

The clinical trials application form available on the 1 Clinical Trials Application Form Agency's website must be used.

TURKISH MEDICINES AND MEDICAL DEVICES AGENCY GUIDELINE ON CLINICAL TRIAL APPLICATIONS SUBMITTED TO THE CLINICAL TRIALS DEPARTMENT KAD-KLVZ-02

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Applications are made to the Agency by the sponsor, who may be a natural or legal person, by the legal representative of the sponsor, or by a contract research organization 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 delegated is authorized and responsible for making all applications and notifications to the Agency; for sponsors not established in Türkiye, the legal representative of the sponsor or a contract research organization established in Türkiye to which tasks have been delegated is authorized and responsible.

Applications are accepted only in electronic environment through the TİTCK Electronic Application and Process Management System (EBS-ESY), signed in accordance with Electronic Signature Law No. 5070. No physical documentation is requested for applications made through the Electronic Application and Process Management System (EBS-ESY), and exceptions thereto are explained in this Guideline. It is essential that the cover letter and documents submitted in applications be prepared in Turkish. However, certain documents are accepted in English, and these documents are explained in the Guideline. Documents prepared in languages other than Turkish and English must be submitted with their Turkish translation (certified by a notary and a sworn translator). In order to identify the documents submitted in application files and ensure their traceability, the documents must be dated and, where applicable, assigned a version number. The definitions set out 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 also apply 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 legal representative of the sponsor, or a contract research organization. When referencing this Guideline, the abbreviation Application Guideline (KAD-KLVZ-02) may be used.

2. INITIAL ELIGIBILITY 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 and the application form. Templates for the cover letter and relevant documents are published on the Agency's website. These templates are updated as necessary, and the cover letter and documents to be used in the application must be prepared using the current templates.

b) Relevant documents The documents that must be included in the initial application file are prepared in line with the explanations set out in Table 1 and added to the application file. The documents that must be submitted signed are explained in Table 4. Pursuant to paragraph 12 of Article 8 of the Regulation, "Applicants are responsible for retaining the originals of all documents submitted to the Agency and for providing them to the Agency upon request."

Table 1 – Documents to be Included in the Initial Application File

No Document Description

It must be prepared in accordance with GCP Section 9.

If the trial protocol is in English, submission of the 2 Trial Protocol original is sufficient. If the trial protocol has been prepared in languages other than English, the Turkish translation of the entire protocol (certified by a notary or a sworn translator) must be submitted.

In multicenter trials, the protocol signature page signed by 3 Protocol Signature Page the coordinating investigator; in single-center trials, the protocol signature page signed by the principal investigator is submitted.

The draft document available on the Agency's website must be used. The benefit-risk assessment must include scientific Plan/report on the benefit-risk assessment 4 explanations stating that the benefit expected from the clinical trial is greater than the risks likely to be encountered in the trial. A risk assessment regarding the participant, the investigational product, and the protocol design must be performed, and the measures to be taken against possible risks must be included.

5 Information shall be provided in the relevant protocol regarding the dose to be used in children, the selection of the indication, age, etc.

Interim analysis report or Independent Data Monitoring 6 Committee report (if applicable)

The informed consent form (ICF) shall be prepared in 7 Bilgilendirilmiş Gönüllü Olur Formu (BGOF) accordance with ICH-GCP Section 10 and the minimum information document required to be included in the

In applications, submission of the investigational product 9 Investigational Product Dossier dossier is mandatory. The documents submitted to the Agency under good manufacturing practices (GMP) must be valid/up to date. If the documents submitted for the manufacturing site(s) are prepared in a language other than Turkish or English, Turkish or English translations certified by a sworn translator and notarized shall also be submitted in addition to the documents in question. Except for the Manufacturing Site License/GMP certificates issued by the Agency, if the Manufacturing Site License/GMP 10 Good Manufacturing Practices (GMP) Certificate/Document certificate submitted for the manufacturing site(s) has not been published in a publicly available database, a signed and apostilled Manufacturing Site License and/or GMP certificate shall be submitted. The apostille must be issued by the country where the relevant document was issued. The Manufacturing Site License/Good Manufacturing Practices (GMP) Certificate/Documents shall be submitted in accordance with the requirements of the "Guideline on Good Practices in Clinical Trial Applications."

(for trials) For Phase I, II, and III trials, adaptive design trials, and bioavailability / bioequivalence (BA/BE) studies, 12 - Insurance certificate insurance is mandatory. - Insurance policy - Insurance endorsements (if any) Where deemed necessary by the Agency and/or the relevant - General and special conditions ethics committee, insurance is mandatory for trials of health-claimed products/methods.

CVs In all trials, the CVs of the principal investigators shall 14 be submitted; in Phase I trials and BA/BE studies, the CVs of the principal investigators together with those of a physician pharmacologist shall be submitted.

15 Previously rejected ethics committee decision (if any)

Applications may be made simultaneously to the ethics committee and the Agency. For this reason, ethics 16 Ethics committee decision for the trial (if any) committee decisions may not be submitted at the time of the initial application to the Agency. However, for the Agency to authorize the trial, it is mandatory that the relevant ethics committee deem the trial to be conducted appropriate.

If the applicant is not the sponsor of the trial, the original and Turkish translation (certified by a notary or sworn Authorization documents translator) of the document specifying the matters in which 17 the legal representative or the contract research organization (if any) acting on behalf of the sponsor has been authorized by the sponsor shall be submitted. In cases where the sponsor is not resident in Türkiye, pursuant to the Regulation, it is mandatory to submit the authorization documents of the legal representative.

Trial team documents (if any) All documents used solely by the trial team or used to - Administration instructions inform the trial team shall be assessed under this category. 18 - Information texts The intended use and place of use of each document shall - Letters to physicians be explained in the cover letter. etc. All documents used by volunteers or used to inform Volunteer documents (if any) volunteers shall be assessed under this category. - Patient card - Patient diary - Survey, instructions for use, administration - Survey, instructions for use, administration instructions, information texts, etc. instructions, information texts, etc. - Advertisement, brochure, etc. - Advertisement, brochure, etc. - Information documents explaining the intended - Information documents explaining the intended use of materials to be given to volunteers use of materials to be given to volunteers (electronic diary, cooler bag, etc.) (electronic diary, cooler bag, etc.) etc. etc. 19 The intended use and place of use of each document shall be explained in the cover letter. Volunteer documents that are not mandatory for the initiation of the trial are not required to be submitted at the time of the initial application. However, ethics committee approval and Agency authorization must be obtained before any of the volunteer documents are used.

If the trial is for academic purposes; a signed document The authorized person is the dean, vice-dean, hospital 20 approved by an authorized person other than the applicant, manager, chief physician, deputy chief physician, head of certifying that the trial is for academic purposes the department, or the education officer.

Only for clinical trials conducted with human medicinal products containing an integral medical device (without a CE certificate); In clinical trials conducted with human medicinal products containing an integral medical device, the signed declaration of the medical device manufacturer stating that the device to be used in the clinical trial complies with the general safety and performance requirements set out in Annex-1 of 21 Declarations of commitment the Medical Devices Regulation published in the Official Gazette dated 02.06.2021 and numbered 31499

The signed declaration of commitment of the sponsor of the trial confirming that all measures have been taken to protect the health and safety of the volunteer with regard to the use of human medicinal products containing an integral medical device

Only for bioavailability/bioequivalence studies;

The batch number and expiry date are stated in the supply

in the package If the investigational product and the reference product(s) are not 22 obtained from within the country, a photocopy of the package Product dossier containing this information, an invoice or a similar document is submitted.

In applications, submission of the investigational product 23 Investigational Product Dossier dossier is mandatory.

Literature/source on pharmacological and If available, literature/source providing pharmacological and 24 pharmacokinetic information (if available) pharmacokinetic information on the tested investigational product is submitted.

