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CLINICAL TRIALS MODULE INFORMATION NOTE

This document contains explanations regarding applications to be submitted through the Clinical Trials Module of the TİTCK Electronic Application System, frequently asked questions about the Module, and explanations of common errors made in the Module. 04.12.2020

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1. PREPARATION OF THE APPLICATION FILE

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a. The documents required to be included in the application file are prepared using the Document Checklist available on the Agency's website.

b. Of the documents contained in the application file, the documents to be signed are prepared as follows. Documents that must be submitted with electronic signature: - Cover letter - Application Form

Documents expected to be submitted with electronic signature: It is essential that these documents be submitted with electronic signature. However, if these documents cannot be submitted with electronic signature, their wet-ink signed versions may be submitted physically. - Research budget form - Insurance documents - Letter of authorization - Curriculum vitae - Protocol signature page - Letter of transfer/acceptance of responsibility - Document indicating that the research is for academic purposes - GMP document*

*If a GMP Certificate or Manufacturing Site License issued by the competent authority of the relevant country for the investigational products is submitted, these documents must be submitted with an apostille or consular certification. Documents prepared in a language other than English must also be submitted with a notarized Turkish translation.

Documents to be submitted with wet-ink signature (may preferably be submitted with electronic signature): - Ethics committee decision (original or a certified copy marked "true copy of the original")

Regarding the electronic signing of documents, the "Electronic Application Guide" should be consulted.

c. The documents must contain the document date and version number. As the documents are updated, a new document date and version number are assigned.

Example document format-1:

Research Protocol Document Date Version No Page 11.05.2020 1.0 1/41

Example document format-2:

If an existing document is updated (in case of an update by the applicant or when a revision is requested by the Agency/Ethics Committee), the date and version number of the document are also updated. Research Protocol Document Date Version No Page 26.09.2020 2.0 1/41

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d. The documents must be named with "expressions describing the document". Example naming is provided in the table below. The documents uploaded to the system must be named in a manner that describes and distinguishes the document, not with file names such as Annex1, Annex2.

No Clinical Trial Document Type Example Naming 1 Research Summary (Application Form) Summary (AF) 2 Protocol Protocol Protocol_TR ProSign 3 Research Flow Chart Flow 4 Informed Consent Form (ICF) ICF ICF_TR ICF_Global ICF_Coord ICF (Parent) ICF (ages 6-9) ICF (Biomarker Substudy) ICF (over 18 years of age) 5 Research Brochure IB (Product name 1) IB (Product name 2) 6 Insurance Insurance Certificate Insurance Policy Insurance Endorsement 7 Research Budget Budget 8 Case Report Form CRF eCRF 9 Curriculum Vitae CV (G.Öztürk) CV (M.Yılmaz) 10 Letter of Authorization Authorization 11 Volunteer Document Patient Card Patient Diary ICF Guide Brochure Poster EQ5DL MMSE 12 Ethics Committee Decision ECD 13 Other Investigator Letter Sponsor Letter Protocol Clarification Letter DMC Letter SmPC/PIL GMP (Product Name) Publication_1 Publication_2

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Example application file screenshot:

e. All documents must be in the form of "Searchable PDF (OCR PDF)" files. On this matter, the "Electronic Application Guide" should be consulted. Documents that are not in this format will not be accepted by the system.

Document Preparation and Naming The documents in the application file are prepared and named with expressions describing the document. Signing It is essential that the signed documents in the application file be submitted with electronic signature. In exceptional cases, wet-ink signed

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documents may be submitted. Module Operations Data entry is made on the Research Detail screen. The documents are uploaded to the system. Submit Application The Submit Application button is clicked and the application is saved in the system. The module assigns a Research Code to the research. Formal Application If required; The application fee is paid. Physical documents are delivered to the Agency's document unit. Assessment The assessment process is initiated by the Agency.

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2. INITIAL APPLICATION MODULE OPERATIONS 2.1. NEW APPLICATION PROCESS To make a new application, the Initial Application process is selected in the Clinical Trials Module.

The New Application option is selected.

2.2. DOCUMENT TYPE SELECTION

The document type appropriate to the research is selected. Applications made by selecting the wrong document type are not taken into assessment.

2.3. COMPLETING THE RESEARCH DETAIL SECTION The form information is completed in accordance with the table below.

Section 1 - General Information 1 Application Information 1.1 Application year Automatically assigned by the system. Closed to data entry. 1.2 Type of research In accordance with the Regulation on the Duties and Working Procedures and Principles of the Service Units of the Affiliated Organizations of the Ministry of Health, published in the Official Gazette No. 30278 dated 22/12/2017, it is the duty of the Department of Clinical Trials to carry out the procedures related to clinical trials of treatment methods and human medicinal products and health-claim products, with the exception of stem cell, organ and tissue transplantation and traditional complementary medicine practices. The definitions set forth in the Regulation on Clinical Trials of Drugs and Biological Products apply to Phase I, II, III and IV trials, observational drug studies, and BA/BE studies. A health claim is defined as all statements indicating, asserting or implying that a product is directly or indirectly beneficial to human health or that it is effective against, protects against, or treats diseases or their symptoms. Human medicinal products and medical devices are excluded from this definition. Clinical trials of health-claim products and clinical trials of treatment methods (excluding stem cell, organ and tissue transplantation and traditional complementary medicine practices) are assessed as health-claim product/method research. In light of these explanations, one of the following types is selected:

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- Phase 1 - Phase 2 - Phase 3 - Phase 4 - Observational Study - Bioavailability/Bioequivalence Study - Health Claimed Product/Method Research

If the trial is designed as a combination of two phases, the earlier phase is selected (e.g., in a Phase 1/2 trial, Phase 1 is selected), or if only one of these two phases is to be conducted in our country, the applicable phase is selected. 1.3 Protocol code This is the identifier assigned by the sponsor to the trial protocol. This identifier code information is entered. 1

