ethics committee member on the decision indicates the absence of a conflict of interest. 7.8. The ethics committee secretary shall also act with due sensitivity regarding the matter of conflict of interest. 7.9. In cases where advisory opinions are obtained regarding trials, the advisor's conflict of interest shall be questioned before the opinion is obtained. Another advisor shall be appointed in place of an advisor who declares a conflict of interest. Advisors are also required to sign the confidentiality agreement and the conflict of interest undertaking published on the TİTCK website, and these shall be archived for submission upon request by TİTCK. 8. ETHICS COMMITTEE SECRETARIAT 8.1. It is essential that at least one person be assigned as the ethics committee secretary solely to perform these and similar duties, including receiving applications made to the ethics committee, informing the applicant, archiving documents, conducting necessary correspondence, and organizing meetings.

8.2. Depending on the intensity of ethics committee activities, the assignment of more than one ethics committee secretary may be requested by the ethics committee chairperson. 8.3. Ethics committee secretaries are appointed upon the proposal of the rector at universities, the chief physician at training and research hospitals, and the provincial health director at provincial health directorates, and with the approval of TİTCK, and assume duty as of the date of approval. 8.4. After ethics committees commence their activities upon application made as set out in Section 5.3, they conduct their correspondence, except for procedures concerning membership and secretariat changes, directly with TİTCK or with the sponsor, the sponsor's legal representative, or the contract research organization, through their own secretariat and with the signature of the ethics committee chairperson. 8.5. Ethics committee secretaries are obliged to comply with the principle of confidentiality for all kinds of information reaching them, and commence their duty by signing

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

the confidentiality agreement and the conflict of interest undertaking published on the TİTCK website. Every year in January, and in the event of any change in the declaration made, these documents shall be renewed and submitted to TİTCK within at most five business days. 8.6. The ethics committee chairperson shall explain the duties to the ethics committee secretary and shall provide information on all affairs and procedures to be carried out concerning the ethics committee. 8.7. The ethics committee secretariat area shall consist of an archive, a file acceptance area, a meeting hall, and sections where secretariat services are conducted. The ethics committee archive area shall be allocated to the ethics committee in such a way that access is provided only by ethics committee members, the ethics committee secretary, and authorized persons specified in the relevant legislation; the necessary measures shall be taken to prevent access by unauthorized persons, and the responsibility for any adverse situations that may arise lies with the ethics committee. Other areas should preferably be allocated solely to the ethics committee. 8.8. The provision and continuity of the premises, secretariat, archive, and other equipment essential for the conduct of ethics committee activities, as well as the financing in this regard, shall be ensured by the institution within which the ethics committee is established. In this context, it is essential to provide: 8.8.1. A secretariat and file acceptance area for performing administrative procedures, and an archive area for the safe and confidential storage of documents belonging to the ethics committee; 8.8.2. A suitable area where ethics committee meetings are to be held and the means members need to communicate at meetings; 8.8.3. Computers, stationery, telephones, photocopiers, shredders, and similar equipment. 8.9. It is essential to provide a sufficient number of support personnel, in addition to the ethics committee secretary, to enable the fulfillment of technical and administrative responsibilities. 8.10. Application fees collected from applications made to the ethics committee shall be administered by the university, training and research hospital, or provincial health directorate within which the ethics committee is established. The relevant directorate or health facility takes the necessary measures to prevent any situation that may affect the independent and impartial work of ethics committee members depending on the application fees collected. 8.11. On the computers used in the ethics committee secretariat area, encryption procedures shall be carried out, the necessary measures shall be taken, and antivirus programs shall be used for the purpose of protecting the confidentiality of applications. 8.12. The ethics committee secretary ensures the publication of the contact details of the ethics committee secretariat, the monthly meeting calendar of the ethics committee, the current application forms, and the current application fees on the ethics committee's own website, if available, or otherwise on the website of the institution to which the ethics committee secretariat is affiliated. 9. PROCEDURES AND PRINCIPLES OF ETHICS COMMITTEE OPERATIONS 9.1. The ethics committee shall follow the Convention on Human Rights and Biomedicine, the current Declaration of Helsinki, good clinical practice standards, and the relevant legislation.

They shall comply with the working procedure principles in order to ensure that trials are examined independently from an ethical and scientific perspective within the periods specified in the legislation. 9.2. Ethics committees are independent in evaluating and deciding on clinical trial applications from a scientific and ethical perspective. In this respect, no organ, authority, office or person may give orders or instructions to ethics committees. 9.3. Ethics committees are accountable to TİTCK with regard to the implementation of the ethics committee working procedures and principles. 9.4. The Clinical Trials Ethics Committee, 9.4.1. Clinical trials and scientific studies of medicinal products for human use within the scope of the Regulation on Clinical Trials of Medicinal Products for Human Use; post-market studies and medical device clinical trials within the scope of the Regulation on Medical Device Clinical Trials published in the Official Gazette No. 31890 dated 8/7/2022; performance evaluation studies and post-market performance follow-up studies conducted with in vitro diagnostic medical devices within the scope of the Regulation on Medical Devices for In Vitro Diagnostic Purposes published in the Official Gazette No. 31499 dated 2/6/2021; observational studies conducted with medicinal products for human use; clinical trials of human-derived tissues and cells and products obtained therefrom