2.2. Submission of the Application Initial applications to be made to the Agency with the prepared application file are submitted via the Electronic Application and Process Management System (EBS-ESY):

a) Selection of the Initial Application Process in the Electronic Application and Process Management System (EBS-ESY) In the Clinical Trials Module, the "Initial Application" process is selected. From the list on the page that opens, "New Application" is selected.

b) Selection of Document Type The application document type appropriate for the application is selected from the Document Type field. This selection is required for determining the application fee applicable to the application. In order for applications for which payment of an application fee is required to be evaluated, the correct application fee published on the Agency's website must be paid. No application fee is requested for specialist theses or research for academic purposes.

c) Completion of the Trial Details Screen The Trial Details screen consists of 4 main sections (General Information, Trial Information, Site Information, Volunteer Information). The necessary information is entered into the fields in these sections in accordance with the explanations provided in Table 2.

Section 1 - General Information

1 Application Information

1.1 Application year Automatically assigned by the system. Closed to data entry.

1.2 Type of trial It is the duty of the Department of Clinical Trials to carry out the procedures relating to clinical trials of medicinal products for human use, including traditional herbal medicinal products, homeopathic medicinal products and advanced therapy medicinal products; studies on the intended use of foods for special medical purposes; studies on the use of health claims for foods and food supplements; studies on human tissue- and cell-based products; and studies on treatment methods, excluding organ tissue transplantation and traditional complementary medicine practices. For clinical trials of medicinal products for human use, including traditional herbal medicinal products, homeopathic medicinal products and advanced therapy medicinal products, the application is made by selecting the trial phase appropriate to the trial design (Phase I, II and III trials, trials with adaptive designs, low-risk scientific studies, and BA/BE studies). Studies on the intended use of foods for special medical purposes, studies on the use of health claims for foods and food supplements, studies on human tissue- and cell-based products, and clinical trials of treatment methods (excluding organ tissue transplantation and traditional complementary medicine practices) are applied for as product/method studies with health claims. In accordance with these explanations, one of the following types is selected: - Phase I - Phase II - Phase III - Adaptive Design - Phase I/II - Adaptive Design - Phase I/III - Adaptive Design - Phase II/III - Low-Risk Scientific Study - Bioavailability/Bioequivalence Study - Product/Method Study with Health Claim

1.3 Protocol code It is the identifier assigned by the sponsor for the trial protocol. This identifier code information is entered.

1.3.a NCT Code (if available) The identifier code assigned to each trial during registration on Clinicaltrials.gov is entered.

1.3.b CTIS Code (if available) The identifier code assigned to each trial during registration in the European Medicines Agency (EMA) - Clinical Trials Information Systems is entered.

1.4 Title of the trial The Turkish title of the trial corresponding to the title of the protocol is entered.

1.5 Sponsor status The sponsor is defined as the person, institution or organization responsible for the initiation, management or financing of the trial. The sponsor may be a commercial institution/organization such as a pharmaceutical company, a non-commercial

non-profit institution/organization such as an association, or an investigator. In trials, public funding institutions (The Scientific and Technological Research Council of Türkiye (TÜBİTAK), Presidency of Turkish Health Institutes

2 Sponsor Information

2.1 Sponsor name The title of the legal entity or the name and surname of the natural person that is the sponsor of the trial is entered. In this field, a selection can only be made from among legal or natural persons registered in the Electronic Application and Process Management System (EBS-ESY).

2.2 Name of sponsor not registered The title of the legal entity or the name and surname of the natural in the system person that is the sponsor of the trial is entered. In this field, only the information of legal or natural persons not registered in the Electronic Application and Process Management System (EBS-ESY) shall be entered.

2.3 Name-surname of contact person The name and surname of the person to be contacted on behalf of the sponsor regarding the trial is entered.

2.4 Contact person e-mail The e-mail address of the person to be contacted on behalf of the sponsor regarding the trial is entered.

2.5 Contact person telephone The telephone number of the person to be contacted on behalf of the sponsor regarding the trial is entered.

3 Contract Research Organisation Information

3.1 Contract Research Organisation The application may be submitted by the sponsor or the Contract name Research Organisation. Where the application is submitted by the Contract Research Organisation, the trade title of the organisation acting as the Contract Research Organisation is selected from among the companies registered in the Electronic Application and Process Management System (EBS-ESY).

3.2 Name-surname of contact person The name and surname of the person to be contacted on behalf of the Contract Research Organisation regarding the trial is entered.

3.3 Contact person e-mail The e-mail address of the person to be contacted on behalf of the Contract Research Organisation regarding the trial is entered.

3.4 Contact person telephone The telephone number of the person to be contacted on behalf of the Contract Research Organisation regarding the trial is entered.

4 Legal Representative Information

4.1 Legal representative name Where applicable, the name of the legal representative of the sponsor is stated.

Where the sponsor is not established in Türkiye, the information of natural or legal persons established in Türkiye who are responsible for ensuring compliance with the sponsor's obligations is entered. Where the legal representative is a legal person, the trade title of the organisation acting as the legal representative is selected from among the companies registered in the Electronic Application and Process Management System (EBS-ESY).

The name and surname and contact details of the person to be contacted on behalf of the legal representative are specified.

4.2 Name-surname of contact person The name and surname of the person to be contacted on behalf of the legal representative regarding the trial is entered.

4.3 Contact person e-mail The e-mail address of the person to be contacted on behalf of the legal representative regarding the trial is entered.

4.4 Contact person telephone The telephone number of the person to be contacted on behalf of the legal representative regarding the trial is entered.

5 Coordinator Information

5.1 Coordinating site Clinical trials may be conducted in healthcare institutions and organisations and research and development centres that have, as a minimum, the means and equipment suitable for ensuring the safety of trial volunteers and for the proper conduct and follow-up of the trial: a) the necessary and sufficient personnel and equipment according to the nature of the trial, b) the premises and facilities required for the storage and distribution of the product according to the nature of the investigational product, c) the means and equipment to provide appropriate care for the volunteer, including situations that may require emergency medical treatment, ç) sufficient means and equipment to enable the transfer of the volunteer to a more advanced healthcare institution or organisation when necessary, d) sufficient means and equipment to be able to retain the information and documents relating to the clinical trial and the volunteers after completion of the trial, and that meet the standards determined by the Agency. In multicentre trials, the coordinator is selected by the sponsor from among the principal investigators. The trial site where the principal investigator selected as coordinator is located is regarded as the coordinating site. In line with these explanations, the trial site designated as the coordinating site is selected from the list of opened sites.² In a single-centre trial, the site where the trial will be conducted is selected as the coordinating site.

5.2 Coordinator's name-surname Only the name and surname of the principal investigator selected as coordinator is entered, without title information. In a single-centre trial, only the name and surname of the principal investigator is entered, without title information.

2 University faculties of medicine appear in the list as "Research and Application Hospital", "Research and Application Centre" or "Faculty of Medicine Hospital". In order to ensure that the sites in the list are distinguishable, the names of most sites are preceded by city names. These points should be taken into account when searching. (Example: Ankara Hacettepe University Faculty of Medicine Adult Hospital) 2 Where more than one trial site exists within the same training and research hospital or university hospital (for example, different departments each being a trial site) and one of these sites is the coordinating site, the training [and research hospital or university hospital] to which [the coordinating site is] affiliated ...

5.4 Coordinator telephone The telephone number of the responsible investigator selected as coordinator is entered. In a single-site trial, the telephone number of the responsible investigator is entered.

Section 2 - Trial Information

6 Information on the Scope of the Trial

6.1 Scope The purpose or purposes of conducting the trial are selected from the following: - Diagnosis - Treatment - Prophylaxis - Safety - Efficacy - Pharmacokinetic - Pharmacodynamic - Pharmacogenetic - Pharmacoeconomic - Other; selected for trials that do not fall within the scope of the above and the relevant explanation is written in the text field.

