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GUIDELINE ON CLINICAL TRIAL APPLICATIONS MADE TO ETHICS COMMITTEES KAD-KLVZ-03

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1. INTRODUCTION

This Guideline has been prepared to provide guidance on the applications to be made to the clinical trials ethics committee or the bioavailability/bioequivalence studies ethics committee in order to conduct clinical trials and scientific studies falling within the scope of the legislation in force and the area of responsibility of the Department of Clinical Trials of the Turkish Medicines and Medical Devices Agency (TİTCK). Applications are made to the ethics committee by the sponsor, which is a natural or legal person, by the sponsor's legal representative, or by the contract research organization to be appointed by the sponsor. For sponsors established in Türkiye, the sponsor itself, or a contract research organization established in Türkiye to which tasks have been transferred, is authorized and responsible for making all applications and notifications to be made to the ethics committee; for sponsors not established in Türkiye, the sponsor's legal representative, or a contract research organization established in Türkiye to which tasks have been transferred, is authorized and responsible. It is essential that the cover letter and documents submitted in applications be prepared in Turkish. However, some documents are accepted in English, and these documents are explained in this Guideline. For documents prepared in languages other than Turkish and English, a Turkish translation thereof (certified by a notary and a sworn translator) must be submitted. In order to identify the documents submitted in the application files and to ensure their traceability, the documents must be assigned a date and, where necessary, a version number. The definitions specified in the Regulation on Clinical Trials of Medicinal Products for Human Use, published in the Official Gazette No. 32203 dated 27/5/2023, and in the Good Clinical Practice (GCP) Guideline are also applicable to this Guideline. In this Guideline, the term "Regulation" refers to the Regulation on Clinical Trials of Medicinal Products for Human Use; the term "ethics committee" refers to the Clinical Trials Ethics Committee and the Bioavailability/Bioequivalence Studies Ethics Committee; the term "trial" refers to both trials and studies; and the term "applicant" refers to the sponsor, the sponsor's legal representative, or the contract research organization. Ethics committees may establish electronic systems for the purpose of receiving applications for trials and conducting correspondence with the applicants. When referencing this Guideline, the abbreviation Ethics Committee Application Guideline (KAD-KLVZ-03) may be used. 2. INITIAL SUITABILITY APPLICATION 2.1. Application File The application file is prepared before the initial application is made. The application file consists of the relevant documents, including the cover letter (which must be addressed to the ethics committee to which the application is to be made) and the application form. The cover letter (which must be addressed to the ethics committee to which the application is to be made) and the relevant document templates are published on the Agency's website. The said templates are updated as necessary, and the cover letter (which must be addressed to the ethics committee to which the application is to be made) and the documents to be used in the application must be prepared using the current templates.

Table 1 – Documents Required in the Initial Application File No Document Explanation 1 Clinical Trials Application Form The clinical trials application form available on the Agency's website should be used. 2 Trial Protocol It must be prepared in accordance with GCP Chapter 9. If the trial protocol is in English, it is sufficient to submit the original. If the trial protocol is prepared in languages other than English, a Turkish translation of the entire protocol (certified by a notary or a sworn translator) must be submitted. 3 Protocol Signature Page In multicenter trials, signed by the coordinator; in single-center trials, signed by the principal investigator

the protocol signature page shall be submitted. 4 Benefit-Risk Assessment Plan/Report

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The template document available on the Agency's website shall be used. The benefit-risk assessment shall include scientific explanations to the effect that the benefit expected from the clinical trial is greater than the risks likely to be observed in the trial. A risk assessment shall be conducted regarding the participant (volunteer), the investigational product, and the protocol design, and the measures to be taken against possible risks shall be included. 5 Pediatric Investigation Plan (if applicable)