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

within the scope of the Regulation on Products Obtained from Human Tissues and Cells and Centers Related to These Products published in the Official Gazette No. 33007 dated 4/9/2025, and, if requested by the Agency, clinical practices, 9.4.2. Studies concerning treatment methods other than research related to traditional and complementary medicine practices pursuant to Article 10 of Additional Article of the Fundamental Law on Health Services No. 3359, and scientific studies concerning the use of health claims on foods and food supplements for the purpose of use in foods for special medical purposes, shall evaluate. 9.5. Clinical trials ethics committees may not evaluate research and studies outside the scope of Articles 9.4.1 and 9.4.2. 9.6. The bioavailability and bioequivalence studies ethics committee evaluates only bioavailability and bioequivalence studies from a scientific and ethical perspective. 9.7. The ethics committee bears the responsibility to act in accordance with the requirements of the relevant legislation and society. 9.7.1. The institution within which the ethics committee is established shall ensure the conditions necessary for the independence defined in 9.2 and the continuity of these conditions. 9.8. In order to ensure that the process of evaluating and conducting trials is accurate and compliant with ethical principles and the relevant legislation, ethics committees shall cooperate closely with TİTCK. 9.9. In case any doubt arises on any matter related to ethics committee activities, an application shall be made to TİTCK in writing or via e-mail through the ethics committee secretariat. 9.10. Ethics committee members, the ethics committee secretary and, if invited, advisors shall observe the confidentiality of meeting topics. 9.11. The chair, vice chair and member responsible for notifications of the ethics committee may not be appointed by the officials of the institution to which the ethics committee is affiliated. Following the establishment of the ethics committee with the approval of TİTCK, the members shall convene within 12 business days at the latest and elect, by secret ballot among themselves, a chair, vice chair and member responsible for notifications. TİTCK approval is not required for the elected persons to assume their duties. However, the elected persons must be reported to TİTCK within five business days at the latest for registration purposes. 9.12. In the event that the membership of the ethics committee chair, vice chair or member responsible for notifications terminates, or the persons do not wish to carry out the specified duties in accordance with their preferences, the persons who will carry out these duties shall be determined by re-election at the first meeting held. Following the election, the meeting agenda shall continue as TİTCK approval is not required. However, for registration

selected are notified to TİTCK within at most five business days. The ethics committee chairperson, deputy chairperson, or members responsible for notifications commence their duties following their selection.

9.13. The ethics committee convenes with a two-thirds majority of the full number of principal members. Where the quorum for the meeting cannot be achieved with principal members, a quorum is achieved by inviting substitute members to the meeting.

9.13.1. Where the quorums for meetings and decisions, depending on the number of ethics committee members, are not whole numbers, the whole number obtained by rounding the fractional number up shall be accepted as the quorum for meetings and decisions. For example, for an ethics committee with eleven principal members, the quorum for a meeting is eight.

9.14. Meetings may be held face-to-face, online, or in a hybrid manner, whereby members who can attend the meeting remotely attend online and the other members attend face-to-face.

9.14.1. Where meetings are held online or in a hybrid manner, the necessary measures must be taken to ensure confidentiality.

9.15. By the ethics committee secretary, all ethics committee members are contacted two days prior to the meeting date, and their attendance status is queried.

9.16. The excuses of ethics committee members who will not attend the meeting are queried. The status of members who do not attend the meeting is recorded.

9.17. For applications, a rapporteur, preferably from among the members who are healthcare professionals, is selected to evaluate the application documents and to summarize and present the information in the file to the other ethics committee members regarding the

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

application. Care must be taken to ensure that applications are distributed in a balanced manner among the rapporteurs. The assignment of a rapporteur does not remove the obligation of the other ethics committee members to review the application. Rapporteurs are designated by the ethics committee chairperson from among the ethics committee members.

9.17.1. In cases where the rapporteur cannot attend the meeting, they may submit their opinion to the ethics committee in writing.

9.18. Where necessary and when needed, ethics committees obtain the written opinion of experts from the relevant major or minor specialty related to the subject and, where necessary, may invite these persons to the meeting as advisors.

9.19. The advisor must submit their opinion to the ethics committee in writing. The advisor's opinion is indicated in the relevant section of the ethics committee decision form. Written opinions obtained from advisors must be archived for submission upon request by TİTCK.

9.20. In clinical trials to be conducted on children, the ethics committee may not approve such a trial without a positive opinion from a physician specializing in child health and diseases regarding the conduct of the trial on children. Where deemed necessary for these trials, the opinion of a physician or dentist who has obtained a doctorate or specialty in the scientific discipline related to the subject of the trial is obtained, and whether the trial may be approved is evaluated based on the outcome of this opinion. Furthermore, during the conduct of such trials, protocol amendments that may affect the children's continuation in the trial must also be evaluated by the relevant specialist. The ethics committee may not approve an amendment without a positive opinion from the relevant specialist regarding the amendment.

9.20.1. In clinical trials to be conducted on neonates (the first 28 days after birth), a physician specializing in neonatology must have a positive opinion regarding the conduct of the trial on neonates. This opinion is evaluated as the positive opinion of a specialist in child health and diseases.

9.20.2. Regarding the subject of the trial, the positive opinion of a specialist physician who has completed a minor specialty in the field of child health and diseases is evaluated as the positive opinion of a specialist in child health and diseases.

9.20.3. Where there is no specialist in child health and diseases among the principal and substitute members of the ethics committee, or where the ethics committee member who is a specialist in child health and diseases has a conflict of interest in the relevant trial, the ethics committee must obtain an advisor opinion from persons holding the relevant expertise regarding the trial.

9.21. In clinical trial applications conducted in the field of dentistry, where required, the scientific and ethical appropriateness of the trial must be evaluated and a positive opinion must be obtained from a dentist specialized in the relevant field. 9.22. Ethics committees should consider obtaining consultant opinions on the matters set out below, depending on the subject and/or risks of the trial, without being limited thereto. TİTCK (Turkish Medicines and Medical Devices Agency) may request that the ethics committee obtain a consultant opinion depending on the subject of the trial. 9.22.1. In applications for clinical trials conducted on pregnant women, women in the postpartum period, and breastfeeding women, particularly with regard to fetal or infant health, from a physician who has obtained specialization in a field related to the trial, on the clinical, ethical, psychological, and social problems related to the trial; 9.22.2. In medical device clinical trial applications, from persons who have graduated from the engineering and science faculties of universities and who have experience with the medical device to be used for clinical trial purposes; 9.22.3. From a person holding a doctorate in the field of biostatistics, a public health specialist who has completed medical specialty training, or persons who have completed a doctorate in the field of public health, regarding the statistical data of the trial; 9.22.4. From persons who hold a doctorate or specialization in the field of medical ethics or deontology, for the ethical evaluation of the trial. 9.23. Where deemed necessary, ethics committees may also obtain opinions from non-governmental organizations. 9.24. Persons whose opinions are obtained must sign the