6.2 Randomization Selected as yes or no depending on whether participants are assigned to one of the trial arms.

6.3 Design The strategy for assigning participants to trial arms is selected from the following: - Single arm - Parallel group - Withdrawal - Cross-over - Factorial - Basket - Umbrella - Replicate - Semi-replicate - Other; selected for trials that do not fall within the scope of the above and the relevant explanation is written in the text field.

6.4 Group Selected as adult and/or pediatric depending on the participant population in which the trial is conducted.

6.5 Blinding/Masking Selected from the following depending on whether the parties involved in the trial are prevented from having knowledge of the interventions (trial product/method) administered to participants: - Open label - Single blind - Double blind - Double dummy - Triple blind - Other; selected for trials that do not fall within the scope of the above and the relevant explanation is written in the text field.

6.6 Control type Selected from the following depending on the comparison status of the trial product/method: - Placebo

6.7 Special status Where applicable, selected from the following according to the specific status of the disease or medical condition under investigation and of the trial product/method: - Rare disease / Orphan drug - Biotechnological / Biological product - Biosimilar product - Vaccine - Advanced therapy medicinal product - Gene therapy

7 Trial Field

7.1 Trial fields The trial field to which the disease or medical condition that is the focus of the trial belongs is selected from the drop-down list as one or more.

7.2 Medical condition or disease The name of the disease or medical condition that is the focus of the trial is entered. under investigation Scientifically recognized disease classifications (such as ICD, SNOMED and MeSH) are used for the information in this field, and abbreviations are not made.

8 Information on the Products/Methods Used in the Trial

8.1 Product/Method name The names of the products/methods used in the trial are entered by adding a new record: - For products used in the trial, the international nonproprietary name (INN) and generic name, if available, are entered; for products that do not yet have an INN or generic name, the chemical name, company code or serial number may be used temporarily. Once the INN or generic name of the product has been determined, the relevant field is updated to include that name. - For methods used in the trial, a method name with sufficient detail to allow it to be distinguished from other similar methods is entered.

8.2 Product/Method type Selected from the following according to the role of the products and methods used in the trial: - Investigational product/method - Comparator product/method - Other

8a Information on the Auxiliary Human Medicinal Products Used in the Trial

8a.1 Product name The names of the auxiliary human medicinal products used in the trial are entered by adding a new record:

If the auxiliary medicinal product for human use is licensed in Turkey, the relevant product is selected from the list of licensed products that opens. (Selecting a single commercial product containing the same active substance from the list is sufficient.) If the auxiliary medicinal product for human use is not licensed in Turkey, the name of the auxiliary medicinal product for human use is entered.

8a.3 Authority If not licensed in Turkey, information on the country/authority where it is licensed is entered.

8b Information on the Medical Device Without a CE Certificate Used in the Trial

8b.1 MDCS Application Status Information regarding the Medical Device Clinical Study (MDCS) Application Status for the medical device used is selected.

8b.2 Device name The name of the medical device without a CE certificate used in the clinical trial is entered.

8b.3 Agency document number If a "medical device clinical study application" has been made for the medical device used, please indicate the Research Code/Agency Document Tracking Number/Agency Document Number of the Department of Medical Device Notified Bodies and Clinical Trials.

9 End Dates and Budget

9.1 Estimated trial end date The estimated end date of the trial in our country is selected. If only the month is known, the last day of the month is selected.

9.2 Estimated end date of enrollment The estimated end date of enrollment in our country is selected. If only the month is known, the last day of the month is selected.

9.3 Trial budget The total budget allocated for our country must be entered in Turkish Lira.
Section 3 - Site Information

10 Site Information

10.1 Trial site name By adding a new record, the name of each trial site is entered. The trial site that is the coordinating site must be entered first. Site names are written to include the department, and, if applicable, the division or clinic information, according to the hospital types. For Phase I trials and BA/BE studies, the name specified in the activity license certificate of the site where the trial will be conducted must be written.

10.2 Principal investigator For each trial site, only the name and surname of the principal investigator must be entered, without the title. For Phase I trials and BA/BE studies, only the name and surname of the physician-pharmacologist investigator, who has completed his/her specialization or doctorate and is involved in the trial/study, must be entered, without the title.

Section 4 – Volunteer Information

11 Volunteer Group Information

12 Age Information

12.1 Lower limit According to the design of the trial, the minimum age of potential volunteers is entered using the relevant time units (such as weeks, months, years). If there is no lower limit, data is entered as "-". (For example; 28 days, 12 months, 18 years of age)

12.2 Upper limit According to the design of the trial, the maximum age of potential volunteers is entered using the relevant time units (such as weeks, months, years). If there is no upper limit, data is entered as "-". (For example; 14 weeks, 24 months, 89 years of age)

12.3 Age range The age ranges of the volunteers planned to be included in the trial are selected from the following: - 0 – 27 days - 28 days – 2 years - 2 – 11 years - 12 – 17 years - 18 – 64 years - 65 years and over

13 Gender Information

13.1 Gender The gender information of the volunteers planned to be included in the trial is selected as male and/or female.

14 Volunteer Number Information

14.1 Total The total number of volunteers planned to be included according to the trial protocol is entered. For trials conducted only in our country, the number of volunteers planned to be included from our country is entered (the same number as in 13.2 must be entered).

14.2 Turkey The number of volunteers planned to be included in the trial from our country is entered.

d) Adding Documents The documents included in the application file are uploaded to the system by pressing the Add Document button: (1) Adding a Cover Letter - The electronically signed cover letter is uploaded to the system. - The document upload type must be Cover Letter. - Cover Letter is selected as the clinical trial document upload type.

te is selected. In the case of more than one signatory, the date of the last signature is selected. - The document version is left blank. (2) Adding the Relevant Documents - The documents that must be included in the application file, as specified in Table 1, are uploaded to the system in sequence via the document upload field. When uploading a document: By pressing the Add Document button, the document in pdf format is uploaded to the system from the file selection window (file field). The document upload type must be "Ek" (Attachment). The clinical trial document upload type is selected. The clinical trial document type serves to categorize the documents, and more than one document may be uploaded for each category. The clinical trial document types are listed in Table 3. For the documents uploaded to the system, the document

date and, if available, the version information are entered in accordance with the descriptions provided in Table 3. - The names of the documents uploaded to the system must identify the document. (For example: Protocol, ICF, IB, CV (G. OZTURK), Insurance, CRF, Patient Card, etc.) - If the documents contain more than one date and version information (for example, where the global model and the Turkey date/version differ), the date and version information applicable in our country must be entered. - The presence of a date on the documents is essential. However, if only the year is available for a document, it is entered in the format 01/01/YYYY; if only the month and year are available, in the format 01/MM/YYYY; and for documents for which it is not possible to have a date, this date is selected as the application date. The actual date stated on the document and declared in the cover letter will be taken as the basis for the assessment.

Table 3 – Adding Documents

No Clinical trial document type Document date Version

The date on which the document was 1 Application Form No information is entered. created is entered.

2 Protocol The document date is entered. The version number is entered.

The date on which the document was 3 Trial Flow Chart3 No information is entered. created is entered.

4 Informed Consent Form (ICF) The document date is entered. The version number is entered.

The version number/edition 5 Investigator's Brochure (IB) The document date is entered. number is entered.

6 Insurance The issuance date is entered. The policy number is entered.

8 Case Report Form (CRF) The document date is entered. The version number is entered.

The date on which the document was 9 Trial Team List4 No information is entered. created is entered.