1.4 Trial name The Turkish name 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 (such as the Scientific and Technological Research Council of Turkey (TÜBİTAK), the Health Institutes of Turkey (TÜSEB), University Scientific Research Projects Units) or private organizations may provide funding/grants for the trial. However, this does not mean that the funding provider has sponsor status in the trial. The responsibilities of the sponsor are set out in Section 6 of the GCP. In line with these explanations, one of the following types is selected: - Commercial institution/organization - Non-commercial institution/organization - Investigator (Academic/Investigator-initiated trial) 2 Sponsor Information 2.1 Sponsor name The title of the

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legal entity that is the sponsor of the trial, or the first and last name of the natural person, is entered. In this field, a selection can only be made from among the legal or natural persons registered in the Electronic Application System. 2.2 Name of the sponsor not registered in the system The title of the legal entity that is the sponsor of the trial, or the first and last name of the natural person, is entered. In this field, only the information of legal or natural persons not registered in the Electronic Application System should be entered. 2.3 Contact person's first and last name The first and last name of the person to be contacted regarding the trial on behalf of the sponsor is entered. 2.4 Contact person's e-mail The e-mail address of the person to be contacted regarding the trial on behalf of the sponsor is entered. 2.5 Contact person's telephone The telephone number of the person to be contacted regarding the trial on behalf of the sponsor is entered.

1 Note for investigators: The protocol code is the abbreviation or code number assigned by you, the investigator, to identify the trial. Therefore, this code will be determined by the investigator (the applicant) and entered in the relevant field. (Example protocol codes: KAD0001, 2020-TR-KAD-01, COVID-FAV-PMS, etc.)

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3 Legal Representative Information 3.1 Legal representative's name The application may be made by the sponsor or the sponsor's legal representative. If the application is made by a legal representative, the trade title of the institution/organization acting as the legal representative is selected from among the companies registered in the Electronic Application System. 3.2 Contact person's first and last name The first and last name of the person to be contacted regarding the trial on behalf of the legal representative is entered. 3.3 Contact person's e-mail The e-mail address of the person to be contacted regarding the trial on behalf of the legal representative is entered. 3.4 Contact person's telephone The telephone number of the person to be contacted regarding the trial on behalf of the legal representative is entered. 4 Coordinator Information 4.1 Coordinating site Clinical trials may be conducted, preferably in places designed for conducting clinical trials, at university health practice and research centers, approved research and development centers affiliated with universities, and Ministry training and research hospitals, which have the personnel, equipment, and laboratory facilities suitable for ensuring the safety of the persons on whom the trial is to be conducted, for the sound conduct, follow-up, and, where necessary, emergency intervention in the trial, and appropriate to the nature of the trial. In clinical trials conducted at these centers and hospitals, other healthcare institutions and organizations possessing the specified qualities may also be included, provided that this is done under the coordination or administrative responsibility of these centers and hospitals. In multicenter 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 considered the coordinating site. In line with these explanations, the trial site designated as the coordinating site is selected from the list of sites opened 2 . In a single-center trial, the site where the trial will be conducted is selected as the coordinating site. 4.2 Coordinator's first and last name The first and last name of the principal investigator selected as coordinator is entered. In a single-center trial, the first and last name of the principal investigator is entered. The title should not be written. 4.3 Coordinator's e-mail The e-mail information of the principal investigator selected as coordinator is entered. In a single-center trial, the e-mail information of the principal investigator is entered. 4.4 Coordinator's telephone The telephone information of the principal investigator selected as coordinator is entered. In a single-center trial, the telephone information of the principal investigator is entered.

2 University faculties of medicine appear in the list as "Research and Application Hospital," "Research and Application Center," or "Faculty of Medicine Hospital." To ensure the distinguishability of the sites in the list, 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)

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2 Where there is more than one trial site within the same training and research hospital or university hospital (e.g., different departments being trial sites) and one of these sites is the coordinating site, the training and research hospital or university hospital to which they are affiliated is selected.

Section 2 – Trial Information 5 Information on the Scope of the Trial 5.1 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 not covered by the above, and the relevant explanation is written in the text field. 5.2 Randomization Selected as present or absent depending on whether participants are assigned to one of the trial arms. 5.3 Allocation The strategy for assigning participants to the trial arms is selected from the following: - Single arm - Parallel group - Withdrawal - Cross-over - Factorial - Basket - Umbrella - Replicate - Semi-replicate - Other; selected for trials not covered by the above, and the relevant explanation is written in the text field. 5.4 Group Selected as adult and/or child according to the participant population in which the trial is conducted. 5.5 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 not covered by the above, and the relevant explanation is written in the text field. 5.6 Control type Selected from the following depending on what the trial product/method is compared with: - Placebo - No treatment control - Dose comparison - Active control (standard treatment) - Historical control - Other; selected for trials not covered by the above, and the relevant explanation is written in the text field. 5.7 Special situation If 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 6 Trial Field 6.1 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 options. 6.2 Medical condition or disease under investigation The name of the disease or medical condition that is the focus of the trial is entered. The information in this field uses scientifically accepted disease classifications (such as ICD, SNOMED and MeSH) and is not abbreviated. 7 Information on the Products/Methods Used in the Trial 7.1 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 non-proprietary name (INN), if available, and the generic name 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. When the INN or generic name of the product is determined, the relevant field is updated to include this name. - For methods used in the trial, a method name with sufficient detail to distinguish them from other similar methods is entered. - In observational studies, the name of the active substance about which information is to be collected is entered. 7.2 Product/Method type The products and methods used in the trial are selected from the following according to their role in the trial: - Investigational product/method - Comparator product/method - Other 8 Completion Dates and Budget 8.1 Estimated trial completion date The estimated completion date of the trial in our country is selected. If only the month is known, the last day of the month is selected. 8.2 Estimated completion date of participant enrollment The estimated completion date of participant enrollment in our country is selected. If only the month is known, the last day of the month is selected. 8.3 Trial budget The total budget amount allocated for our country must be entered in Turkish Lira. Section 3 – Site Information 9 Site Information 9.1 Trial site name The name of each trial site is entered by adding a new record. The trial site that is the coordinating site should be entered first. Site names are written to include the department, and where applicable the subdivision or clinic, according to the hospital type. 9.2 Responsible