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

confidentiality agreement and conflict of interest declaration document published on the TİTCK website before beginning to evaluate the relevant file. The confidentiality agreement and conflict of interest declaration signed by the consultant shall be archived by the ethics committee secretary and submitted to TİTCK upon request by TİTCK. 9.25. The consultant may not vote on the decision taken regarding the trial, may not sign the decision form, and may not continue to attend the meeting for the other matters discussed at the meeting. 9.26. For trials other than those specified in Articles 9.20 and 9.21, the consultant opinion is of an advisory nature but must be taken into consideration in the decisions to be taken by the ethics committee. However, for the trials specified in Articles 9.20 and 9.21, a positive decision by the consultant is required for the ethics committee to approve the trial. Nevertheless, for the trials specified in Articles 9.19 and 9.20, even if the consultant issues a positive decision, the ethics committee may decide to the contrary, together with the necessary scientific explanations. 9.27. Members should allocate time to review and evaluate the working methods of the ethics committee. The chair of the ethics committee should obtain and evaluate the views and suggestions of the members aimed at enhancing the efficiency of the committee. 9.28. Ethics committees may communicate and exchange views with other ethics committees, provided that confidentiality is observed, on matters such as the operations of the ethics committee and the review of trial applications. This communication contributes to achieving similarity and harmonization in the nature of operations and reviews. 9.29. Bioavailability/bioequivalence ethics committees must communicate their opinion (approval/rejection/deficiency) to the applicant within a maximum of seven business days from the date of application, and clinical trials ethics committees must communicate their opinion (approval/rejection/deficiency) to the applicant within a maximum of twelve business days from the date of application. 9.30. For trials deemed by TİTCK, as a result of its evaluation, to be in exceptional circumstances, the clinical trials ethics committee must communicate its opinion (approval/rejection/deficiency) to the applicant within a maximum of seven business days from the date of application. 9.31. For trials to be conducted using products containing genetically modified organisms, cellular therapies, or gene therapy products, and for non-drug clinical

trials, an additional period of thirty business days may be added to the twelve-business-day period specified in Article 9.28. 9.32. All information and documents contained in the application must be evaluated by the ethics committee, and the ethics committee's opinion (approval/rejection/deficiency) must be communicated to the applicant within the review period. 9.33. Where the ethics committee identifies deficiencies as a result of its review, all requested information and documents must be communicated to the applicant in writing in a single submission. The requested information and documents shall be submitted by the applicant to the ethics committee within thirty business days at the latest. Except in cases deemed necessary by TİTCK, force majeure, or compulsory circumstances; if the additional information and documents, or the necessary explanation regarding the inability to submit such information and documents together with the information on the date on which they will be submitted, are not provided to the ethics committee, the application shall be deemed withdrawn and cancelled. 9.34. Where the ethics committee identifies deficiencies again, the process specified in Article 9.32 shall be applied. 9.35. In evaluations relating to applications, where the application is placed on the meeting agenda but cannot be evaluated due to insufficient time, the evaluation may not be postponed to the next meeting in a manner that would exceed the evaluation period. In such cases, a new meeting must be convened in the following days in accordance with the timelines set forth in the legislation. 9.36. Ethics committees are required to submit to TİTCK, in three-month periods: • Copies of their rejection decisions for trials falling within the scope of the relevant legislation that they evaluate for the first time; • The list and summary protocols of observational studies of medicinal products for human use that they have approved; • The activity report prepared in accordance with the sample Clinical Trials Ethics Committee Activity Report/Bioavailability and Bioequivalence Ethics Committee Activity Report published on the TİTCK website. 9.36.1. In applications, the appropriate cover letter sample published on the TİTCK website must be used. 9.36.2. Applications for the

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

submission of the lists and summary protocols relating to observational studies, the activity reports, and the copies of decisions shall be submitted to TİTCK within the first fifteen days of April for the January-February-March period, July for the April-May-June period, October for the July-August-September period, and January of the following year for the October-November-December period. Administrative sanctions shall be imposed, in accordance with the Regulation, on ethics committees that fail to submit the relevant applications. 9.36.3. TİTCK may, where necessary, request from the ethics committees copies of the approval decisions relating to the trials they have evaluated. 10. DUTIES AND AUTHORITY OF ETHICS COMMITTEES The duties and authority of the ethics committee in the trial application approval process are as follows: 10.1. Primarily, the scientific, medical, and ethical appropriateness of the trial shall be evaluated by the ethics committee. This evaluation must be conducted in accordance with the relevant legislation. 10.1.1. A trial is ethically acceptable only if it is based on valid scientific methods. A trial that is not scientifically valid exposes the volunteer to the risk of harm without any possibility of benefit to the volunteers or society. However, a scientifically valid trial may still conflict with the ethical principles of society. For this reason, the ethics committee must evaluate the trial in all respects. 10.2. In forming its opinion during this evaluation, the ethics committee must, at a minimum, consider the following: 10.2.1. The evaluation of the plan/report on the benefit-risk assessment of the trial and, accordingly, the appropriateness of conducting the trial; 10.2.1.1. In an ethically acceptable trial, the measures to be taken to minimize the potential harms and the adverse effects in the event that the potential harm materializes