10 Curriculum Vitae The signature date is entered. No information is entered.

11 Letter of Authorization The date of the last signature is entered. No information is entered.

12 Volunteer Document The date of the document is entered. The version number is entered.

The decision date stated on the The decision number stated on 13 Ethics Committee Decision ethics committee decision form is entered. the ethics committee decision form is entered.

14 Other The date of the document is entered. The version number is entered.

15 Interim Analysis Result Reports The date of the document is entered. No information is entered.

16 Risk Management Plan The date of the document is entered. No information is entered.

17 Pediatric Investigation Plan The date of the document is entered. No information is entered.

IMPD (investigational medicinal 18 The date of the document is entered. The version number is entered. product dossier/IMPD)

Good Manufacturing Practice (GMP) 19 The date of the document is entered. No information is entered. Certificate

e) Submitting the Application The initial application file is submitted to the Agency by pressing the Submit Application button. After the application is submitted, the application is formally converted into documentation by following the instructions regarding the payment of the application fee. A unique trial code (TiTCK Code) is generated by the system for each trial. Applicants shall submit all applications related to that trial through this trial code or shall refer to this trial code in any application referring to this trial. Pursuant to paragraph 12 of Article 8 of the Regulation, "Applicants are responsible for retaining the originals of all documents submitted to the Agency and for presenting them to the Agency upon request." In this context, there is no need

to submit any physical documentation in applications to the Agency. Applications must be made with electronic copies of the documents. It is the applicant's responsibility to retain the originals of the documents in order to submit them to the Agency if requested. It is essential that the signed documents included in the application be submitted with an electronic signature in accordance with Electronic Signature Law No. 5070. However, if these documents cannot be submitted with an electronic signature, an electronic copy of the wet-ink signed documents is submitted.

The Agency may make changes to the documents to be submitted physically, where it deems necessary, provided that such changes are published on the Agency's website.

It is essential that the documents listed below be submitted with an electronic signature in accordance with Electronic Signature Law No. 5070. However, if these documents cannot be submitted with an electronic signature

the case, an electronic copy of the wet-signed documents is submitted. - Trial budget form - Insurance documents - Authorization document - Curriculum vitae - Protocol signature page - Handover/acceptance of responsibility document - Document certifying that the trial is for academic purposes - Good Manufacturing Practices (GMP) certificate/document (Apostille-certified) - Ethics committee decision

2.3. Follow-up and Revision of Initial Applications In order to list initial applications, view the details of applications, or edit applications, the "My Initial Applications" section in the Clinical Trials Module of the Electronic Application and Process Management System (EBS-ESY) is used.

a) Submission of the Ethics Committee Decision The applicant may apply to the ethics committee and the Agency simultaneously. For this reason, the ethics committee decision may not be submitted to the Agency at the time of application. In such a case, in order to submit the ethics committee decision of a trial for which an initial application has been made to the Agency: - "My Initial Applications" is selected from the Clinical Trials Module of the Electronic Application and Process Management System (EBS-ESY). - The Edit button is pressed on the row of the relevant trial in the "My Initial Applications" section. - An electronically signed cover letter and at least one ethics committee decision are uploaded to the system from the Document Addition screen. - The instructions in item 2.2(d) - Document Addition regarding the uploading of documents are followed. - The ethics committee decision is transmitted to the Agency by pressing the Send Application button.

b) Revision of the Initial Application The deficiencies identified as a result of the Agency's evaluation of the applications, together with any additional information and explanations required, are notified to the applicant by official letter. In this case, after the trial is made editable by the Agency, in order to revise the initial application file, a revision application is submitted by the applicant together with the necessary information, documents, and explanations: - "My Initial Applications" is selected from the Clinical Trials Module of the Electronic Application and Process Management System (EBS-ESY).

2.4. Withdrawal of the Trial Application The applicant may withdraw the trial application at any time during the evaluation process. In order to withdraw the application, an application is submitted through the General Documents Application of the Electronic Application and Process Management System (EBS-ESY), together with the reasons. After the trial application has been withdrawn, it may be resubmitted to the Agency as a new trial application; however, this matter must be stated in the cover letter.

2.5. Evaluation of Application Files and Trial Authorization If additional information and documents are to be submitted for a trial whose evaluation process is ongoing, an application is submitted to the Agency through the General Documents Application of the Electronic Application and Process Management System (EBS-ESY), together with the reasons. If the justification for the application is deemed valid, the application is made editable by the Agency and the evaluation period is restarted from the beginning. It is the principle that, provided the application is duly made, there are no deficiencies in the information and documents that must be included in the application, and the ethics committee decision is submitted, the application shall be examined by

the Agency and concluded within twenty-two working days. For the trials specified below, a period of thirty working days may be added to the period determined for the review by the ethics committee and the Agency:

- Trials to be conducted using products carrying genetically modified organisms or products involving cellular therapies or gene therapy.

- Trials in which 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 No. 31890 dated 8/7/2022, are conducted together in such a way as to form the subject of the same trial.

The deficiencies identified as a result of the Agency's examination of the initial eligibility application file, together with any additional information and explanations required, are communicated to the applicant. The requested information and documents are submitted by the applicant to the Agency or the ethics committee within thirty working days at the latest. Except in cases deemed necessary by the Agency, force majeure, or compulsory circumstances; if the additional information and documents, or the necessary explanation, together with the information on the date on which they will be submitted, that these information and documents cannot be submitted, are not submitted to the Agency or the ethics committee, the application is deemed withdrawn and cancelled. If the Agency has made a negative decision regarding the conduct of the trial, it notifies the applicant thereof by official letter, stating the reasons. The applicant may, on one occasion only, make the necessary changes on the matters specified in the decision and reapply, or object to the decision with justification within thirty working days. During this process, the review period is suspended. If the requested changes are not fulfilled or an acceptable justification cannot be submitted in this regard, the Agency may reject the trial. If the Agency authorizes the trial, the Initial Eligibility Letter pertaining to the trial is issued and this official letter is notified to the applicant. In accordance with the relevant legislation, the Agency may not authorize trials that do not have ethics committee approval. Trials for which Agency authorization is mandatory may not be initiated without the Agency's authorization. The follow-up of the official letters prepared as a result of the evaluations made by the Agency regarding initial applications is carried out in the "Application List/My Answered Applications" section of the Electronic Application and Process Management System (EBS-ESY). In order to list approved trials and view the details of the trials, the "My Approved Trials" section in the Clinical Trials Module of the Electronic Application and Process Management System (EBS-ESY) is used. The data contained in the "My Approved Trials" section are for informational purposes only and do not signify any approval.

3.1. Substantial Modification Application Any change, made after trial authorization, to any aspect of the trial which may have a significant impact on the safety and rights of the participants and/or on the reliability and validity of the data to be obtained in the trial is defined as a substantial modification.

r. Significant changes in the conduct of the trial may arise from the protocol or from new information regarding the scientific documents supporting the trial. The sponsor shall address the cases one by one and assess whether the change is significant. Significant changes shall 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 significant changes)

Table 5 – Types of Substantial Modifications

1 Changes to the information in the application form

2 Changes to the trial protocol

3 Changes to the informed consent form (ICF)

Changes to the investigator's brochure (those requiring approval from the Agency pursuant to the relevant legislation) 4 Where changes made in the EU are changes that need to be reflected in the informed consent form (ICF) or the trial protocol, ethics committee approval and the Agency's permission must be obtained for the EU change.

5 Changes to the budget form

6 Changes related to insurance (excluding extension of duration)

7 Increase in the number of volunteers planned to be enrolled from our country

8 Changes to documents provided to volunteers/patients

9 Changes related to urgent safety measures

10 Temporary halt of the trial

11 Request for restart of the trial

12 Changes in the safety or health status of volunteers

Changes related to the quality of the investigational medicinal product For changes deemed substantial according to the table in Annex-1 of the Guideline on the Chemical and 13 Pharmaceutical Quality Requirements of Medicinal Products for Human Use in Clinical Trials and the Guideline on the Quality Requirements of Biological Medicinal Products Used in Clinical Trials, ethics committee approval and the Agency's permission must be obtained. According to the relevant Guidelines, the changes shall be presented in the table format set out in Annex-2 of the Guidelines.

