GUIDELINE ON THE ASSESSMENT OF CLINICAL TRIALS IN EXCEPTIONAL CIRCUMSTANCES
KAD-KLVZ-23

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1. PURPOSE The purpose of this Guideline is to establish the procedures and principles regarding the assessment processes of clinical trials within the scope of exceptional circumstances and to regulate the measures for the safe and effective conduct of clinical trials in exceptional circumstances. 2. SCOPE Clinical trials falling within the scope of at least one of the situations described below are considered clinical trials relating to exceptional circumstances: a) Clinical trials to be conducted with investigational medicinal products (IMP) 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 planned to be conducted for the prevention, diagnosis, treatment or control of situations considered by the World Health Organization or our country to seriously threaten public health (epidemics, pandemics, disasters or other public health emergencies). Furthermore, it covers the special measures to be taken for clinical trials whose conduct may be affected due to the emergence of an exceptional circumstance considered by the World Health Organization or our country to seriously threaten public health. 3. LEGAL BASIS This Guideline has been prepared based on Article 16 of the fifth section of the Regulation on Clinical Trials on Human Medicinal Products, which was published in the Official Gazette No. 32203 dated 27/5/2023 and entered into force. 4. DEFINITIONS The definitions set forth in the Good Clinical Practice Guideline and the relevant legislation shall apply. 5. DETERMINATION THAT A CLINICAL TRIAL RELATES TO EXCEPTIONAL CIRCUMSTANCES With regard to the situations set forth in paragraph (a) of Article 2 of this Guideline; in order to determine whether the trial is a trial relating to exceptional circumstances, a determination application is submitted to the Turkish Medicines and Medical Devices Agency (Agency) by the sponsor or the legal representative of the sponsor. The determination application is made to the Conformity Assessment Unit of the Department of Clinical Trials. The application, together with a cover letter, shall contain the information and documents that will demonstrate that the trial bears the characteristics of a clinical trial relating to exceptional circumstances. With regard to the situations set forth in paragraph (b) of Article 2 of this Guideline; there is no need to submit a determination application to the Agency in order to determine whether the trial is a trial relating to exceptional circumstances. Other cases will be announced on the Agency's website in advance.

The Agency reviews determination applications within 3 (three) business days and, where deemed necessary, may request additional explanations and information from the applicant. The requested explanations and information shall be submitted to the Agency within 3 (three) business days. Together with the additional information and explanations, the application shall be re-examined by the Agency within 3 (three) business days. As a result of the assessment of the determination application, the outcome of the assessment as to whether or not the trial relates to exceptional circumstances shall be notified to the applicant together with its justification. Trials assessed as not being clinical trials relating to exceptional circumstances as a result of the assessment of the determination application shall be submitted by the applicant to the Agency within the scope of the initial application. The files relating to clinical trial applications to be made to the Agency shall be prepared and submitted in accordance with the "Guideline on Clinical Trial Applications Made to the Department of Clinical Trials of the Turkish Medicines and Medical Devices Agency", while the files relating to clinical trial applications to be made to the relevant ethics committee shall be prepared and submitted in accordance with the "Guideline on Clinical Trial Applications Made to Ethics Committees". Said applications shall be assessed within the

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framework of the procedures and principles for initial applications and within the general assessment periods stipulated in the relevant legislation. The special or expedited assessment procedures and periods applied to clinical trials relating to exceptional circumstances shall not apply to these applications. The workflow diagrams regarding the process are provided in Figure-1 and Figure-2. 6. ASSESSMENT OF APPLICATIONS FOR CLINICAL TRIALS RELATING TO EXCEPTIONAL CIRCUMSTANCES Trials assessed as being clinical trials relating to exceptional circumstances as a result of the assessment of the determination application shall be submitted by the applicant to the Agency within the scope of the initial application. The files relating to clinical trial applications to be made to the Agency shall be prepared and submitted in accordance with the "Guideline on Clinical Trial Applications Made to the Department of Clinical Trials of the Turkish Medicines and Medical Devices Agency" and the files relating to clinical trial applications to be made to the relevant ethics committee shall be prepared and submitted in accordance with the "Guideline on Clinical Trial Applications Made to Ethics Committees". In the cover letter of the application, an explanation shall be included, pursuant to Article 16 of the Regulation, stating that the said clinical trial has been determined by the Agency as a clinical trial relating to exceptional circumstances, together with the date and number of the relevant letter. It is the principle that, where the applications for the trial are duly made and there is no deficiency in the information and documents required to be included in the application, the application shall be reviewed by the ethics committee and the Agency within 7 (seven) business days. For the trials specified below, a period of seven business days may be added to the period determined for the review period of the ethics committee and the Agency: a) Trials to be conducted using products containing genetically modified organisms, as well as cellular therapies or gene therapy products. b) Trials within the scope of the Regulation on Clinical Trials on Human Medicinal Products published in the Official Gazette No. 32203 dated 27/5/2023, and the Regulation on Clinical Trials of Medical Devices published in the Official Gazette No. 31890 dated 8/7/2022