been determined and the minimization of the risk has been planned accordingly. The risks must be reasonable in relation to the potential benefits of the trial. The nature of the risks may vary depending on the type of trial to be conducted. Ethics committee members must be aware that risks may arise in different dimensions (e.g., physical, social, financial, or psychological) and must conduct an assessment from every aspect. 10.2.1.2. If it is anticipated that the benefits of the clinical trial for the participant (volunteer) will be greater than the expected risks, the trial may be initiated and continued. 10.2.2. If applicable, the appropriateness of conducting the trial in the pediatric group in accordance with the pediatric investigation plan, 10.2.3. The compliance of the trial with the ethical principles accepted in our country and at the international level, 10.2.4. Whether the trial is based on scientific data and a new hypothesis, 10.2.5. The scientific validity of the trial design and the methods to be used in the trial, 10.2.6. In the case of trials to be conducted on humans for the first time, the necessity that the trial has first been carried out in a non-human experimental setting or on a sufficient number of animals, 10.2.7. Whether, in light of the scientific data obtained from experiments conducted in non-human experimental settings or on animals, the trial has reached the maturity to be conducted on humans for the purpose of achieving the intended objective, and whether this necessitates its conduct on humans, 10.2.8. In accordance with the Good Clinical Practice Guideline, the essential documents required for the conduct of the clinical trial and the appropriateness/sufficiency of these documents, 10.2.9. The content of the investigator's brochure and whether it has been prepared in accordance with the required procedures, 10.2.10. The sufficiency of the trial master file, 10.2.11. The written information provided regarding the trial, and the appropriateness/sufficiency of the method followed for the purpose of obtaining informed consent from the participants (volunteers), 10.2.12. The sufficiency of the justification for trials to be conducted on persons deprived of their liberty, children, pregnant women, women who have recently given birth and breastfeeding women, persons in intensive care and unconscious persons, and other such vulnerable persons, 10.2.13. The sufficiency of the measures taken within the scope of the responsibility of the responsible investigator or investigator, or the sponsor, in cases of injury or death, including permanent health problems likely to arise as a result of the trial, 10.2.14. The appropriateness/sufficiency of the insurance and compensation conditions in the event of an injury or death that may be connected to the trial, 10.2.15. The appropriateness of the conditions for the enrollment (recruitment) of participants (volunteers) in the trial, 10.2.16. The appropriateness of the trial team and the trial

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

site involved in the trial, 10.2.16.1. The trial team involved in the trial must possess the education, training, and experience to assume responsibility for the proper conduct of the trial, must meet all qualifications specified in the applicable regulatory requirements, and must provide evidence thereof. 10.2.16.2. Any condition that may give rise to a conflict of interest within the trial team must be assessed. 10.2.17. The sufficiency of the information submitted and its capacity to respond to ethical questions that may arise during the trial, 10.2.18. The appropriateness of the trial protocol/plan, the data collection forms, and the sample size with respect to the objectives of the trial, 10.2.19. The appropriateness of the statistical analysis, the sufficiency of the trial power, and the acceptability of the foreseeable risks and discomforts in view of the expected benefits for the participants (volunteers), 10.2.20. The sufficiency of the medical follow-up of the trial, 10.2.21. That the written and verbal information to be provided to the participants (volunteers) and, where necessary, their legal representatives regarding the trial is sufficient, complete, and comprehensible.

10.2.22. The sufficiency of the measures taken to ensure the confidentiality and protection of the personal information of the participants (volunteers), 10.2.23. Where applicable, the assessment of the payments to be made to the participants (volunteers), 10.2.23.1. Both the amount and the method of the payment made to the participants (volunteers) must be reviewed, and it must be ensured that it will not create coercion or undue influence on the participants (volunteers). Payments made to participants (volunteers) must be proportionate and must not be contingent upon the participant's (volunteer's) completion of the trial. 10.2.23.2. It must be ensured that information regarding the payments made to the participants (volunteers), including the methods, amounts, and schedule of payment, is included in the informed consent form (ICF) and in the other written documents to be provided to the participants (volunteers). The manner in which the payment is to be distributed must be specified. 10.2.24. In trials that will include sensitive and vulnerable populations, the justification for the inclusion of such populations and the sufficiency of that justification, 10.2.25. Other documents that the ethics committee may require in order to fulfill its responsibilities, 10.2.26. The appropriateness/sufficiency of the monitoring method and its frequency. 10.3. In accordance with the Guideline on Clinical Trial Applications Submitted to Ethics Committees, it must be verified that the documents attached to the trial application are appropriate and complete. 10.4. As a result of the assessment made by the ethics committee, where it is concluded that the provision of additional information in the informed consent form (ICF) would make a meaningful contribution to the protection of the rights, safety, and well-being of the participants (volunteers), the ethics committee may request that such additional information be included. 10.5. As a result of the assessment made, the ethics committee: 10.5.1. May approve the application as submitted. 10.5.2. May request information, documents, and actions regarding the application, together with the justification. In this case, all requests are communicated to the applicant in a single notification. 10.5.3. May reject the application, together with the justification. The applicant may reapply, on one occasion only, by making the necessary changes on the matters specified in the decision, or may appeal the decision with justification within 30 working days. Where the requested changes are not implemented or no acceptable justification is submitted in this regard, the ethics committee may reject the trial again. 10.5.4. The duties and powers of the ethics committee during the conduct of the trial are as follows: 10.5.5. The ethics committee reviews and communicates its opinion on applications and notifications for modification/information made during the conduct of trials, from a scientific and ethical perspective, in accordance with the minimum matters specified in 10.2. 10.5.6. As a result of the assessment made: 10.5.7. May deem it appropriate that the modifications be implemented as proposed, 10.5.8. May request information, documents, and actions regarding the application, together with the justification. In this case, all requests are communicated to the applicant in a single notification. 10.5.9. May reject the implementation of the modifications as proposed, together with the justification. 10.6. The ethics committee must review the approval it has granted for the trial as a result of these assessments and of new information and developments arising in

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

connection with the scope of the trial. 10.7. In the event that a non-negligible risk arises in the trial, or where the safety, well-being, and health of the participants (volunteers) are adversely affected, the ethics committee may request that the sponsor take the necessary measures. 10.8. The ethics committee may monitor, on site, any clinical trial it has approved, with or without prior notice. Furthermore, TİTCK (Turkish Medicines and Medical Devices Agency) may request the ethics committee to monitor a clinical trial on site. The ethics committee sends the monitoring report to TİTCK within 12 working days at the latest. These reports are evaluated by TİTCK.