14 Changes in the manner of conduct or management of the trial

15 Change of coordinator (in single-centre trials, change of principal investigator)

16 Change of administrative responsible person

17 Change of sponsor

18 Change of legal representative

19 Change of Contract Research Organization

20 Addition of centres (site additions)

Closure of a centre 21 The circumstances under which centre closure applications fall within the scope of substantial modifications are explained in Table 7.

22 Changes in the transfer of essential duties of the trial

3.2. Modification Application The changes listed in Table 6 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 changes or cancel these changes together with the justification.

Table 6 – Types of Changes

Changes related to the principal investigator 1 In multicentre trials, a modification application must be submitted for a change of principal investigator.

Extension of the insurance period For insurance documents previously granted ethics committee approval and the Agency's permission, a 2 modification application must be submitted solely for the extension of the insurance period (policy term), without any of the insurance conditions being altered. There must be no change in the content of the Certificate/Policy or in the policy conditions to which it is linked. If it contains a change, the application is assessed within the scope of a substantial modification.

3 Changes to the patient card/diary in use for authorized trials

4 Extension of the trial duration

5 Extension of the recruitment period

6 Change of the ORF after initial suitability has been granted

7 Changes to the investigator's brochure that do not require ICF/protocol changes

Documents not to be implemented in our country and not containing safety reporting information

8 In international multicentre clinical trials, a modification application must be submitted for changes made to documents that will not be implemented in our country and do not contain safety-related information, such as the Protocol, the IB and the ICF.

3.3.

Notification application

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All modifications/situations/information not falling within the scope of Articles 3.1 and 3.2, but which may affect the oversight and inspection of the trial by the ethics committee and the Agency or the risk/benefit balance of the trial, must be reported 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. The templates for the cover letter and relevant documents are published on the Agency's website. These 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 It is prepared using the cover letter template published on the Agency's website and signed electronically by the authorized person(s) and attached to the application file.

In cases where the modification affects more than one protocol for a specific investigational medicinal product, the applicant must indicate this in the cover letter and must apply to the Agency separately for each study, including a list containing the full name of the trial and, where 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 included: - Updated overall risk/benefit assessment (may be submitted as a separate document) - Possible consequences for the volunteers included in the trial, - Possible consequences for the assessment of the data obtained from the trial, - Situations that may affect the informed consent process.

In responsive submissions to deficiency letters issued by the Agency, the cover letter includes the following information: - The date of the relevant deficiency letter and the outgoing document number, - Responses/explanations regarding the information and documents requested by the Agency, - References to the documents in the file annex relating to the responses/explanations. In an application linked to a previously made application, the cover letter includes information on the date and document number of the relevant application and an explanation of the link between the applications. By signing the cover letter, the applicant undertakes that the information submitted for the modification is sufficient, that the documents in

the file annex accurately reflect the current information, and that the proposed modification is suitable to be implemented.

b) Relevant Documents For modifications to be made to documents already used in the trial or in which the Agency has identified deficiencies; the document showing the modifications and the new document with an updated date and, where available, version number are attached to the application file. The relevant documents are prepared in accordance with the explanations set out in Table 1. The documents to be attached to the application according to the types of modification are set out in Table 7. The modifications that may be made are not limited to the modification types listed in Table 7. The documents to be submitted in signed form are described in Table 4.

Table 7 – 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 template (if available)⁵ - Final version – global template (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 conditions

Insurance Period Extension - Insurance documents for 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

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

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

For modifications that are not related to the trial; solely formal/editorial modifications regarding the visual design of the application, such as font size, typeface, color, screen layout, logo, icon or similar, no permission from the Agency is required. However; in the first modification application to be submitted, a modification history regarding such formal/editorial modifications, also indicating the date/version number, must be submitted to the Agency. Coordinator Change - Responsibility handover/acceptance document between the outgoing and incoming coordinator - Curriculum vitae of the new coordinator - Protocol signature page belonging to the new coordinator

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

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

The draft responsibility handover/acceptance document available on the Agency's website may be used. The trial budget form and insurance documents need not contain the principal investigator's information. If the names of the principal investigator appear in these documents, these 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)

For an increase in the number of volunteers to be enrolled from our country, approval must be obtained from the ethics committee and permission from the Agency, together with the justification. The number of volunteers is not indicated in the trial budget form; however, if the amounts/figures in the budget form change as a result of the update of the number of volunteers, 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 need not be updated. Addition of a Center - 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 the trial sites, the insurance documents shall be updated. Site Closure In site closure applications, the Site List located on the Research Detail screen shall not be updated by the applicant. Closure procedures on the Module are carried out by the Agency. The status of the sites can be tracked from the "My Approved Trials" screen.

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

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

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

Sponsor Change All documents shall be reviewed. The documents updated pursuant to the sponsor change shall be 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, shall be signed by the new sponsor and attached to the application file.

- Transfer document between the old and new sponsors - Updated documents - Undertaking for documents that remain valid (if required) Legal Representative / Contract Research Organization / Applicant Change - Document of authorization - Documents that need to be updated depending on the change (trial budget, insurance, etc.) Temporary Suspension of the Trial Document containing at least the following information regarding the temporary suspension of the trial: (if not submitted as a separate document or if the required information is not available in the relevant document, the missing matters shall be explained in the cover letter) - Date of the temporary suspension (day, month, year), - Reasons for the temporary suspension, - Number of participants continuing to receive treatment at the time of suspension of the trial and their distribution by trial site, - Procedures to be carried out for participants receiving treatment during the temporary suspension, - Evaluation of the results of the temporary suspension and the actions to be taken, - Overall risk/benefit assessment, - Procedures and actions to be taken for the investigational medicinal products remaining at the trial sites and with the participants.

Request for Restarting the Trial Document containing at least the following information regarding the request to restart the trial: (if not submitted as a separate document or if the required information is not available in the relevant document, the missing matters shall be explained in the cover letter) - The planned restart date (day, month, year), if the trial is planned to be started at a date later than the date on which the Agency permitted the restart, - Justification for the restart request, - Actions taken following the temporary suspension and their results, - Overall benefit/risk assessment.

shall be terminated. The rejection of applications does not eliminate the applicant's right to resubmit the modification application. The follow-up of official letters issued as a result of the assessment made by the Agency regarding modifications is carried out through the "Application

List/Answered Applications" section of the Electronic Application and Process Management System (EBS-ESY).

3.7. Urgent Safety Measure If new circumstances arising during the conduct of the trial or the development of the investigational medicinal product (IMP) are likely to affect the safety of participants (volunteers), the sponsor or the responsible investigator may need to take appropriate urgent safety measures in order to protect the participants against such circumstances that may arise. These safety measures may also be implemented without obtaining approval from the ethics committee and permission from the Agency. The sponsor or the sponsor's legal representative notifies the ethics committee and the Agency of the developing urgent safety situation, new circumstances that may arise, and the measures taken against them within seven days at the latest. An application regarding an urgent safety measure falls within the scope of a substantial modification. (Table 5 – No. 9)

3.8. Temporary Halt of the Trial When the sponsor halts the trial (such as halting the enrollment of new participants (volunteers) or discontinuing the treatment of participants who are in the implementation phase of the trial), the sponsor notifies the ethics committee and the Agency of this situation within 15 days. The trial cannot be restarted unless the Agency permits the restart of the trial. Applications regarding the temporary halt and restart requests of the trial fall within the scope of a substantial modification. (Table 5 – No. 10/11) (Table 7) If it is decided to prematurely terminate the trial after the sponsor's decision on temporary halt, a "Notification of Completion of the Trial" is made.