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investigator The name and surname of the responsible investigator at each trial site must be entered. The title should not be written. Section 4 – Participant Information 10 Participant Group Information 10.1 Group The participant groups planned to be included in the trial are selected from the following: - Healthy - Patients - Children

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- Pregnant, postpartum and breastfeeding women - Impaired - Persons in intensive care / unconscious - Geriatric - Other; selected for trials not covered by the above, and the relevant explanation is written in the text field. 11 Age Information 11.1 Lower limit The minimum age of potential participants is entered according to the design of the trial, 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) 11.2 Upper limit The maximum age of potential participants is entered according to the design of the trial, 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) 11.3 Age range The age ranges of participants 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 12 Sex Information 12.1 Sex The sex information of participants planned to be included in the trial is selected as male and/or female. 13 Number of Participants Information 13.1 Total The total number of participants planned to be included according to the trial protocol is entered. For trials conducted only in our country, it must be the same as the figure for Türkiye. 13.2 Türkiye The number of participants planned to be enrolled from our country in the trial is entered.

2.4. ADDING DOCUMENTS 2.4.1. Adding a Cover Letter

The Add Document button is clicked. The electronically signed cover letter to be uploaded is located in the file upload window and selected. The Cover Letter is selected.

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The date on which the cover letter was signed is selected. If there is more than one signatory, the date of the last signature is selected. It is left blank.

2.4.2. Adding Application Documents

The Add Document button is clicked. The document to be uploaded is located in the upload window and selected.

The relevant clinical trial document type is selected.

The document date is selected. The existence of a date on the documents is essential. However, if only the year of the documents is known, it is entered in the format 01/01/YYYY; if only the month and year are known, 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 assessment. The version number is entered.

No Clinical trial document type Document date Version 1 Application Form (Trial Summary) The date on which the document was created is entered. No information is entered. 2 Protocol The document date is entered. The version number is entered.

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3 Trial Flow Chart 3 The date on which the document was created is entered. No information is entered. 4 Informed Consent Form (ICF) The document date is entered. The version number is entered. 5 Investigator's Brochure (IB) The document date is entered. The version number/edition number is entered. 6 Insurance The issue date is entered. The policy number is entered. 7 Trial Budget The date of the last signature is entered. No information is entered. 8 Case Report Form (CRF) The document date is entered. The version number is entered. 9 Trial Team List 4 The date on which the document was created is entered. No information is entered. 10 Curriculum Vitae The signature date is entered. No information is entered. 11 Biological Material Transfer Form (BMTF) 5

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The date on which the document was created is entered. No information is entered. 12 Letter of Authorization The date of the last signature is entered. No information is entered. 13 Volunteer Document The document date is entered. The version number is entered. 14 Ethics Committee Decision The decision date stated on the ethics committee decision form is entered. The decision number stated on the ethics committee decision form is entered. 15 Other The document date is entered. The version number is entered.

2.5. SUBMITTING THE APPLICATION After the required information has been entered into the form fields (trial details) and the documents have been uploaded to the system, the application is submitted to the Agency by pressing the Submit Application button.

In order for an application made through the system to become an official application;

3 The trial flow chart is presented within the Application Form (Trial Summary) document. In the event that this chart is updated during the initial application process, this document type shall be used when the chart is submitted separately during revision applications or upon request by the Agency. 4 The trial team list is presented within the Application Form (Trial Summary) document. In the event that this list is updated during the initial application process, this document type shall be used when the list is submitted separately during revision applications or upon request by the Agency. 5 There is no need to submit Biological Material Transfer Forms in applications. They will be submitted only upon request by the Agency, in which case this document type shall be used.

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- If it is a paid application, the application fee is paid. - If required, the physical documents requested are delivered to the Agency's document unit.

In order for an application to become an official application, it must have an incoming document number and date issued by the Agency. The fact that an application has received a tracking number does not mean that it has become an official application.

2.6. SAVING A DRAFT APPLICATION Trial applications can be saved as Drafts. In Draft Applications, no mandatory field checks will be performed by the system. (Section 8) More than one initial application draft can be saved.

Draft applications can be accessed later from the Application List. Processing on the draft application can be continued by pressing the Detail button.

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2.7. TRACKING INITIAL APPLICATIONS

The My Initial Applications process is selected in order to see the status of trials in the initial application process (the period until Agency authorization is obtained). VIEW BUTTON FUNCTION: The View button is pressed to see the details of applications:

Applications that have not been made official are not listed on the My Initial Applications screen. The Application List is used to view the details of these applications. EDIT BUTTON FUNCTION: The Edit function for trials is explained below:

Operations that can be performed with the Edit Button New Y For applications in "New" status, only an "Ethics Committee Decision Submission" application can be made. More than one Ethics Committee Decision can be submitted. Deficiency E For applications that have been placed in "Deficiency" status, a revision application can be made. In this case, the status of the trial appears as "Revised". More than one revision application cannot be made. Revised V For applications in "Revised" status, only an "Ethics Committee Decision Submission" application can be made. More than one Ethics Committee Decision can be submitted. Rejection R No further action can be taken for trials not approved by the Agency. Cancelled İ No further action can be taken for trials withdrawn by the applicant or cancelled by the Agency.