10.9. On-site monitoring is carried out by the chair of the ethics committee or the members designated by the chair of the ethics committee. This monitoring is carried out for the purpose of verifying that the trial is being conducted in accordance with the protocol, that the documents belonging to the volunteers (participants) are duly received and archived, that data entry is performed correctly, and that the necessary measures regarding data storage are taken. In light of the findings obtained as a result of the monitoring, the TİTCK (Turkish Medicines and Medical Devices Agency) may be requested to conduct an inspection of the site. 10.10. The assessment of an ongoing trial is carried out through the progress report, which must be submitted to the ethics committee at least once a year in accordance with the Regulation. The ethics committee may request a report within a shorter period in short-term trials or where it deems necessary. 10.11. For trials in which non-compliance is identified, the ethics committee may request the TİTCK to make modifications, together with the justification, to suspend or to terminate the trial. The duties and powers of the Ethics Committee at the stage of completion of the trial are as follows: 10.12. The completion notification to be made following the early termination or completion of the trial is assessed by the ethics committee. 10.13. In the event of early termination of the trial, the ethics committee assesses the reasons for the termination of the trial as well as the measures for the continuation of the treatment of the volunteers (participants) already enrolled in the trial. 10.14. The notification to be made regarding the summary of the final trial report and the version of this summary prepared in a manner understandable by the volunteers (participants) is assessed by the ethics committee. 10.15. In line with Article 34 of the Declaration of Helsinki, the ethics committee assesses the post-trial accessibility of interventions found to be beneficial to all volunteers (participants) during the trial. 11. DUTIES AND RESPONSIBILITIES OF THE CHAIR OF THE ETHICS COMMITTEE, THE VICE CHAIR, THE MEMBER RESPONSIBLE FOR NOTIFICATIONS, THE SECRETARY, AND THE MEMBERS REQUIRED AT A MINIMUM: 11.1. The chair of the ethics committee shall be selected from among healthcare professionals who have completed their specialization. Previous membership in an ethics committee should be a preferred criterion for the chair of the ethics committee. 11.2. The chair of the ethics committee may delegate part of his/her duties to the vice chair of the ethics committee. 11.3. The duties and responsibilities of the chair of the ethics committee are as follows: 11.3.1. To ensure that the activities of the ethics committee are conducted in compliance with the legislative requirements and the principles of standard operating procedures, 11.3.2. To chair the meetings of the ethics committee, 11.3.3. To ensure that the agenda is followed during the meetings of the ethics committee, 11.3.4. To ensure that the ethics committee operates effectively and regularly, 11.3.5. To ensure the internal and external representation of the ethics committee within and outside the institution, 11.3.6. To ensure the follow-up of the notifications to be made to the TİTCK and the institution, and of the correspondence to be conducted with the TİTCK and the institution, 11.3.7. To ensure that the terms of validity of the duties and training of the members of the ethics committee are tracked by the secretary of the ethics committee and, where necessary, notified, 11.3.8. To ensure the follow-up and organization of the secretariat operations of the ethics committee, 11.3.9. To perform other duties related to the management and functioning of the ethics committee, 11.3.10. To coordinate and direct the activities of the ethics committee, 11.3.11. To identify the needs of the ethics committee and the secretariat premises and request them from the institution, 11.3.12. To notify the TİTCK of requests for changes in the membership of the ethics committee,

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

11.3.13. To ensure that meetings are held on time and that assessment results are communicated to the applicant in due time, 11.3.14. To determine and follow up the training activities related to the duties of the members and secretaries of the ethics committee, and to encourage their participation, 11.3.15. To sign all notifications and correspondence to be made to the TİTCK other than changes in membership, 11.3.16. To ensure that applications are forwarded to the rapporteurs within the required period, 11.3.17. To sign, where necessary, the corrections made in the decisions of the ethics committee, 11.3.18. In cases where, in accordance with the legislation, notification is sufficient, to sign the decision together with the member responsible for notifications, 11.3.19. To approve the meeting dates and schedule, 11.3.20. To follow up on the legal regulations concerning clinical trials, 11.3.21. To take measures to ensure that each member of the ethics committee is able to express his/her opinion freely during the assessment of applications, and to ensure that sufficient and at the same time efficient time is allocated for the discussions on trial applications, 11.3.22. In cases where he/she and the vice chair are unable to attend a meeting, to designate the member who will act as their proxy. 11.4. The duties and responsibilities of the vice chair of the ethics committee are as follows: 11.4.1. To act as proxy for the chair of the ethics committee in his/her absence, 11.4.2. To assist the chair of the ethics committee in chairing the meetings, 11.4.3. To perform the duties delegated by the chair of the ethics committee. 11.5. The duties and responsibilities of the member responsible for notifications are as follows: 11.5.1. To assess applications made in cases where, in accordance with the legislation, notification is sufficient. 11.5.2. To sign the decisions concerning applications made in cases where notification is sufficient. 11.6. The minimum duties and responsibilities of the pharmacologist member are as follows: 11.6.1. To assess the suitability of the trial protocol design, 11.6.2. To assess the scientific and ethical sufficiency and suitability of the preclinical and clinical data contained in the investigator's brochure and the trial product file. 11.7. The minimum duties and responsibilities of the members from the Basic, Surgical, and Internal Medicine disciplines are as follows: 11.7.1. To scientifically and ethically assess the sections of the trial protocol related to their own fields of expertise. 11.8. The minimum duties and responsibilities of the legal professional member are as follows: 11.8.1. To assess the compliance of the application and its content with the relevant international and national legislative provisions, 11.8.2. To assess the arrangements in the application regarding the physical and mental integrity of the volunteers, their confidentiality, and the protection of their relevant data pursuant to Law No. 6698. 11.9. The minimum duties and responsibilities of the member who is not a healthcare professional are as follows: 11.9.1. To voice potential concerns that may arise in the volunteers or in society regarding the trial under assessment, 11.9.2. To express opinions in a manner reflecting the perception of the volunteers or society regarding the trial under assessment, 11.9.3. To review the informed consent form (ICF) and assess its comprehensibility by the volunteers. 11.10. The duties and responsibilities of the secretary of the ethics committee are as follows: 11.10.1. To assess whether the applications made to the ethics committees are complete with respect to the documents that must be submitted depending on the nature of the application,