7 Informed Consent Form (ICF) It shall be prepared in accordance with GCP Section 10 and the document on the minimum information that must be included in the informed consent form, available on the Agency's website. It is the responsibility of the research team, led primarily by the principal investigator, to provide information regarding the participation in the trial of foreign residents living in Turkey (foreigners who have acquired Turkish citizenship, etc.) whose native language is other than Turkish and who are not within the scope of the vulnerable population, to ensure that the information provided is fully and accurately understood by the participant, and to obtain the ICF. The principal investigator shall assess whether the relevant participant understands the Turkish ICF. Where the principal investigator deems it necessary, the version of the ICF translated into the relevant language shall be used and the consent shall be obtained in the presence of an interpreter of the relevant language. 8 Investigator's Brochure (IB) It shall be prepared in accordance with GCP Section 11. In applications, submission of the investigator's brochure is essential; however, if there is no investigator's brochure, the Turkish summary report on the information supporting this trial obtained from previous studies, together with the relevant literature/other documents, must be submitted. If the investigator's brochure is in English, submission of its original is sufficient. If the investigator's brochure has been prepared in languages other than English, the Turkish translation of all of them (certified by a notary or a sworn translator) must be submitted. For low-risk scientific studies, the summary of product characteristics (SmPC)/patient information leaflet (PIL) of the investigational product may be submitted instead of the investigator's brochure. If the investigational product has been authorized by the competent authorities, the summary of product characteristics (SmPC)/patient information leaflet (PIL) of the investigational product may be submitted instead of the investigator's brochure.

9 Investigational Product File — In applications, submission of the investigational product file is mandatory. 10 Good Manufacturing Practice (GMP) Certificate/Document The documents submitted to the Agency within the scope of good manufacturing practices (GMP) must be valid/up to date. If the documents submitted for the manufacturing site(s) have been prepared in a language other than Turkish or English, in addition to the said documents, their Turkish or English translations, certified by a sworn translator and a notary, must also be submitted. Except for the Manufacturing Site Permit Certificates/GMP certificates issued by the Agency, where the Manufacturing Site Permit Certificate/GMP certificate submitted for the manufacturing site(s) has not been published in a publicly available database, a signed and apostilled Manufacturing Site Permit Certificate

If the CRF is in English, submission of its original is sufficient. If the CRF has been prepared in languages other than English, the Turkish translation of all of them (certified by a notary or a sworn translator) must be submitted. A draft CRF may also be submitted at the initial application. 12 Insurance (for trials requiring insurance under the relevant legislation) - Insurance certificate - Insurance policy - Insurance endorsements (if any) - General and special conditions It shall be prepared in accordance with the Guideline on Insurance Coverage to be Taken Out for Clinical Trials. Insurance is mandatory for Phase I, II, and III trials, trials with adaptive designs, and bioavailability/bioequivalence (BA/BE) studies. Where deemed necessary by the Agency and/or the relevant ethics committee, insurance is mandatory for trials on products/methods bearing health claims.

13 Trial Budget The trial budget form available on the Agency's website shall be used. 14 Curricula Vitae — The curriculum vitae form available on the Agency's website shall be used. In all

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trials, the curricula vitae of the principal investigators shall be submitted; in Phase I trials and BA/BE studies, the curricula vitae of the principal investigators, together with those of a pharmacologist who is a medical doctor, shall be submitted. 15 Previously Rejected Ethics Committee Decision (if any)

16 Authorization Documents (if any) If the applicant is not the sponsor of the trial, the original and the Turkish translation (certified by a notary or a sworn translator) of the document indicating the matters for which the legal representative or the contract research organization acting on behalf of the sponsor has been authorized by the sponsor shall be submitted. Where the sponsor is not resident in Turkey, submission of the authorization documents of its legal representative is mandatory pursuant to the Regulation.

1 It is the printed, optical, or electronic document prepared for recording, as defined in the trial protocol, the data and other information belonging to each participant in the trial.

Only for clinical trials conducted with medicinal products for human use containing an integrated medical device (without a CE certificate); 20 Commitment Documents — In clinical trials conducted with medicinal products for human use containing an integrated medical device, the signed commitment document of the medical device manufacturer stating that the medical device to be used complies with the general safety and performance requirements set out in Annex-1 of the Medical Devices Regulation published in the Official Gazette dated 02.06.2021 and numbered 31499 The signed commitment document of the sponsor of the trial stating that all measures have been taken to protect the health and safety of the participant with regard to the use of the medicinal products for human use containing an integrated medical device

Only for bioavailability/bioequivalence studies; 21 Supply document of the investigational product and the reference product(s) If the batch number and the expiry date are not included in the supply document, a photocopy of the package, an invoice, or a similar document containing this information shall be submitted. 22 Investigational Product File In applications, submission of the investigational product file is mandatory. 23 Literature/sources on pharmacological and pharmacokinetic information (if any) If available, the source/literature providing the pharmacological and pharmacokinetic information of the tested investigational product shall be submitted.