STATUS COLUMN FUNCTION: The meanings of the letters in the Status column for trials are explained below:

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Initial Application Trial Status New Y New application made to the Agency Deficiency E Application for which a deficiency has been identified by the Agency and/or for which additional information and explanation has been requested Revised V Application revised by the applicant Rejection R Application not approved by the Agency Cancelled İ Application withdrawn by the applicant or cancelled by the Agency

2.8. VIEWING THE APPLICATION

The details of Initial Application / Initial Application Revision / Ethics Committee Decision applications and the Agency's evaluation letters can be accessed from the Application List.

The application made is viewed in the "Detail" section.

The Agency's response letters are accessed from the "Signed Document and Attachments" section.

2.9. RULES AND REMINDERS RULE-1 If a trial has an "Initial Application Revision" or "Ethics Committee Decision Submission" application that has not been made official (not documented), the system does not allow a second application to be made. In this case, the following warning text appears in the system:

If the existing application is not intended to be cancelled, Cancel is selected in the warning text.

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If it is decided to abandon making the existing application, approval is given for the cancellation of the application and a new application is started to be created.

If the OK button is pressed, approval is given for the CANCELLATION of the undocumented application. No further action can be taken for the cancelled application.

RULE-2 More than one "Initial Application Revision" application draft cannot be saved for a trial. In such a case, the following warning text appears in the system:

Cancel is selected in the warning text and processing on the existing draft application can be continued, or approval is given for the deletion of the existing draft application from the system and a new revision application is started to be created. No further action can be taken for the cancelled draft application.

REMINDER-1 Regarding the coordinating site information in the application form (trial details) filled in on the system when making a new application; 1. The coordinating site list includes all sites that can be a coordinating site. 2. Pursuant to Article 11 of the Regulation, university health practice and research centers, approved research and development centers affiliated with universities, and Ministry training and research hospitals can be coordinating sites. For this reason, university faculties of medicine appear in the list as "Practice and Research Hospital", "Practice and Research Center" or "Faculty of Medicine Hospital". 3. In order to ensure that the sites in the list are distinguishable, most site names are preceded by city names. This should be taken into consideration when searching. (For example, Ankara Hacettepe University Faculty of Medicine Adult Hospital) 4. For sites that cannot be found in the list despite the checks performed, or whose naming is determined to be incorrect, an email should be sent to kainfo@titck.gov.tr.

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3. MY APPROVED TRIALS SCREEN

Information on the trials authorized by the Agency for the applicant is displayed on this screen. Current information and documents pertaining to the trials can be viewed, and authorization procedures can be performed.

The abbreviations in the Approved Status column are explained in the table below: Approved Status Column Approved (Active) O Trial that continues as Approved and Active Temporarily Suspended GD Trial for which a decision of temporary suspension has been taken by the applicant Suspended D Trial suspended by the Agency Early Terminated ES Trial for which a decision of early termination has been taken Completed T Trial completed in accordance with the

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protocol

The abbreviations in the Participant Status column are explained in the table below: Participant Status Column Enrollment not started GAB Trial for which enrollment has not been started Enrollment active GAA Trial for which enrollment is ongoing Enrollment suspended GAD Trial for which enrollment has been suspended Enrollment completed GAT Trial for which enrollment has been completed

The function of the View button is as shown in the table: View Button The View button is pressed to view the latest information and documents of the trials. The data contained in the My Approved Trials section is for informational purposes only and does not imply any approval.

The function of the Authorization button is as shown in the table: Authorization Button In order to submit safety notifications and personnel assignment notifications, one or more contract research organizations and, where the application is submitted by the legal representative, the sponsor, other than the applicant, may be authorized on the system.

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4. MODIFICATION/INFORMATION AND NOTIFICATION APPLICATIONS

All applications to be made to the Monitoring and Evaluation Unit (except notifications) are submitted through the Modification/Information menu in the Clinical Trials Module: - Modification Applications (Substantial Modification and Modification) - Modification Revision Applications (such as Deficiency Responses and Ethics Committee Decision submissions) - Information Applications (such as Data Monitoring Committee Letters, Investigator Letters, Protocol Deviation Notifications)

The notifications listed below will be submitted via the "Notification Application" screen: - Annual Notification - End-of-Trial Notification - Safety Notification: CAO/SUSAR Notification - Safety Notification: SUSAR 6-Monthly Line Listing Notification - Safety Notification: Annual Safety Report (ASR) Notification - Safety Notification: Development Safety Update Report (DSUR) Notification - Date Notification: Start Date Notification - Date Notification: Date of First Visit of First Participant Notification - Date Notification: Date of End of Enrollment Notification - Personnel Assignment Notification: Sub-Investigator - Personnel Assignment Notification: Trial Pharmacist - Personnel Assignment Notification: Trial Nurse - Personnel Assignment Notification: Monitor - Personnel Assignment Notification: Participant Physician - Personnel Assignment Notification: Site Staff - Personnel Assignment Notification: Data Entry Support Personnel - Personnel Assignment Notification: Other - Trial Final Report Notification - Personnel Assignment End Notification

Applications made through the wrong screen will not be taken into evaluation.

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5. MODIFICATION/INFORMATION MODULE PROCEDURES 5.1. TRIAL QUERY

Each applicant can search only among their own trials. The information displayed on the screen is verified and the process continues.

5.2. MODIFICATION

- The appropriate document type is selected. Applications made with the wrong document type will not be taken into evaluation. - If the Information document type is selected, the Modification Lists are not displayed. - At least one selection is made from the Modification Lists. - The justification for the modification is entered.

5.3. TRIAL DETAIL UPDATE

- The trial detail becomes editable in accordance with the selected modification types.