3.9. Change of Applicant Applications are submitted to the Agency by the sponsor, who is a natural or legal person, or by a contracted research organization residing in Turkey or the sponsor's legal representative to be appointed by the sponsor. In the event of a change of applicant, the new applicant applies through the Electronic Application and Process Management System (EBS-ESY) General Document Application. (Table 5 – No. 17/18) (Table 7) As a result of the Agency's assessment, the trial is assigned to the new applicant in the system.

3.10. Failure to Initiate the Trial If a trial has not been initiated within ninety days following the authorization date despite the authorization granted by the Agency, the reason for failure to initiate is notified to the Agency in accordance with Article 3.3. If this situation persists, the notification application is repeated in each ninety-day period. If no participant (volunteer) has been enrolled in the trial in our country within two years from the date the trial authorization was communicated to the applicant, the authorization granted by the Agency shall be revoked unless an extension is approved upon the applicant's request. If the trial authorization is revoked, the application may be resubmitted to the Agency as a new trial application; however, this matter must be stated in the cover letter.

Table 8 – Notification Types

1 Annual Notification (Progress Report)

2 Notification of Completion of the Trial

3 Notification of Completion of the Trial in All Countries

4 Safety Notification: SUSAR Notification

5 Safety Notification: Development Safety Update Report (DSUR) Notification

6 Date Notification: Notification of Start Date

7 Date Notification: Notification of First Visit Date of First Participant (Volunteer)

8 Date Notification: Notification of Enrollment Completion Date

9 Notification of Investigator Assignment/Assignment Termination

10 Notification of Trial Results Report

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 participants (volunteers) (conduct of the initiation visit) is the start date of the trial. This date is notified to the Agency within 15 days. The notification specifies which site has been opened. The electronically signed cover letter regarding the notification is uploaded to the system.

4.2. Notification of First Visit Date of First Participant (Volunteer) The first visit date of the first participant (volunteer) in our country in the trial is notified to the Agency within 15 days. The notification specifies at which site this participant is located. The electronically signed cover letter regarding the notification is uploaded to the system.

4.3. Notification of Enrollment Completion Date The date on which the enrollment of participants (volunteers) in our country in the trial is completed is notified to the Agency within 15 days. In order to restart enrollment, an application is made to the Agency together with the justification for restarting (Table 7). The electronically signed cover letter regarding the notification is uploaded to the system.

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 date range of 01.01.2025 – 31.12.2025 must be made by 31 January 2026.) In cases it deems necessary, the Agency may change the annual notification calendar, provided that it is published on the Agency's website. 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 must be made until the trial is completed.

1 Notification period start Provided by the system; closed for data entry.

2 Notification period end For ongoing trials, 31 December of the relevant year is selected.

Assessment of the therapeutic efficacy of the investigational 3 medicinal product (IMP) or other Selected as Good, Moderate, Poor, or Unknown based on the studied efficacies according to observations within the notification period. the observations

The total amount of payments made to trial sites on behalf of 4 Investigator payment investigators within the notification date range is entered. Specified in TRY.

The total amount of payments, excluding investigator payments 5 Trial site payment made to trial sites within the notification date range, is entered. Specified in TRY.

Total budget amount; within the notification date range, it covers Total budget amount spent on all payments made in our country for the relevant trial, such as the trial in our country within the investigational medicinal product (IMP), comparator product, 6 the date range covered by the premedication and rescue medication costs, investigator payments, notification audit and other treatment costs, necessary equipment costs, field staff service procurement costs, and customs and import payments. Specified in TRY.

If an efficacy assessment of the investigational medicinal products 7 Explanation has been made within the notification period, it is specified.

Where applicable, matters considered useful to explain regarding the trial are specified.

From the start of the trial until the end date of the notification, the numbers 8 Volunteer number information of volunteers screened, enrolled, withdrawn and completing the trial within the scope of the trial are entered on a site basis.

Within the date range covered by the notification and throughout the trial, 9 Adverse event number information the figures for Serious Adverse Events / Reactions and Suspected Unexpected Serious Adverse Reactions (SUSAR) occurring in our country are entered.

10 Adding documents The electronically signed cover letter is uploaded to the system.

4.5. Investigator Assignment / Assignment Termination Notification For investigator assignments, a notification is made to the Agency and 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 commence their duties as of the notification date or, if specified in the application, on a date subsequent to the notification date.

Table 10 – Investigator Assignment Notification Module Operations

The site or sites where the investigator will serve are opened and selected 1 Site(s) of assignment from the list.

A query is made using the investigator's Turkish ID number; upon the query 2 Turkish ID number result, the Turkish ID Number, First Name and Surname information are displayed in the system. It is preferable that the notification be made using the Turkish ID number.

Telephone number 3 The investigator's current contact information is entered. E-mail address

Institution/organization of The name of the institution/organization where the investigator works or to 4 employment Affiliated institution/organization which the investigator is affiliated is entered.

5 University/faculty of graduation The investigator's educational information is entered.

6 Academic title The investigator's academic title is opened and selected from the list.

If the investigator has Good Clinical Practice / Clinical Trial Training, the relevant box is ticked. Information regarding the training is entered: - Name of the training, 7 GCP training - Date of the training (for trainings lasting more than one day, the start date is selected), - Name of the Institution where the training was received (the Institution organizing the training), - If required, an explanation.

Other trials in which the The other clinical trials in which the investigator takes part are entered, 8 personnel is involved specifying the protocol code – TITCK code.

Where applicable, matters considered useful to explain regarding the 9 Explanation assignment are specified.

The electronically signed cover letter is uploaded to the system. 10 Document The relevant documents are uploaded to the system. (The uploading of the documents specified in row 10 is mandatory)

Table 11 – Safety Notifications

No Type Notification Time Explanation

Suspected unexpected serious Made by selecting the "SUSAR" tab in the adverse reactions resulting in 1 Within 7 days Clinical Trials Module of the Electronic death or life-threatening Application and Process Management (SUSAR) System (EBS-ESY). Made by selecting the "SUSAR" tab in the Clinical Trials Module of the Electronic Other suspected Application and Process Management unexpected serious adverse System (EBS-ESY). In cases where SUSARs reactions (SUSAR) Within 15 days not covered by No: 1 subsequently become 2 (SUSAR other than those suspected unexpected serious adverse specified in No: 1) reactions resulting in death or life-threatening, a new SUSAR notification is made within seven days.

Made by selecting the "SUSAR" tab in the Clinical Trials Module of the Electronic Follow-up for No: 1 and No: 2 Application and Process Management 3 Within 8 days

within 8 days report If the information is incomplete in the initial notification made for SUSARs, the full report shall be notified within an additional eight days. In the Clinical Trials Module of the Electronic Application and Process Management System (EBS-ESY), after entering the trial code in the Once a year "Notification Application" tab, it is done by Development safety selecting "Safety Notification: 4 Data locking update report (DSUR) Development Safety Update Report point plus 60 (DSUR) Notification". The Agency may days request the report within a shorter period in cases it deems necessary or in short-term trials.

In the Clinical Trials Module of the Electronic Application and Process Management System (EBS-ESY), after entering the trial code in the 5 6-month foreign SUSAR line Once every 6 months "Notification Application" tab, it is done by list selecting "Safety Notification: Suspected Unexpected Serious Adverse Reaction (SUSAR) 6-Month Line Listing Notification".

- (<https://ebs.titck.gov.tr/Basvuru/KlinikArastirmalar/SUSAR>) The "Make New Notification" button located in the upper right corner of the page is selected.

- On the page that opens, "Domestic" is selected in the Notification Source field. This selection indicates that the SUSAR subject to the notification will be recorded in the system as originating domestically and within the scope of a trial conducted in Türkiye.