Only for observational studies of medicinal products for human use; 24 The list of all medicinal preparations containing the active substance on which information is collected in the study

2.3. Revision of the Initial Applications As a result of its evaluation, the ethics committee notifies the applicant of the deficiencies it has identified and of the additional information, documents, and explanations it requires during the review process. In this case, a revision application is submitted by the applicant together with the necessary information, documents, and explanations. 2.4. Withdrawal of the Trial Application The applicant may withdraw the trial application at any time during the evaluation process. To withdraw the application, an application shall be made to the ethics committee together with the reasons. After the trial application has been withdrawn, it may be resubmitted to the ethics committee as a new trial application; however, this matter must be stated in the cover letter. 2.5. Evaluation of the Application Files and Ethics Committee Approval If additional information and documents are to be submitted for a trial whose evaluation process is ongoing, an application shall be made to the ethics committee together with the reasons. If the justification for the application is deemed valid, the evaluation period of the application is restarted together with the new information and documents. The members of the ethics committee convene with a two-thirds majority of the full number of principal members and take decisions by an absolute majority of the full number. Where a two-thirds majority cannot be achieved with the principal members, a quorum is achieved by inviting the substitute members to the meeting. Ethics committee decisions are notified to the applicants using the ethics committee decision form published on the Agency's website. Provided that the applications for the trial are duly made and that there are no deficiencies in the

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information and documents required to be included in the application, it is essential that the application be concluded by the clinical trials ethics committee within 12 business days and by the bioavailability/bioequivalence studies ethics committee within seven business days. For products carrying genetically modified organisms and

...trials to be conducted using products involving cellular therapies or gene therapy, and trials within the scope of the Regulation, and trials within the scope of the Regulation on Clinical Trials of Medical Devices published in the Official Gazette dated 08/07/2022 and numbered 31890, where such trials are conducted jointly so as to constitute the subject of the same trial, a period of 30 days may be added, in addition to the period determined for the review period of the ethics committee, in the evaluation of such trials. The ethics committee notifies the applicant of the deficiencies it identifies as a result of its evaluation and of the additional information, documents, and explanations it requires during the review process. The ethics committee may reject the application together with its justification. In this case, it conveys the grounds for rejection to the applicant. The applicant may, on one occasion only, reapply by making the necessary modifications on the matters specified in the decision, or may object to the decision with justification within 30 business days. Where the requested modifications are not fulfilled or where no acceptable justification is submitted in this regard, the ethics committee may reject the trial again. Where the ethics committee grants approval for the trial, it notifies the applicant of the decision regarding this approval. The ethics committee may attach a non-binding recommendation to the approval decision. The official letter by which the decision is notified shall state whether permission from the Turkish Medicines and Medical Devices Agency (TİTCK) is required for the trial under review pursuant to the relevant legislation. The Agency may not grant permission to trials that do not have ethics committee approval as required by the relevant legislation. Trials may not be initiated without the Agency's permission.

3. MAKING MODIFICATIONS IN TRIALS After trial authorization has been obtained, modifications may be made to the trial. A modification may take the form of updating existing information and documents or adding new information and documents. Modifications to be made in a trial may be submitted as a substantial modification application, a modification application, or a notification application. During the conduct of the trial, those of the changes occurring that are of a notification nature and those requiring ethics committee approval and/or Agency permission are determined by the Good Clinical Practice Guideline.

3.1. Substantial Modification Application Any modification, made after trial authorization, to any aspect of the trial that may have a significant impact on the safety and rights of the volunteers and/or on the reliability and validity of the data to be obtained in the trial is defined as a substantial modification. Substantial modifications in the conduct of a trial may arise from the protocol or from new information relating to the scientific documents supporting the trial. The sponsor must address the cases one by one and assess whether the modification is substantial. Substantial modifications may not be implemented without ethics committee approval and the Agency's permission. (The urgent safety measure specified in Article 3.7 and the temporary halt of the trial specified in Article 3.8 fall within the scope of substantial modification and are exceptional cases in terms of being implemented without ethics committee approval and the Agency's permission) Table 2 – Substantial Modification Types 1 Modification to the information in the application form 2 Modification to the trial protocol 3 Modification to the informed consent form (ICF)

3.2. Modification Application These modifications set out in Table 3 may be implemented on the basis of the date of application to the ethics committee and the Agency. Where the application dates differ, the latest application date shall be taken as the basis. However, the ethics committee and/or the Agency may request corrections regarding these modifications or may cancel these modifications together with their justification.