11.10.2. To return improperly submitted applications to the applicant within three business days, 11.10.3. To include in the meeting agenda applications that are complete with regard to the documents required to be submitted depending on the nature of the application, 11.10.4. To prepare the meeting agenda and have it approved by the chair of the ethics committee, 11.10.5. To communicate the meeting agenda and the application files included in the agenda to the members of the ethics committee, 11.10.6. To determine the dates of meetings to be held on a planned basis at three-month intervals, taking into account the timeframes specified in the legislation, 11.10.7. To set a meeting date outside the planned meetings where necessary, in order to ensure that the application is responded to within the specified timeframes, 11.10.8. To invite the members of the ethics committee to the meeting, 11.10.9. To prepare the decision forms prior to the ethics committee meeting, to attend the ethics committee meetings and record the decisions taken at the meeting on the form, and to check the information specified in the decision

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

form, 11.10.10. Where necessary, to give a "certified true copy" approval on copies of ethics committee decisions, 11.10.11. Where necessary, to contact the relevant person in order to invite the applicant and/or the responsible investigator to the ethics committee meetings, 11.10.12. To ensure that the signatures, attendance statuses and relevant sections on the ethics committee decision form are completed appropriately and completely, 11.10.13. To prepare the environment required for the meetings (preparing the meeting room, obtaining and sharing the meeting link, etc.), 11.10.14. To prepare all application files, including applications for membership changes to be submitted to the TİTCK and applications made regarding cases where notification is sufficient, to ensure that they are duly signed, and to follow up on the responses to the applications, 11.10.15. To track the terms of office and training validity periods of the ethics committee members and to prepare notification applications, 11.10.16. To duly record and archive the applications made to the ethics committee and all documents and correspondence belonging to the ethics committee, 11.10.17. To prepare activity reports, 11.10.18. To ensure the tracking of the timeframes specified in the legislation, 11.10.19. To follow the current legislation and announcements regarding clinical trials published on the TİTCK website and to inform the chair of the ethics committee. 12. APPLICATION TO THE ETHICS COMMITTEE AND THE METHOD OF PROCESSING THE APPLICATION 12.1. In clinical trial ethics committees, application files are accepted up to at most five business days before the meeting; in bioavailability/bioequivalence ethics committees, up to at most three business days before the meeting. 12.2. All applications made in due form are accepted and given a registration number. These applications are taken into process by the ethics committee secretariat for preliminary review. 12.3. In the preliminary review, the secretary of the ethics committee assesses, in line with the Guideline on Clinical Trial Applications Made to Ethics Committees, whether the application is complete with regard to the documents required to be submitted depending on the nature of the application. 12.4. The necessary preliminary review is carried out within three business days from the receipt of the application file by the ethics committee. Files not returned to the applicant within three business days are deemed accepted. 12.5. Applications taken into process are included in the meeting agenda according to the date of application. The registration number and date of the applications taken into process, the research ethics committee code, if any, and the meeting date are notified to the applicant by e-mail.

12.6. Where deficiencies are identified in the preliminary review, the applicant is contacted for the deficiencies to be completed within the specified timeframe or for the application file to be returned. 12.7. Applications that cannot be included in the meeting agenda due to the high number of applications are included in the agenda of the next meeting. Where the date of the planned meeting would exceed the evaluation period for the relevant applications, a new meeting is planned outside the planned meetings. 12.8. Meeting dates shall be planned, taking official holidays into account, in such a way as not to exceed the evaluation period specified in the legislation. 12.9. In applications to be made to the ethics committee, where the ethics committee so requests, the application fee shall be deposited to the address indicated by the institution within which the ethics committee is established, in an amount not exceeding the application fees determined and published on the website by the TİTCK. Ethics committees may not request fees other than the application fees determined and published on the website by the TİTCK. No application fee is requested for specialty theses or academic research. 12.9.1. The fees collected are managed by the university, training and research hospital or provincial health directorate within which the ethics committee is established. The relevant directorate or health facility takes the necessary measures to prevent any situation that may affect the independent and impartial work of the ethics committee members, depending on the application fees collected. 12.10. The application is made by the sponsor or the legal representative of the sponsor, and the ethics committee secretariat conducts all correspondence with the sponsor of the application or the legal representative of the sponsor. 12.11. Ethics committees may establish electronic systems for the purpose of receiving applications for the research and conducting correspondence with the