- The code of the approved trial in which the SUSAR occurred is entered completely and accurately in the "Trial Code" field. The trial code entered into the system must exactly match the code of the trial approved by the Agency.

- The trial site where the SUSAR occurred is selected from the drop-down list in the relevant field.

- The electronically signed cover letter is uploaded to the relevant section at the bottom of the page. The relevant cover letter template is available on the official website of the Agency.

- The ICSR file is uploaded to the system in XML format. This file contains the SUSAR report for the case subject to the notification and must be prepared in accordance with the technical requirements determined by the Agency. The relevant technical requirements are detailed in the Guideline on Safety Notifications in Clinical Trials (KAD-KLVZ-07). 1 SUSAR Notification - Following the check performed by the system, if the file is found to be appropriate, the notification is successfully recorded; if it is not found appropriate, the errors or deficiencies must be corrected and the application must be rearranged.

- In order to add a follow-up notification to the system, the Global Case Id of the relevant case is first searched in the relevant column in the system. As a result of the search, a notification previously entered into the system for the case in question must exist.

- If the notification is reached as a result of the search, the "Follow-up Notification" option is clicked on the processing screen of the relevant record. With this action, the data entry and document upload screen for the follow-up notification opens.

- On the follow-up notification screen that opens, the electronically signed cover letter on which the follow-up notification is based and the file containing the SUSAR report are added to the system in accordance with the procedure followed in the initial notification.

- When entering the follow-up notification into the system, care is taken to correctly associate the notification with the previously made application.

- However, if the notification related to the follow-up application to be added to the system is not found in the system, the follow-up notification cannot be associated with the existing application since the relevant record is not available in the system. In this case, the notification is entered into the system by creating a new record, treating it as if an initial notification were being made in the system.

- The start and end dates of the development safety update report are selected. Development Safety 2 Update Report - The electronically signed cover letter is uploaded to the system. (DSUR) Notification - The DSUR is uploaded to the system. (It is submitted in English.)

Safety Notifications - The electronically signed cover letter is uploaded to the system. 3 Information - The reference letter responded to is specified in the cover letter. Safety Notifications 4 Deficiency/Response - The electronically signed cover letter is uploaded to the system.

4.7. Early Termination The trial protocol shall include a section specifying the matters related to the termination of the trial. The date of the last visit of the last volunteer included in the trial may be defined as the termination of the trial.

can be defined. Any exceptional case shall be justified in the protocol. The premature termination of a trial for any reason before the conditions specified in the protocol for the completion of the trial have been fulfilled is defined as early termination. If the sponsor decides

not to initiate a trial for which authorization has been obtained, not to restart a trial for which it has decided to temporarily halt, or to prematurely terminate an ongoing trial for any reason, an early termination notification is made. The early termination notification is carried out by selecting the "Notification of Trial Completion" procedure. In this notification, the reasons for not initiating or terminating the trial and the measures regarding the continuation of treatment of the volunteers already enrolled in the trial are explained. When a trial is prematurely terminated, at a minimum the following information shall be presented at the end of the clinical trial report: - The justification for the premature termination of the trial, - The number of volunteers/patients still receiving treatment at the time of trial termination, - The proposed volunteer/patient management for volunteers/patients receiving treatment at the time of trial termination, - The evaluation of the trial results.

4.8. Notification of Trial Completion The completion of a trial is defined as the date on which the trial has been completed in accordance with the protocol and all sites in our country have been closed. The notification of trial completion shall be made to the ethics committee and the Agency within 15 days.

Table 13 – Notification of Trial Completion Module Procedures

In the case of early termination described in Article 4.7, "Early 1 Early termination of the trial Terminated" is marked.

Date of completion of the trial 2 The date on which the trial was completed in our country is selected. in our country

Reason for termination/ 3 In the case of early termination of the trial, it is explained in detail. completion

In the case where the trial is completed as foreseen in the protocol, this is explicitly stated.

Recommended procedures In the case of early termination of the trial, the measures to be 5 regarding the treatment of taken for participants continuing to receive treatment are explained. participants continuing treatment

If it is an international trial, the other countries where the trial has been completed along with our country 6 Countries where the trial was are specified. In the case where the trial has been completed in all terminated/completed countries, this is additionally stated.

In the case of early termination of the trial, the management of investigational medicinal products remaining at the trial site Investigational medicinal (including those in the possession of participants) is explained in 7 products remaining at the detail. trial site In the case where the trial is completed as foreseen in the protocol, there should be no investigational medicinal products at the trial sites; this is explicitly stated.

The total amount of payments made to the trial sites on behalf of the 8 Investigator payment investigators throughout the trial is entered. It is stated in TL.

The total amount of payments made throughout the trial to the trial 9 Trial site payment sites, excluding investigator payments, is entered. It is stated in TL.

The total budget amount covers all payments made in our country for the trial throughout the trial, such as the costs of investigational medicinal products, comparator products, premedication and rescue medications, investigator payments, audit and other treatment costs, 10 Total trial budget necessary equipment costs, field staff service procurement costs, customs and import payments. It is stated in TL.

Throughout the trial, the numbers of participants targeted, screened, 11 Participant number information enrolled, withdrawn, and who completed the trial are entered on a per-site basis.

Budget figures for the last year The budget figures for the period between 1 January of the calendar year of the date on which the trial was completed and the completion date are entered. (For example, for a trial completed on 28 May 2019, the payment amounts made between 1 January 2019 and 28 May 2019 must be reported when submitting the trial completion notification.)

The total amount of payments made to the trial sites on behalf of the investigators during the period between 1 January of the relevant year 12 Investigator payment and the completion date of the trial is entered. It is stated in TL.

The total budget amount covers all payments made in our country for the trial during the period between 1 January of the relevant year and the completion date of the trial, such as the costs of investigational medicinal products, comparator products, premedication and rescue 14 Total trial budget medications, investigator payments, audit and other treatment costs, necessary equipment costs, field staff service procurement costs, customs and import payments. It is stated in TL.

15 Document Attachment The electronically signed cover letter is uploaded to the system.

4.9. Notification of Completion of the Trial in All Countries Completion of the 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 submitted to the ethics committee and the Agency within 30 days.

Table 14 – Module Operations for the Notification of Completion of the Trial in All Countries

In the case of early termination described in Article 4.7, "Early 1 Early termination of the trial Termination" is marked.

Date of completion of the trial 2 The date on which the trial was completed in our country is selected. in our country

Date of completion of the trial 3 The date on which the trial was completed in all countries is selected. in all countries

Number of volunteers enrolled The number of volunteers who completed the trial in all countries 4 from all countries throughout the trial is entered.

5 Adding a Document The electronically signed cover letter is uploaded to the system.

4.10. Submission of the Clinical Trial Results Report Within one year of the termination of the trial at all sites, a summary of the trial results report and a version of this summary prepared in a manner understandable to volunteers shall be submitted to the ethics committee and the Agency. The results report summaries are prepared in accordance with the format published/accepted by the Agency. The electronically signed cover letter regarding the submission and the results report summaries are uploaded to the system.

4.11. Making Notification Applications Notifications to be made to the Agency, together with the prepared application file, are carried out through the Electronic Application and Process Management System (EBS-ESY): a) The "Notification Application" process is selected in the Clinical Trials Module of the Electronic Application and Process Management System (EBS-ESY).