Table 3 – Modification Types 1 Modification regarding the principal investigator In multicenter trials, a modification application must be submitted for a change of principal

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investigator. 2 Extension of the insurance period For insurance documents that have previously obtained ethics committee approval and Agency permission, a modification application must be submitted solely for the extension of the insurance period, without altering any of the insurance conditions. There must be no change in the content of the Certificate/Policy or in the policy conditions to which it is linked. In case of any change, the application is evaluated within the scope of substantial modification. 3 Modification of the patient card/diary in use in authorized trials 4 Extension of the trial duration 5 Extension of the recruitment period 6 ORF modification made after initial approval is granted 7 Investigator's Brochure modification not requiring ICF/protocol modification 8 Documents that will not be implemented in our country and do not contain information pertaining to safety reporting In international multicenter clinical trials, a modification application must be submitted for the changes made to documents such as Protocol, IB, and ICF modifications that will not be implemented in our country and do not contain safety-related information.

3.3. Notification Application

All modifications/situations/information that do not fall within the scope of Articles 3.1 and 3.2 but that may affect the oversight and inspection of the trial by the ethics committee and the Agency, or the benefit-risk balance of the trial, shall be notified to the ethics committee and the Agency without delay (within 15 days at the latest following implementation/obtaining thereof).

3.4. Application File

The application file consists of a cover letter and the relevant documents. Templates for the cover letter and relevant documents are published on the Agency's website. The said templates are updated as necessary, and the cover letter and documents to be used in the application must be prepared using the current templates.

a) Cover Letter and Application Form

In cases where the modification affects more than one protocol for a specific investigational medicinal product, the applicant shall indicate this in the cover letter and shall also include a list containing the full title of the trial and, if available, the protocol number for all protocols affected by the modification.

The detailed justification of the modification is explained in the cover letter, and where applicable, the following information is also included: - Updated overall benefit-risk assessment (may be submitted as a separate document), - Possible consequences for volunteers enrolled in the trial, - Possible consequences regarding the evaluation of the data obtained from the trial, - Situations that may affect the informed consent process.

In responsive applications against ethics committee decisions requesting information, documents, and explanations regarding applications, the following information is included in the cover letter:

- The date and decision number of the relevant deficiency decision, - Responses/explanations regarding the requested information, documents, and explanations, - References to the documents attached to the file in relation to the responses/explanations.

In an application linked to a previously made application, an explanation regarding the linkage of the relevant applications is included in the cover letter.

In applications to be made to the ethics committee, the appropriate application form published on the Agency's website according to the type of trial shall be used.

The cover letter and application form are signed by the authorized person(s) and attached to the application file.

By signing the cover letter and application form, the applicant undertakes that the information submitted for the modification is sufficient, that the documents attached to the file accurately reflect the current information, and that the proposed modification is suitable for implementation.

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b) Relevant Documents

In the case of modifications to be made to documents currently used in the trial or in which the ethics committee has identified deficiencies, the document showing the modifications and the new document with its date and, if available, version number updated are attached to the application file.

The relevant documents are prepared in line with the explanations in Table 1.

The documents that must be attached to the application according to the types of modification are set out in Table 4.

The modifications that may be made are not limited to the types of modification set out in Table 4.

Table 4 – Documents Required in Substantial Modification/Modification Applications

Protocol - Document showing the modifications - Final version - Protocol signature page signed by the coordinator in multicenter trials and by the principal investigator in single-center trials

Informed Consent Form (ICF) - Document showing the modifications – global model (if available)1 - Final version – global model (if available)1 - Document showing the modifications - Final version

Investigator's Brochure (IB) - Document showing the modifications - Final version

Investigational Medicinal Product Dossier (IMPD) - Document showing the modifications - Current status–proposed modification justification table regarding the modifications - Final version

Insurance - Insurance certificate - Insurance policy - Insurance endorsements (if any) - General and special terms

Extension of Insurance Period - Insurance documents of the previous period (certificate, policy, endorsements) - Insurance certificate / Insurance policy / Insurance endorsement

Trial Budget - Document showing the modifications - Final trial budget form

Case Report Form - Document showing the modifications - Final version

Volunteer / Patient Documents - Document showing the modifications - Final version

1 The global model ICF is submitted for informational purposes; its submission is not mandatory.

The stage of the trial at which they will be used, for what purpose they will be used, and where they will be used shall be explained in the cover letter.