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

applicants, and may request that the application documents be submitted electronically. Where the originals of the documents in the application file are requested, they may ask the applicant to keep them so that they can be submitted to the ethics committee. 12.12. In cases such as a change of coordinating center, temporary suspension of the activities of the ethics committee, or revocation of the approval granted by the TİTCK for the establishment of the ethics committee and similar situations, a change of ethics committee is made for the research. The new ethics committee is determined in accordance with the relevant legislative provisions. In changes of ethics committee: 12.12.1. A single ethics committee decision is sufficient for research. Decisions given by ethics committees established within the scope of the Regulation remain valid, and in the event of a change of ethics committee, it is not required to obtain an ethics committee decision for a renewed research approval. 12.12.2. The new ethics committee has the right to request, for the purpose of obtaining information on the research, the previously reviewed documents of the research and the ethics committee decisions. 12.12.3. Legal, administrative and ethical responsibility for the decisions given by the ethics committees continues. A change of ethics committee does not affect this situation. 12.13. Where the ethics committee whose activities have been temporarily suspended resumes its activities with the approval of the TİTCK, or where an ethics committee is established with the approval of the TİTCK in the place where the coordinating center is located, applications shall be made to the ethics committee operating within the coordinating center, in accordance with the requirements of the Regulation. In this case too, the requirements specified in Article 12.12 shall be taken as the basis. 13. METHOD OF REVIEW 13.1. The ethics committee shall primarily verify that the research application falls within its area of competence in accordance with the legal regulations. 13.2. When reviewing the applications, the members of the ethics committee shall evaluate the scientific, medical and ethical aspects of the research, take into consideration the concerns of society, and protect the rights, safety and well-being of the volunteers. Special attention shall be paid to research conducted with vulnerable populations.

13.3. During the evaluation of an application, ethics committee members shall take into consideration national and international regulations concerning clinical trials and the Guidelines published by TİTCK. In addition to the documents required to be included in the application dossier as specified in the legislation, documents that may affect the decision to be taken may be requested from the applicant.

13.4. The ethics committee provides timely, comprehensive and independent review of the ethical and scientific aspects of the trials submitted, in accordance with the current Declaration of Helsinki, by following standards of good clinical practice and the relevant legislation.

13.5. The ethics committee must hold meetings in accordance with the regularly scheduled meeting dates announced by the ethics committee secretary in three-month periods. Meeting dates shall be planned so that, for the Clinical Trials Ethics Committee, there are no more than 12 business days between two meetings, and for the bioavailability/bioequivalence studies ethics committee, no more than seven business days between two meetings. In the event that there is no application to be reviewed, the meetings shall be cancelled. A justified minutes shall be drawn up by the ethics committee secretary regarding the cancelled meeting.

13.6. If a meeting is postponed, a new meeting date shall be determined in order for the applications on the agenda to be evaluated within the period specified in the legislation.

13.7. Provided that they announce it one month in advance, ethics committees may declare a holiday for a period of 15 days or less, at most twice, in different periods during the year. During the declared holiday period, no application dossiers shall be accepted except safety reports.

13.8. In clinical trial ethics committees, application dossiers shall be submitted to the ethics committee members at least five business days before the meeting; in bioavailability/bioequivalence ethics committees, at least three business days before the meeting.

13.9. Substitute members may also attend other meetings for the purpose of obtaining information on the evaluations made in the ethics committee, except for meetings they attend in

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

cases where the meeting quorum cannot be achieved or meetings they attend in place of a mandatory member with the same qualifications. Where the evaluation conducted is related to their own field of expertise and upon the request of the other ethics committee members, they may express an opinion; however, they shall not participate in the decision taken and shall not sign the decision.

13.10. Where necessary, the applicant or the coordinating investigator shall be invited to the ethics committee meeting for the purpose of obtaining information. In face-to-face meetings, in cases where the applicant or the coordinating investigator cannot attend the meeting, an alternative means of communication such as telephone, teleconference or videoconference may be offered.

13.11. The ethics committee meeting shall be chaired by the ethics committee chairperson or the vice-chairperson. In cases where the chairperson and the vice-chairperson cannot attend the ethics committee meeting, the member to whom the ethics committee chairperson has delegated may chair the meeting.

13.12. Priority shall be given to the evaluation of seasonal trials (clinical trials conducted with allergen products, etc.), early phase clinical trials, and trials to be conducted concerning orphan drugs and rare diseases.

14. METHOD FOR DECISION-MAKING AND COMMUNICATION OF THE DECISION

14.1. The members who are mandatory in the ethics committee membership structure must be present at every ethics committee meeting and must express an opinion on all trials. In cases where a mandatory principal member cannot attend, a substitute member with the same qualifications shall be invited to the meeting and shall express an opinion on the trial.

14.2. Ethics committee members shall make their evaluations regarding the application under review after members with a conflict of interest and third parties have left the meeting.

14.3. During ethics committee meetings, members shall participate in discussions in order to raise all concerns and opinions regarding the trial under review. During the discussions, all

members shall be respectful of the expressed opinions and shall allow diverse views to be voiced. The chairperson shall foster a respectful and inclusive manner. 14.4. Sufficient time shall be allotted for discussions. 14.5. Decisions are taken by the votes of the members present throughout the discussion. In decisions taken by voting, a decision shall be reached by an absolute majority of the full number of principal members. It does not require all ethics committee members to support the decision; however, all members must find the decision at least acceptable and no member may consider the decision unacceptable. 14.6. Only members who have participated in the review and discussion of the research shall vote, express their opinions and/or make recommendations. 14.7. The ethics committee secretary attends the meeting during the decision-making process and records the decisions on the form. 14.8. After a decision is reached regarding the application, the ethics committee members sign the ethics committee decision form at the end of the meeting. If any, members who do not agree with the decision shall state the matters they object to during the meeting and shall not sign the ethics committee decision. These members shall state their dissenting opinions, including their justifications, by means of a written record (minutes). Where the ethics committee decision is for deficiency or rejection, this shall be explicitly stated together with the justification of the decision. 14.9. The ethics committee may append a non-binding recommendation to the decision. Failure of the applicant to implement this recommendation does not affect the research approval granted. 14.10. Pursuant to the relevant legislation, assessments concerning cases where the information/notification is deemed sufficient shall be concluded by decision with the signature of the member responsible for notifications and the chairperson of the ethics committee. 14.11. The ethics committee decision shall be communicated to the applicant by the ethics committee secretary by means of an official letter, without exceeding the periods specified in the relevant legislation. Within two business days following the date of the decision, the applicant shall be informed by e-mail that the decision has been issued. 14.12. The ethics committee decision form must conform to the format published on