4.12. Evaluation of Notification Applications The outcome of the evaluation carried out by the Agency regarding notifications is followed through the "Electronic Application and Process Management System (EBS-ESY) Application List/Answered Applications" and "My Notifications" screens: - If a complete application has been made in terms of the information and documents to be submitted according to the nature of the notification, and there is no explanation, information, or document requested regarding the notification, the notification is closed on the system and no separate official letter is issued by the Agency. However, in cases the Agency deems necessary according to the nature of the notification, the Agency may notify the applicant of the outcome of the evaluation by official letter. - If a complete application has not been made in terms of the information and documents to be submitted according to the nature of the notification, and/or there is any explanation, information, or document requested regarding the notification, the outcome of the evaluation is notified to the applicant by official letter by the Agency. - If the information in the notification application needs to be updated pursuant to the deficiency letters issued by the Agency, the corrected notification is made as a new notification application. This matter should be indicated in the cover letter. If a deficiency is identified regarding the application as a result of the evaluation and information, documents, and actions are requested, the relevant requests are fulfilled by the applicant and a notification is made to the Agency again.

4.13. Authorization of Safety and Investigator Assignment Notifications Making and following up applications for trials in the Electronic Application and Process Management System (EBS-ESY), as well as following all processes to be carried out in the system, is the responsibility of the applicant. The sponsor may delegate part of its duties to a contract research organization operating in accordance with scientific principles and good clinical practice, provided that a written contract is made and the Agency is informed. In order to make safety notifications and investigator assignment notifications, one or more contract research organizations and the sponsor (in case the application is made by the legal representative) may be authorized on the system, in addition to the applicant. Authorization is made by the applicant by selecting the "Authorization" process on the "My Approved Trials" screen.

5. OVERSIGHT AND INSPECTION OF TRIALS BY THE AGENCY During the trial process, fulfilling the matters specified in the initial suitability letter and conducting the trial in accordance with the approved trial protocol, the relevant legislation, and good clinical practice are the responsibility of the sponsor, the contract research organizations, the principal investigator and the members of the trial team, and all other parties involved in the trial. If the Agency has justified grounds that the trial is not being conducted in accordance with the relevant legislation and good clinical practice and/or that the relevant parties (such as the sponsor, its legal representative, the principal investigator, members of the trial team, third parties involved in the trial) are not complying with their obligations, it may determine and take the necessary actions to remedy these breaches. These measures may be: - Requesting that the necessary changes be made in the trial, - Suspension of the trial, - Termination of the trial, In necessary cases, before taking measures, the views of the sponsor or its legal representative or the relevant principal investigator on the matter may be requested. In this case, the sponsor or the sponsor's legal representative or the relevant principal investigator submits its views on the matter to the Agency within fifteen days. The action plan regarding the implementation of the measures to be taken by the Agency includes the implementation schedule and the date on which the sponsor will report to the Agency on the progress and completion of the implementation. The ethics committee is also informed about this action plan. The sponsor must immediately implement the action plan determined by the Agency and must report the information regarding the progress and completion of the plan in accordance with the determined schedule. The Agency may inspect trials conducted domestically or abroad, investigators, the sites where trials are conducted, the sponsor and the contract research organization, the sites where the investigational products are manufactured, and the laboratories where analyses related to the trial are carried out, with regard to compliance with the relevant legislative provisions, with or without prior notice.

6. OTHER PROVISIONS

6.1. Import Applications for Investigational Products Applications regarding the import of investigational products are made in accordance with the "Guideline on the Import of Investigational Products to Be Used in Clinical Trials."

6.2. Publication of Trial Information Information on trials and trial results, and, in cases the Agency deems necessary, the Agency's summary assessment reports on trials are published by the Agency in a publicly accessible database, provided that commercial secrets and the confidentiality of personal data are observed. The content of the information to be published in the database is announced on the Agency's website.

6.3. Transition to the Electronic Application and Process Management System (EBS-ESY) for Trials Initiated by Investigators As of the date of entry into force of this Guideline, only legal entities are defined as users in the Electronic Application and Process Management System (EBS-ESY). In case the sponsor is a natural person

(for investigator-initiated trials) to be submitted through the Electronic Application and Process Management System (EBS-ESY), investigators who will submit an application must register in the system as users. As of the date determined and announced by the Agency, investigators will

be able to register in the Electronic Application and Process Management System (EBS-ESY). Until the Electronic Application and Process Management System (EBS-ESY) is put into use by investigators, the matters stated in this Guideline regarding the Electronic Application and Process Management System (EBS-ESY) requirements shall not apply to investigators. However, general matters concerning applications (application contents, timings, etc.) shall remain valid for investigators as well.

During this process, all documents contained in the applications to be submitted to the Agency by investigators must be physically submitted to the Agency's document unit.

6.4. Ongoing Clinical Trials As of the date of entry into force of this Guideline, trials that have been authorized by the Agency and are ongoing shall be recorded in the Clinical Trials Module by the applicants within the period determined and announced by the Agency. For the recording of an authorized trial: - The "Initial Application" procedure is selected in the Clinical Trials Module of the Electronic Application and Process Management System (EBS-ESY). The "Legacy Application" option is selected from the list on the page that opens. - The trial code previously assigned by the Agency is entered. (For example, 13- ABC-1) - The status of the trial, the enrollment (recruitment) status, and the approval date (the date of the first suitability letter) are selected. - The application year is selected in accordance with the year contained in the trial code previously assigned by the Agency to the trial. (For example, for the trial with code 13-ABC-1, the figure "13" is taken as the basis and 2013 is selected) - The Trial Details are filled in accordance with the explanations set out in Table 2. The form fields must be filled in according to the most up-to-date approved information of the trial. - The electronically signed cover letter (prepared using the cover letter template published on the Agency's website) and a copy of the first suitability letter are uploaded to the system. - The recording process is completed by pressing the Save button. The recorded information is checked by the Agency, and the applicant is informed. Until the applicants record their ongoing trials in the Clinical Trials Module, they will continue to submit applications for these trials through the Electronic Application and Process Management System (EBS-ESY) General Document Application. However, general matters concerning applications (application contents, timings, etc.) shall remain valid for these trials as well.

6.5. Clinical Trials with an Ongoing Initial Application Process As of the date of entry into force of this Guideline, trials whose initial application process is ongoing will continue to submit their applications through the Electronic Application and Process Management System (EBS-ESY) General Document Application. After the trial is approved, it will be recorded in the Clinical Trials Module by the applicants. For the recording process, the recording procedure specified in Article 6.4 applies.

6.6. Summary of Results Report The version of the summary of results report specified in Article 4.10 of this Guideline, prepared in a manner understandable to participants (volunteers), is submitted to the Agency and the ethics committee.

6.7. Investigator Meeting Applications Applications relating to investigator meetings are made in accordance with the "Clinical Trial Investigator Meeting Application Guideline".

7. REPEALED PROVISIONS The "Guideline on Clinical Trial Applications Made to the TİTCK Department of Clinical Trials (Revision 09)", published on 04.12.2020, has been repealed.

8. ENTRY INTO FORCE This Guideline shall enter into force on the date of its approval.

9. EXECUTION This Guideline shall be executed by the President of the Agency.

REVISION HISTORY

Revision No Revision Date Rationale and Explanations

00 09.04.2010 An update was made before the establishment of the quality management system.

01 20.12.2010 An update was made before the establishment of the quality management system.

02 05.09.2011 An update was made before the establishment of the quality management system.

03 17.04.2013 An update was made before the establishment of the quality management system.

04 06.08.2014 An update was made before the establishment of the quality management system.

05 13.11.2015 An update was made before the establishment of the quality management system.

06 01.12.2019 An update was made due to a change in the Regulation.

07 04.12.2020 An update was made due to a change in the Regulation.

08 18.03.2024 An update was made due to a change in the Regulation.

09 01.04.2024 Word and spelling corrections were made.

10 Updates were made due to a change in the Regulation and the revision of the Pharmacovigilance Applications Guideline. Word and spelling errors were corrected. With the launch of the national SUSAR module, an update was made in the Safety Reports section due to changes occurring in the application processes.