A modification application must be made to the Agency regarding the use of volunteer documents in electronic environment (tablet, mobile device, web-based platform, etc.). In applications, the content of the printed document must be submitted as a transcript, and the relevant document must bear a date/version number. Screenshots of the printed document content shall not be submitted.

Permission from the Agency is not required for changes unrelated to the trial that solely concern the visual design of the application, such as font size, typeface, color, screen layout, logo, icon, or similar cosmetic/editorial changes. However, in the first modification application to be submitted, a summary of the change history, also indicating the date/version numbers pertaining to such cosmetic/editorial changes, must be communicated to the Agency.

Coordinator Change - Responsibility handover/acceptance document between the former and the new coordinator - Curriculum vitae of the new coordinator - Protocol signature page of the new coordinator

Administrative Responsible Person Change - Responsibility handover/acceptance document between the former and the new administrative responsible person - Curriculum vitae of the new administrative responsible person

Principal Investigator Change - Responsibility handover/acceptance document between the former and the new principal investigator - Curriculum vitae of the new principal investigator

Principal investigator information is not required to be included in the trial budget form and insurance documents. If the names of the principal investigator appear in these documents, the

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documents are updated and the application is submitted as a substantial modification application.

Change in the Number of Volunteers - Trial budget form (if update is required) - Insurance (if update is required)

In order to increase the number of volunteers to be enrolled from our country, approval from the ethics committee and permission from the Agency must be obtained together with the justification.

The trial budget form does not specify the number of volunteers; however, if the update of the number of volunteers results in changes in the quantities/amounts in the budget form, the budget form is updated.

If the number of volunteers in the approved insurance documents is equal to or greater than the number of volunteers to be updated, the insurance documents do not need to be updated.

Addition of a Site (Site Inclusion) - Curriculum vitae of the principal investigator - Trial budget form (if update is required) - Insurance (if update is required)

If the insurance documents contain information regarding site details, the insurance documents are updated.

Site Closure

In site closure applications, the applicant does not update the Site List on the Trial Detail screen. Closure operations on the Module are performed by the Agency. The status of sites can be tracked from the "My Approved Trials" screen.

Closure of a site that has not been opened despite the Agency's permission to conduct the trial The application may be made as a notification. Updating of the trial budget and insurance documents is not required.

Closure of a site that has been opened but where no volunteers have been screened and no volunteer enrollment has been carried out The application may be made as a notification. Updating of the trial budget and insurance documents is not required.

Closure of a site where volunteers have been screened and/or volunteer enrollment has been carried out but which has no active volunteers (including those in the follow-up period) The application may be made as a notification. Updating of the trial budget and insurance documents is not required.

Closure of a site with active volunteers (including those in the follow-up period) The application is made as a substantial modification. Information on the status of the volunteers and on what will be done with the products remaining at the site is added to the cover letter. Updating of the trial budget and insurance documents is not required.

Sponsor Change

All documents shall be reviewed. Documents updated pursuant to the sponsor change are attached to the application file. For documents that remain valid, a declaration/undertaking stating that the said documents will be used, together with a list specifying these documents, is signed by the new sponsor and attached to the application file.

- Transfer document between the former and the new sponsor - Updated documents - Undertaking for documents that remain valid (if required)

Legal Representative / Contract Research Organization / Applicant Change - Authorization document - Documents that need to be updated depending on the change (trial budget, insurance, etc.)

Temporary Halt of the Trial

A document containing at least the following information regarding the temporary halt of the trial: (if not submitted as a separate document or if the relevant document does not contain the required information, the missing matters are explained in the cover letter) - Date of the temporary halt (as day, month, year), - Reasons for the temporary halt, - Number of volunteers continuing treatment at the time the trial was halted and their distribution by site, - Procedures to be performed for volunteers under treatment during the temporary halt, - Evaluation of the consequences of the temporary halt and actions to be taken, - Overall benefit-risk assessment,

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Procedures to be performed and actions to be taken for the investigational medicinal products remaining at trial sites and with volunteers.