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- The relevant fields in the trial detail are updated in accordance with the application made. 5.4. ADDING DOCUMENTS 5.4.1. Adding a Cover Letter

The Add Document button is pressed. The electronically signed cover letter to be uploaded is located and selected in the file upload window. The Cover Letter is selected. The date on which

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the cover letter was signed is selected. Where there are multiple signatories, the last signature date is selected. It is left blank.

5.4.2. Adding Application Documents

The Add Document button is pressed. The document to be uploaded is located and selected in the file upload window.

File names cannot be EK1, EK2, etc.! (Preparation of the Application File)

The relevant clinical trial document type is selected.

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The document date is selected. The presence of a date on the documents is essential. However, if only the year information is available for the documents, it is entered in the format 01/01/YYYY; if only the month and year information is available, in the format 01/MM/YYYY; and for documents for which it is not possible to have date information, 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 evaluation. The version number is entered.

No Clinical trial document type Document date Version 1 Application Form (Trial Summary) The date on which the document was created is entered. No information is entered. 2 Protocol The document date is entered. The version number is entered. 3 Trial Flow Chart The date on which the document was created is entered. No information is entered. 4 Informed Consent Form (ICF) The document date is entered. The version number is entered. 5 Investigator's Brochure (IB) The document date is entered. The version number/Edition number is entered. 6 Insurance The date of issue is entered. The policy number is entered. 7 Trial Budget The last signature date is entered. No information is entered. 8 Case Report Form (CRF) The document date is entered. The version number is entered. 9 Trial Team List The date on which the document was created is entered. No information is entered. 10 Curriculum Vitae The signature date is entered. No information is entered. 11 Biological Material Transfer Form (BMTF) The date on which the document was created is entered. No information is entered. 12 Authorization Document The last signature date is entered. No information is entered. 13 Participant Document The date of the document is entered. The version number is entered. 14 Ethics Committee Decision The decision date stated on the ethics committee decision form is entered. The decision number stated on the ethics committee decision form is entered. 15 Other The date of the document is entered. The version number is entered.

5.5. SUBMITTING THE APPLICATION After the required information has been entered into the form fields (trial detail) and the documents have been uploaded to the system, the application is submitted to the Agency by pressing the Submit Application button.

For an application made through the system to become an official application;

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- If it is a paid application, the application fee is paid. - If required, the physical documents requested are delivered to the Agency's document unit.

For an application to become an official application, it must have an incoming document number and date issued by the Agency. The fact that an application has received a tracking number does not mean that it has become an official application.

5.6. SAVING A DRAFT APPLICATION Trial applications can be saved as Drafts. For Draft Applications, no mandatory field checks will be performed by the system. (Section 8) More than one initial application draft can be saved.

Draft applications can be accessed later from the Application List. Processing on the draft application can be continued by pressing the Detail button.

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5.7. VIEWING APPLICATIONS

Details of modification applications and the Agency's assessment letters can be accessed from the Application List.

The application made is viewed from the "Detail" section.

The Agency's response letters are accessed from the "Signed Document and Attachments" section.

5.8. RULES AND REMINDERS RULE-1 If there is a modification/notification application that has not been made into an official application for a trial (not converted into a document), the system does not allow a second application to be made. In this case, the following warning text appears in the system:

If the existing application is not intended to be cancelled, "Cancel" is selected in the warning text. If it is decided to abandon making the existing application, approval is given for the cancellation of the application and a new application is started to be created. If the OK button is pressed, the process continues for the CANCELLATION of the application that has not been converted into a document. In the system, together with the tracking number, an approval checkbox appears for the CANCELLATION process. No further action can be taken on the cancelled application.

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RULE-2 More than one "Initial Application Revision" application draft cannot be saved for a trial. In such a case, the following warning text appears in the system:

"Cancel" is selected in the warning text and the existing draft application can continue to be edited, or approval is given for the deletion of the existing draft application from the system and a new revision application is started to be created. No further action can be taken on the cancelled draft application.

REMINDER-1 (Sample Modification Application) For a Sample Modification Application, Section 10 should be reviewed.

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6. NOTIFICATION APPLICATION MODULE OPERATIONS 6.1. TRIAL QUERY AND NOTIFICATION TYPE SELECTION

- Each applicant can search only among their own trials. - The type of notification to be made is selected.

6.2. DATA ENTRY AND DOCUMENT ATTACHMENT

- The required data are entered. - Documents are attached and the notification is submitted.

6.3. TRACKING NOTIFICATIONS

Notifications can be tracked and viewed on the My Notifications screen.

The Agency's feedback on notifications can be tracked from this screen.

Details of the notifications can be accessed by pressing the View button.

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The abbreviations in the Status column are explained as in the table below: Status Column New Y Notification not assessed by the Agency Approved O Notification recorded by the Agency Rejected R Notification rejected by the Agency

- If a complete application has been made in terms of the information and documents required to be submitted according to the nature of the notification and there is no requested explanation, information or document 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 assessment result by an official letter. In this case, the status of the notification is displayed as "O". - If a complete application has not been made in terms of the information and documents required to be submitted according to the nature of the notification and/or there is any requested

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explanation, information or document regarding the notification, the assessment result is notified to the applicant by an official letter issued by the Agency. In this case, the status of the notification is displayed as "R". - The Agency's response letters regarding notifications can be accessed from the "Application List" and "My Answered Applications" screens. - Based on the deficiency letters issued by the Agency, a new notification application is made with the required explanations and corrections. This matter should be stated in the cover letter. Deficiency response applications regarding notifications must absolutely not be made from the Modification/Notification screen. - The assessment of safety notifications is of a continuous nature. For this reason, the recording of safety notifications does not mean that the assessment has been completed. - The recording of notifications by the Agency does not remove the obligation to notify the ethics committee. All notifications must also be made to the relevant ethics committee simultaneously with the Agency.

6.4. VIEWING APPLICATIONS

Details of notification applications and the Agency's assessment letters can be accessed from the Application List.