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

the website of TİTCK (Turkish Medicines and Medical Devices Agency), and the relevant fields of the form must be completed in full. 14.13. In the ethics committee decision form, the versions and dates of all documents reviewed; the signature date of the research budget; the issuance date of the insurance documents, the policy number and the period of coverage shall be clearly stated, and explicit statements shall be included indicating that applications such as the addition/removal of trial sites, changes in the number of participants (volunteers), and changes of the coordinator have been evaluated. 14.14. The certified true copy approval of the ethics committee decision form shall be made by the ethics committee chairperson or the ethics committee secretariat by affixing a certified true copy stamp, name-surname, signature and date. 14.15. Corrections of clerical errors to be made in ethics committee decision forms must be carried out by the ethics committee chairperson by affixing name-surname, signature and date. In case a correction is made, the reason for the correction shall be stated in the official letter by which the decision is notified. 14.16. Every page of the ethics committee decision form shall be signed by the ethics committee chairperson. In the event the ethics committee chairperson has a conflict of interest regarding the research under review, the chairperson may sign the relevant sections of the decision form, provided that he/she does not interfere with the deliberations on or the taking of the decision. 14.17. The ethics committee decision form shall include the application requirements for the Ministry of Health. Researches that require a permit from the Ministry of Health or that must be notified to the Ministry of Health shall be specified. 15. DOCUMENTATION AND ARCHIVING METHOD 15.1. All documents and correspondence of the ethics committee shall be dated, filed physically or electronically, and archived for a period of fourteen years. 15.2. Among the documents to be filed and archived, the documents specified below shall, at a minimum, be included: 15.2.1. All documents and correspondence relating to the formation of the ethics committee, 15.2.2. The list of ethics committee members (with each change of membership, the previous list shall be preserved and archived together with date information) 15.2.3. Curriculum vitae of all ethics committee members,

15.2.4. Curriculum vitae of the personnel serving in the ethics committee secretariat, 15.2.5. Signed confidentiality agreements and conflict of interest declarations, 15.2.6. Relevant documents concerning members whose ethics committee membership has terminated (resignation petitions, meeting records, TİTCK application file, TİTCK response letter regarding the application, etc.), 15.2.7. Announcements determined and published by the ethics committee, 15.2.8. All information and documents submitted by the applicant, 15.2.9. All correspondence conducted between the ethics committee members and the applicant or other relevant parties concerning the application, the decision and follow-up, 15.2.10. Agendas of ethics committee meetings, 15.2.11. Review forms of ethics committee members and advisors regarding applications, 15.2.12. A copy of the ethics committee decisions and all information sent to the applicant, 15.2.13. Minutes of members who are opposed to the ethics committee decisions, 15.2.14. Written conflict of interest declarations, 15.2.15. Minutes regarding the cancellation or postponement of meetings, 15.2.16. Minutes indicating members' non-attendance at meetings, 15.2.17. All documentation and correspondence records relating to the inspection of the ethics committee, 15.2.18. All correspondence with TİTCK. 16. COMPLIANCE WITH STANDARD OPERATING PROCEDURE PRINCIPLES 16.1. Ethics committees are obliged to comply with the standard operating procedure and good clinical practice principles. TİTCK (Turkish Medicines and Medical Devices Agency) issues a warning to an ethics committee that does not operate in accordance with ethical principles or fails to fulfil the Ethics Committee Standard Operating Procedure principles published by TİTCK. Where the ground for the warning is not remedied within the specified period, or where the ethics committee receives more than two warnings within a one-year period, the establishment approval granted by TİTCK shall be revoked. The ethics committee chairperson may not serve again as ethics committee chairperson in ethics committees within the scope of the Regulation. All ethics committee members, including the chairperson, may not serve in ethics committees within the scope of the Regulation for a period of one year; in case

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

of repetition, this period shall be applied as two years. 16.2. TİTCK issues a warning to an ethics committee where deficiencies are identified, as a result of an inspection conducted, in terms of premises, secretariat, archive and other equipment that are essential for the conduct of the activities of the ethics committee. Where the ground for the warning is not remedied within the specified period, the establishment approval granted by TİTCK shall be revoked. Ethics committees within the scope of the Regulation at the relevant Institution shall not be re-established for a period of six months; in case of repetition, this period shall be applied as one year. 16.3. Where it is determined that the ethics committee has not been active for a period of six months, the approval for the establishment of the ethics committee granted by TİTCK shall be revoked. The establishment of an ethics committee at the same location may not be requested for a period of one year. 16.4. Where it is determined that a member, whose circumstances necessitating the termination of ethics committee membership exist, continues his/her membership, that membership shall be revoked by TİTCK. 16.5. Where the Institution identifies non-compliance by the ethics committee with the standard operating procedures, this situation shall be notified to TİTCK together with its justification. 16.6. For ethics committees for clinical trials and bioavailability/bioequivalence studies, no other Guideline and/or operating procedure may be established apart from this Guideline. 17. REVIEW The "Standard Operating Procedure Principles for Ethics Committees for Clinical Trials and Bioavailability/Bioequivalence Studies" are reviewed every two years by the Turkish Medicines and Medical Devices Agency and, if necessary, renewed. 18. ENTRY INTO FORCE This Guideline enters into force upon the approval of the President of the Agency. 19. EXECUTION The provisions of this Guideline shall be executed by the President of the Agency.

REVISION HISTORY Revision No Revision Date Rationale and Explanations 01 06.12.2011 Updated prior to the establishment of the quality management system. 02 17.04.2013 Updated prior to the establishment of the quality management system. 03 03.06.2013 Updated prior to the establishment of the quality management system. 04 06.08.2014 Updated prior to the establishment of the quality management system. 05 13.11.2015 Updated prior to the establishment of the quality management system. 06 14.05.2020 Updated prior to the establishment of the quality management system. 07 22.03.2024 Updated due to a regulatory amendment and review. 08 23.01.2026 Updated due to a regulatory amendment and review.

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