trials in which trials within this scope are conducted together as the subject of the same trial. Deficiencies identified as a result of the review of the initial eligibility application file by the Agency or the ethics committee, together with any additional information and explanations required, shall be submitted by the applicant to the Agency or the relevant ethics committee within at most ten business days. In the event that the applicant does not reapply within 10 (ten) business days in order to remedy the identified deficiencies and to submit the requested additional information, documents and explanations, the evaluation process for exceptional circumstances shall be terminated and the applicant shall be notified thereof. For applications whose evaluation process within the scope of exceptional circumstances has been terminated, it shall not be necessary to submit a new initial eligibility application. Such applications shall continue to be evaluated by the Agency within the framework of the general evaluation procedures and timelines applicable to clinical trial applications. The Agency may, in the course of reviewing and evaluating such trials and while exercising its powers, make use of relevant decisions issued by official health authorities of other countries and of published reports. For clinical trials intended to address exceptional circumstances, the evaluation procedures and principles set out in this Guideline also cover the post-authorization processes of clinical trials authorized within this scope. The Agency may, in the course of reviewing and evaluating trials and while exercising its powers, obtain the opinion of the scientific advisory committees and their members established pursuant to the Regulation on the Establishment and Duties of the Scientific Advisory Committees of the Turkish Medicines and Medical Devices Agency, published in the Official Gazette No. 30849 dated 1/8/2019. The official letters setting out the initial application evaluation results for clinical trials falling within the scope of subparagraph (b) of the second Article of this Guideline, and, if the Agency authorizes the trial, the initial eligibility letter for the trial, shall be signed by the President of the Agency and communicated to the applicant. The workflow diagrams of the process are provided in Figure-1 and Figure-2.

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7. MEASURES TO BE TAKEN IN EXCEPTIONAL CIRCUMSTANCES The following situations shall be regarded as exceptional circumstances for which measures may be taken by the Agency: - An international pandemic situation declared by the World Health Organization, - A national public health emergency declared by Türkiye, - Epidemic/disaster and similar situations in Türkiye that may affect the health of the entire population. In exceptional circumstances, where the Agency deems it necessary with respect to the conduct of clinical trials intended to address the exceptional circumstance, as well as all clinical trials not intended to address the exceptional circumstance itself but potentially affected by it, measures relating to the trial processes (the activities of trial sites, the transfer of volunteers between trial sites, the conduct of visits, the use of remote assessment methods, the procurement and delivery of the investigational medicinal product, monitoring activities, notification and reporting obligations, etc.) may be determined.

The measures to be taken shall be determined in a risk-proportionate manner, taking into account the nature, scope and duration of the exceptional circumstance, the characteristics of the clinical trial, and the risks it may pose to volunteers. The protection of the rights, safety and well-being of volunteers, as well as the reliability and integrity of the data obtained from the trial, shall be of primary importance. The measures determined by the Agency and the procedures and principles for their implementation shall be communicated to the relevant parties, as deemed necessary according to the nature and development of the exceptional circumstance, through the Agency's website, announcements or other appropriate means of communication. In the event that the exceptional circumstance ends or the conditions change, the measures in question may be reassessed by the Agency. Additional measures may be published during the process, or measures may be partially or entirely lifted.

8. ENTRY INTO FORCE This Guideline shall enter into force upon the approval of the President of the Agency. 9. EXECUTION The provisions of this Guideline shall be executed by the President of the Agency. 10. REVISION HISTORY

Revision No Revision Date Justification and Explanations 1 05.02.2024 An update was made due to an amendment to the Regulation. 2 26.08.2026 In Section 5, the determination that a clinical trial is intended to address exceptional circumstances was elaborated, and the response period for the applicant and the evaluation procedures for trials that, as a result of the evaluation of the determination application, are considered not to be clinical trials intended to address exceptional circumstances were added. In Section 6, the evaluation of clinical trial applications for exceptional circumstances was elaborated. In Section 7, with respect to the measures to be taken in exceptional circumstances, the measures that may be taken concerning the conduct of clinical trials intended to address the exceptional circumstance, as well as all clinical

trials not intended to address the exceptional circumstance itself but potentially affected by it, were elaborated. The workflow diagrams have been updated. 3 14.09.2026 A general review of the evaluation timelines has been carried out.

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