The application made is viewed from the "Detail" section.

The Agency's response letters are accessed from the "Signed Document and Attachments" section.

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7. INSTRUCTIONAL VIDEOS

Below are the links to the videos prepared to assist with the operations to be carried out in the Clinical Trials Module:

Initial Application https://youtu.be/NFZ3vJFJ94M Initial Application Revision https://youtu.be/sc7BcPixnTw Ethics Committee Decision Submission https://youtu.be/y6oBHK3P2M4 Modification/Notification Applications https://youtu.be/pv9etbpL6Gs My Approved Trials https://youtu.be/xYQC9NA2z1E

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8. SAVING A DRAFT APPLICATION

In order to save a draft application, the document type must first be selected. This field can be updated later.

When saving a draft application, for the attached documents, it is mandatory to select the clinical trial document upload type and enter the document date; if documents are attached without entering this information, the application is considered erroneous by the system. NO FURTHER ACTION SHOULD BE TAKEN ON THIS DRAFT.

While saving applications as drafts, no other action should be taken for the Draft Application unless the following warning text is displayed.

If the following error is received while saving a draft or submitting an application, the application is considered erroneous by the system. NO FURTHER ACTION SHOULD BE TAKEN ON THIS DRAFT.

In this case, it should be checked whether all documents are in word-searchable format (PDF OCR). For detailed information on saving PDF files in OCR format, the relevant section of the Electronic Application Guideline should be reviewed. If the following error is received while saving a draft or submitting an application, the application is considered erroneous by the system. NO FURTHER ACTION SHOULD BE TAKEN ON THIS DRAFT.

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When it is desired to re-edit the Draft Application: a. The system's uploading of the documents is awaited.

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b. After the process is completed (the upload status bar disappears), if the documents are not visible (some or all of them), the page is refreshed. c. Upon refreshing the page, the system's uploading of the documents is awaited.

d. After the process is completed (the upload status bar disappears), if the documents are still not visible (some or all of them), the draft application is closed. The draft application is re-entered from the Application List for editing.

e. The system's uploading of the documents is awaited.

If, after the process is completed (the upload status bar disappears), the documents are not visible (some or all of them), your application is considered erroneous by the system. NO FURTHER ACTION SHOULD BE TAKEN ON THIS DRAFT.

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9. FREQUENTLY ASKED QUESTIONS / FREQUENTLY MADE ERRORS 9.1. PERSONNEL ASSIGNMENT FREQUENTLY ASKED QUESTIONS Can only one person be assigned per application? Yes, only one person can be assigned per application.

Can a general cover letter and application form be used? In personnel assignment, a general cover letter specific to the trial can be used. For personnel assignments made through the Module, there is no need to submit an application form.

For the members of the trial team listed in the trial team list during the first eligibility process after the trial authorization, will a personnel assignment notification be made? Yes, for trials approved through the Module, a notification must be made after the trial approval for all personnel, except the principal investigator who will start duty.

Must a curriculum vitae be submitted for personnel assignments made through the Module? No, there is no need to submit a curriculum vitae in printed or electronic form. The information requested in the curriculum vitae form will be declared through the Module.

Is it necessary to submit authorization and acceptance of authorization documents in monitor assignment notifications? No, for monitor assignments made through the Module, there is no need to submit authorization and acceptance of authorization documents.

Is it mandatory to make the notification through the Turkish ID number? Making the notification through the Turkish ID number is the principle, but it is not mandatory.

What should be done if personnel assignment notifications in the Module are to be made by a company other than the main applicant? First of all, the trial must be a trial registered in the Module. Information on whether the trial is registered in the Module is requested from the main applicant. For trials registered in the Module, in order for personnel assignment applications to be made, the main applicant must authorize the relevant company in this regard through the Module. This procedure will be carried out only through the Module and does not require any application. The authorization procedure will be carried out on the screen that appears when the Authorization button on the "My Approved Trials" screen of the Module is pressed.

Until trials are registered in the Module, personnel assignment notifications will continue to be made through the old system (EBS General Document Application).

Can the assignment termination notifications of personnel for whom no assignment notification was made through the Module be made through the Module? No, for personnel for whom no assignment notifications were made through the Module, assignment termination notifications must also be made through the old system (EBS General Document Application).

How are the Agency's feedback on notifications displayed? The Agency's feedback on notifications can be viewed on the "My Notifications" screen in the Module.

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In addition, the Agency's feedback regarding notifications can be viewed in the "Notifications" section on the EBS home page. The feedback in this section can only be viewed by the user who made the notification. A limited number of feedback items can be displayed in this section.

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9.2. CLINICAL TRIAL FINAL REPORT FREQUENTLY ASKED QUESTIONS Is the submission of the summary of the final report sufficient? Yes, the submission of the summary of the final report is sufficient. Submission of the entire clinical trial final report is not mandatory.

Is it mandatory to use the final report summary format published by the Agency? The draft published by the Agency is a sample format, and applicants may also use their own drafts with similar content and in compliance with the relevant guideline (E3-Structure and Content of Clinical Study Reports).

Is the submission of a version of the final report summary prepared in a manner understandable to volunteers (final report summary for volunteers) mandatory? The submission of the final report summary for volunteers will be mandatory as of the date determined and announced by the Agency. However, during this period as well, if a final report summary document for volunteers is prepared, it may be submitted to the Agency and the ethics committee.

The Module gives a warning regarding the addition of the final report summary for volunteers during the notification of the final report summary, but this document has not been prepared in the trial. What should be done in this case? In the final report summary notifications to be made until the submission of the final report summary for volunteers to the Agency and the ethics committee begins; a pdf containing a declaration that the final report summary document for volunteers is not available shall be attached to the Module as an attachment.