Request to Restart the Trial A document containing at least the following information regarding the request to restart the trial: (if not submitted as a separate document or if the relevant document does not contain the required information, the missing matters are explained in the cover letter) - If the trial is planned to be restarted at a date later than the date on which the Agency permitted the restart, the planned restart date (as day, month, year), - Justification for the restart request, - Actions taken after the temporary halt and their results, Overall benefit-risk assessment.

3.5. Making the Application

The modification/notification applications, together with the prepared application file, are submitted to the ethics committee to be evaluated scientifically and ethically. All duly made applications must be accepted for processing to be evaluated by the ethics committee. An application registration number is assigned to all applications accepted for processing. This number and the registration date are notified to the applicant.

For the evaluation of modification applications, if requested by the ethics committee, the fee determined so as not to exceed the application fee determined by TİTCK (Turkish Medicines and Medical Devices Agency) is deposited into the account determined by the university, training and research hospital, or provincial health directorate to which the ethics committee is affiliated. In this case, the ethics committee may request that the original and one photocopy of the deposit slip be attached to the application file. No application fee is requested for specialty theses or academic research.

In the case of combining substantial modification and modification and/or notification applications

the substantial modification application fee shall be paid. Where modification and information applications are combined, the modification application fee shall be paid. Where a response application made on the basis of deficiencies identified by the ethics committee is submitted together with any substantial modification and/or modification application other than the response to deficiencies, the fee for the relevant substantial modification or modification application shall be paid.

4. NOTIFICATIONS The applicant is responsible for the regular submission of notifications to the ethics committee and the Agency. 4.1. Notification of Start Date The date on which the first of the trial sites in our country is opened for the enrollment of volunteers (conduct of the initiation visit) is the start date of the trial. This date is notified to the ethics committee within 15 days. The notification shall specify which site has been opened.

4.2. Notification of the First Visit Date of the First Volunteer The first visit date of the first volunteer in our country in the trial is notified to the ethics committee within 15 days. The notification shall specify at which site this volunteer is located. 4.3. Notification of the End Date of Volunteer Enrollment The date on which volunteer enrollment is terminated in our country in the trial is notified to the ethics committee within 15 days. In order for volunteer enrollment to be restarted, an application is made to the ethics committee and the Agency together with the justification for the restart. (Table 2) 4.4. Annual Notification (Progress Report) The progress of trials is monitored through annual notifications. The annual notifications made for trials are submitted by 31 January of the following year, based on the calendar year. (For example, the annual notification covering the period 01.01.2025 – 31.12.2025 must be submitted by 31 January 2026.) The Agency and/or the ethics committee may request that notifications (progress reports) be made at shorter intervals depending on the nature of the trial. Annual notifications shall be made until the trial is completed. The notification is made using the annual notification form published on the Agency's website.

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4.5. Notification of Investigator Assignment / End of Duty For investigator assignments, a notification is made to the Agency and the ethics committee. For assignments of supporting clinical trial personnel, such as research nurses, field staff, monitors, and clinical trial pharmacists, a notification is made to the ethics committee. The notification is made using the application form published on the Agency's website and the relevant documents specified in the application form. The relevant personnel may assume their duties as of the notification date or, if specified in the application, on a date subsequent to the notification date. Where deemed necessary, assignments may be cancelled by the Agency or the ethics committee, stating the justification. In the case of the end of an investigator's duty, the end-of-duty notification is made to the Agency and the ethics committee; in the case of the end of duty of supporting clinical trial personnel, the end-of-duty notification is made to the ethics committee. 4.6. Safety Notifications The sponsor is responsible for the continuous safety evaluation of investigational medicinal products. The sponsor shall submit individual case reports, all safety updates, and periodic reports to the Agency and the ethics committee in accordance with the relevant legislation. The responsibilities of the sponsor and investigators regarding safety notifications are defined in the tenth section of the Regulation on Clinical Trials of Human Medicinal Products. In addition, the Guideline on Safety Notifications in

Table 5 – Safety Notifications No Type Notification Time Explanation 1 Suspected unexpected serious adverse reactions (SUSARs) occurring in our country that resulted in death or are life-threatening Within 7 days 2 Other suspected unexpected serious adverse reactions (SUSARs) occurring in our country (SUSARs other than those specified in No. 1) Within 15 days Where SUSARs not falling within the scope of No. 1 subsequently become suspected unexpected serious adverse reactions that resulted in death or are life-threatening in nature, a SUSAR notification is made again within seven days. 3 Follow-up report for No. 1 and No. 2 Within 8 days Where the information is incomplete in the initial notification made for No. 1 and No. 2 SUSARs, the complete report is notified within an additional eight days. 4 SUSARs occurring abroad Once every 6 months All SUSARs related to the investigational medicinal product occurring abroad are notified as a six-month line listing in the manner specified in the Guideline on Safety Notifications in Clinical Trials. 5 Development Safety Update Report (DSUR) Once a year Within 60 days after the data lock point