Will the Agency publish a format for the final report summary for volunteers? A document regarding the minimum information that must be included in the final report summary for volunteers will be published by the Agency. However, during this period, applicants may use their own drafts.

9.3. REGISTRATION OF TRIALS IN THE MODULE FREQUENTLY ASKED QUESTIONS Which trials will be registered in the Module? Trials with application years 2019, 2018, 2017 and 2016 will be registered in the Module in accordance with the schedule announced on the Agency's website. 6

Will terminated trials be registered in the Module? No, terminated trials will not be registered in the Module. There is no need to register trials for which a termination notification has been made to the Agency.

Will applications for a trial for which a termination notification has been made continue to be submitted through the old system? Yes, the applications/notifications to be made for a trial for which a termination notification has been made (such as the submission of the final report) will continue to be made through the old system (EBS General Document Application).

Will ongoing bioavailability/bioequivalence studies be registered in the Module? No, ongoing bioavailability/bioequivalence studies will not be registered in the Module.

Must the Agency's review of the registration application be awaited in order to make applications for trials registered in the Module? No, all applications/notifications of an application registered in the Module will now start to be made through the Module. For this, the review of the registration application is not awaited.

6 Two announcements have been published by the Agency for the registration schedule (Announcement 1) (Announcement 2).

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For example, for an application for a substantial modification to be made after the registration application, the review of the registration application is not awaited. The application is made through the Module; applications are not made through the old system (EBS General Document Application). Applications made through the old system are not taken into evaluation.

How will the registration process be carried out for trials whose first application was made through the old system and whose process is still ongoing? Following the issuance of the first eligibility letter for the trial, the relevant trial will be registered in the Module within 5 business days. Until the registration in the Module is completed, no application for this trial shall be made through the old system; the registration process shall be completed first.

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Will applications for trials whose first application was made through the old system and whose process is still ongoing be made through the Module? No, applications for these trials will continue to be made through the old system until the trial is approved. Following the issuance of the first eligibility letter for the trial, the relevant trial will be registered in the Module within 5 business days.

A letter has been received from the Agency regarding the submission of the ethics committee decision for a previously submitted trial site addition application. In this case, should the sites in this application be added to the site list in the registration application? No, trials must be registered in the Module in accordance with the latest approved information and documents. In applications, requesting the ethics committee decision constitutes a deficiency, and these information and documents have not yet been approved. Applications for which a letter has been issued stating "... has been deemed appropriate." or "... has been informed." must be accepted as information and documents approved by the Agency.

What should be done if a modification/information submission made in the old system for a trial affects the Trial Detail screen? The Trial Detail screen must be checked during each modification/information submission. For example, if the ethics committee decision of a change in the number of volunteers made through the old system is to be submitted through the Module, the number of volunteers information on the Trial Detail screen is checked in this application and, if necessary, updated.

According to the announcement dated 30.01.2020, certain fields have been closed to data entry. A deficiency letter has been received from the Agency for the correction of these fields for a previously made registration application. What should be done in this case? According to the announcement published on our Agency's website as of 30.01.2020; due to erroneous data entries made in the "Maximum dose", "Maximum duration of administration" and "Product/method description" sections of the products/methods, these sections have been closed to data entry. If a deficiency letter has been received from the Agency for the correction of these fields for a previously made registration application, corrections for these fields are not required, as it is not possible to update these fields.

9.4. FREQUENTLY MADE ERRORS 1. Application Form – Trial Summary document It has been identified that the application form is submitted with the wrong clinical trial document type. The application form is considered to be the same document as the Trial Summary. Therefore, the application form – trial summary document must be submitted under the "Trial summary/Protocol summary" clinical trial document type. 2. Volunteer age range information It has been identified that invalid/incorrect expressions are entered for the upper or lower limit in the field where the volunteer age range is entered. For example; - Above 65 years of age - Above 18 years of age - >65 - Over 1 year of age If the protocol does not impose a specific limitation on the lower and upper limits, it is sufficient to enter a hyphen (-) in this field. The relevant limits must be entered using time units. (e.g., 18 years, 28 days, 12 weeks)

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3. First and last name information The first and last name information entered must be entered without titles. 4. Information section for products/methods used in the trial It has been identified that incomplete information regarding the trial/comparator products is entered in this section. A product with more than one dose, pharmaceutical form and route of administration must be entered only once. For example, the product KAD001 has both 30 mg oral and 50 mg IV uses. This product is registered as KAD001. Multiple entries such as "KAD001 30 mg oral" and "KAD001 50 mg IV" must not be made.

Example data entries are provided below: Example Product Information Data Entry Example Product Information Data Entry Product/Method Name Product/Method Type Product/Method Name Product/Method Type KAD0001

Investigational product/method KAD0001

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Investigational product/method Denemab Control product/method Denemab Other KAD001 matching placebo Control product/method

5. Numeric entries It has been identified that copy-paste errors are made in the fields where numeric entries are made. Data must be entered in these fields in the 12345.34 format without copy-pasting. 6. Document naming It has been identified that documents submitted as annexes to the application are named Annex 1, Annex 2, etc. Document names must be descriptive of the document. (e.g., Protocol, ICF, Insurance Certificate) 7. Use of Turkish characters It has been identified that data entry is performed using English characters during data entry. For example, the Ege Üniversitesi Tıp Fakültesi site is entered as "Ege Universitesi Tip Fakultesi". Data entry must be performed using Turkish characters.

10. EXAMPLE MODIFICATION APPLICATION

The file described below is an example file. Depending on the content of the application, the documents that must be included in the application file and the operations to be performed in the Module may vary.

A Modification/Information File containing the following four modifications will be created for the trial and the application will be submitted through the Module. The modifications to be made: 1. Addition of two new sites to the trial 2. Closure of one site in the trial 3. Replacement of the principal investigator of one site in the trial 4. Protocol modification

STEP 1: REVIEW OF THE APPLICATION GUIDE Section 3 of the Application Guide contains explanations regarding making modifications to trials. The content of the application file is determined according to the modification to be made in accordance with the Guide.

1. MODIFICATION: Addition of 2 new sites to the trial According to Table 5 of the Application Guide, site addition falls within the scope of a "Substantial Modification". The documents to be submitted for the addition of sites are described in Table 7;

2. MODIFICATION: Closure of one site in the trial According to Table 5 of the Application Guide, site closure may be evaluated within the scope of a "Substantial Modification". Upon the request of the principal investigator, the "Ankara Şehir Hastanesi" site is being closed; no volunteers have been screened or enrolled at this site. The appropriate option is determined according to Table 7;

3. MODIFICATION: Replacement of the principal investigator of one site in the trial According to Table 6 of the Application Guide, a principal investigator change falls within the scope of a "Modification". The documents to be submitted for a principal investigator change are described in Table 7;

4. MODIFICATION: Protocol modification According to Table 5 of the Application Guide, a protocol modification falls within the scope of a "Substantial Modification". The documents to be submitted for a protocol modification are described in Table 7;

STEP 2: PREPARATION OF THE APPLICATION FILE After the list of required documents is prepared in accordance with the Application Guide, the application file is prepared. The application file consists of three parts: (Application Guide Article 3.4) (Preparation of the Application File) - Cover Letter - Application Form(s) - Relevant Documents

The documents among the relevant documents to be submitted electronically or with wet signatures are described in Table 4 of the Application Guide.

- The required cover letter template, application forms and other documents to be used are downloaded from the website. (https://www.titck.gov.tr/faaliyetalanlari/ilac/klinik-arastirmalar)

- Application forms are filled in and signed with electronic signature. - CVs are obtained with electronic signature. (If they cannot be obtained with electronic signature, they are submitted with wet signature.) - The budget form is filled in and signed with electronic signature. (If it cannot be

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obtained with electronic signature, it is submitted with wet signature.) - The Responsibility Handover and Acceptance document is obtained with electronic signature. (If it cannot be obtained with electronic signature, it is submitted with wet signature.) - The protocol signature page belonging to the coordinator is obtained with electronic signature. (If it cannot be obtained with electronic signature, it is submitted with wet signature.) - The cover letter template is filled in and signed with electronic signature. - If there are documents to be submitted physically, these documents are scanned and attached to the file. - All PDFs must be in OCR format. - Document naming must be in a manner that identifies the document, as explained under Preparing the Application File.

Application Summary: Document Version/Date 1_Cover Letter 07.01.2020 2_Substantial Modification BF 07.01.2020 3_Modification BF 07.01.2020 Site Addition Bursa City Hospital Medical Oncology Clinic Principal Investigator: Mehmet Arslan Adana City Hospital Medical Oncology Clinic Principal Investigator: Ceyhun Kaya Annex1a-CV (M ARSLAN) 08.01.2020 Annex1b-CV (C KAYA) 06.01.2020 Annex1c-Budget 11.01.2020 Site Closure Upon the request of the Principal Investigator, Ankara City Hospital is being closed without enrollment of volunteers. Principal Investigator Change At the Hacettepe University Oncology Hospital site, Derya Deniz will be appointed as the principal investigator in place of Kadriye Kurt. Annex2a-CV (D DENİZ) 09.01.2020 Annex2b-PI_Responsibility Acceptance (D DENİZ) 11.01.2020 Annex2c-PI_Responsibility Handover (K KURT) 11.01.2020 Protocol Modification A new cohort was added (1 mg tablet daily) The total number of volunteers was increased to 400 Annex3a-Protocol_Clean 12.12.2019 / Version 2.2 Annex3b-Protocol_TC 12.12.2019 / Version 2.2

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Annex3c-Pro_Signature 08.01.2020

STEP 3: MODULE OPERATIONS - The Modification/Notification screen is opened.

SCREEN 1 (TRIAL QUERY) - The trial code is queried. The code of the trial available in the Module must be used. Each company can only search among its own trials.

- The information displayed on the screen is verified and the process continues.

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SCREEN 2 (MODIFICATION) - The document type is selected. Since the modification application includes a modification falling within the scope of "Substantial Modification", the substantial modification application document type is selected. - The relevant modifications are selected from the Substantial Modification and Modification list.

- The justification for the modification is entered.

SCREEN 3 (TRIAL DETAIL) - The necessary updates are made on the Trial Detail screen.

a. Addition of two new sites to the trial - The "Site Information" section is opened. - The "Add New Record" button is clicked.

- The Site Name and Principal Investigator information are entered.

b. Updating the budget amount on the basis of the addition of two new sites to the trial - With the update in the budget form, the total budget amount has also changed. The budget amount is updated. Existing information:

Updated information:

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c. Closure of a site in the trial - No action is to be taken in the Trial Detail. In site removal/closure applications, no action is taken by the applicant on the Site List on the Trial Detail screen. Closure/removal operations on the Module are performed by the Agency.

d. Changing the principal investigator of a site in the trial - The Update button is clicked for the relevant site in the site list.

- The necessary update is made.

- The Save button is clicked.

e. Updating the total number of volunteers on the basis of the protocol modification - With the protocol modification, the total number of volunteers to be included in the trial is being

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increased to 400. The total number information is updated.

Existing information:

Updated information:

SCREEN 4 (DOCUMENT) For each document; - The document is attached. - The document type is selected. - The date is entered. - If applicable, the version number is entered.

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- The undertaking statements are checked. - the Submit Application button is clicked.

SCREEN 4 (DOCUMENTATION) - After the Submit Application button is clicked, an information screen as below is expected to appear for the trial.

In accordance with the instructions given on the information screen; - If required, the application fee is paid. - Physical documents are delivered to the Agency's document unit.

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