4.7. Early Termination The trial protocol shall include a section specifying matters related to the completion of the trial. The date of the last visit of the last volunteer in the trial may be defined as the completion of the trial. Any exceptional situation shall be justified in the protocol. The completion of the trial earlier than planned for any reason, before the conditions specified in the protocol for the completion of the trial are fulfilled, is defined as early termination. If the sponsor decides not to initiate an authorized trial, not to restart a trial for which it has decided on a temporary halt, or to terminate an ongoing trial earlier than planned for any reason, an early termination notification is made. The early termination notification is made by selecting the "Trial Completion Notification" procedure. In this notification, the reasons for not initiating or terminating the trial and the measures regarding the continuation of the treatment of volunteers enrolled in the trial are explained.

4.8. Notification of Completion of the Trial The completion of a trial is defined as the date on which the trial is completed in accordance with the protocol and all sites in our country are closed. The notification of completion of the trial is made to the ethics committee and the Agency within 15 days. The notification is made using the trial completion notification form published on the Agency's website.

4.9. Notification of Completion of the Trial in All Countries The completion of a trial in all countries is defined as the date on which the trial is completed in all countries where it is conducted. The notification of completion of the trial in all countries is made to the ethics committee and the Agency within 30 days.

4.10. Notification of the Trial Results Report Within one year from the termination of the trial at all sites, a summary of the trial results report and a version of this summary prepared in a

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manner understandable to volunteers are notified to the ethics committee and the Agency. Results report summaries are prepared in accordance with the format published/accepted by the Agency.

4.11. Submission of Notification Applications Notification applications are made to the ethics committee with a cover letter, the forms described in the notification types, and the relevant documents. There is no application fee for notification applications, and all duly made applications must be taken into process for review by the ethics committee. An application registration number is assigned to all applications taken into process. This number and the registration date are notified to the applicant. 4.12. Evaluation of Notification Applications The opinion of the ethics committee regarding the application is notified to the applicant. Where, as a result of the evaluation, deficiencies are identified regarding the application, or information, documents, or actions are requested, the relevant requests are fulfilled by the applicant and an application is submitted to the ethics committee with the necessary explanations and documents.

5. ROLE AND RESPONSIBILITIES OF ETHICS COMMITTEES IN TRIALS The responsibilities of ethics committees cover all stages of the trial: - The primary duty of the ethics committee is to evaluate, before trials are approved, whether they are scientifically and ethically appropriate.

As a result of new information and developments arising in relation to its scope, the ethics committee reviews the approval it has granted for the trial.

- In the event that a non-negligible risk emerges in the trial, or in cases where the safety, well-being and health of the volunteers are adversely affected, the ethics committee may request the Agency to take the necessary measures. - The ethics committee may request an inspection from the Agency for the trials it has approved, together with its justification.

6. ENTRY INTO FORCE This Guide enters into force upon the approval of the President of the Agency.

7. EXECUTION The provisions of this Guide shall be executed by the President of the Agency.

REVISION HISTORY Revision No | Revision Date | Justification and Explanations 00 | 28.01.2009 | Updated before the establishment of the quality management system. 01 | 15.06.2009 | Updated before the establishment of the quality management system. 02 | 05.09.2011 | Updated before the establishment of the quality management system. 03 | 17.04.2013 | Updated before the establishment of the quality management system. 04 | 06.08.2014 | Updated before the establishment of the quality management system. 05 | 13.11.2015 | Updated before the establishment of the quality management system. 06 | 01.12.2019 | Updated before the establishment of the quality management system.

07 | 04.12.2020 | Updated due to an amendment to the Regulation. 08 | 22.03.2024 | Updated due to an amendment to the Regulation. 09 | 15.05.2026 | Updates were made due to an amendment to the Regulation and the revision of the Güven Applications Guide. Word and spelling errors have been corrected. The Safety Notifications section has been updated due to the changes that occurred in the application procedures with the launch of the national SUSAR module.

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