GUIDELINE ON THE PRINCIPLES OF SITE ORGANISATION MANAGEMENT IN CLINICAL TRIALS 13 NOVEMBER 2015

1. PURPOSE AND SCOPE This guideline has been prepared to set out the rules and conditions to be followed where, within the scope of the "Regulation on Clinical Trials of Pharmaceuticals and Biological Products", the coordinator or principal investigator involved in clinical trials conducted in our country wishes to include a qualified person from a contract research organisation in the trial team as a site staff member, under his/her own supervision and oversight, for the purpose of performing site organisation management services at the trial site. It has been prepared to set out the rules and conditions to be followed where, within the scope of the Guideline on Observational Drug Studies, the coordinator physician or participating physicians involved in observational drug studies conducted in our country wish to include a qualified person from a contract research organisation as data entry support personnel, under their own supervision and oversight, in the study team in order for the data to be recorded in the required environment.

2. DEFINITIONS The definitions set out in the Regulation on Clinical Trials of Pharmaceuticals and Biological Products, the Guideline on Observational Drug Studies, the Good Clinical Practice Guideline and the relevant legislation shall apply.

3. GENERAL CONDITIONS 3.1. The person to be included in the trial team as a site staff member should preferably be a member of staff of the trial site or institution where the trial is conducted. 3.2. Where the site staff member to be assigned is not a member of staff of the trial site or institution where the trial is conducted, the principal investigator may make a request to this effect to the contract research organisation, independently of the sponsor, in order for the site organisation management services to be performed. This request must be documented by means of a site staff request letter for the site organisation management service. 3.3. Persons to be assigned as site staff members should preferably be graduates of health/science disciplines. 3.4. A site staff member who is an employee of a contract research organisation should not take part at the same time in trials with different sponsors. However, if the Turkish Medicines and Medical Devices Agency (TİTCK) deems it appropriate and it is justified by the applicant, the site staff member may also take part at the same time in trials with different sponsors, and this matter must be notified to the sponsor. 3.5. Personnel working as site staff members must be authorised by the contract research organisation by which they are employed. 3.6. Site staff members to be assigned to clinical trial projects may provide support to a maximum of 5 (five) different principal investigators. However, taking into consideration circumstances such as the nature of the study and the number of volunteers participating in the study, assignments may also be made for a greater number of principal investigators. 3.7. The contract research organisation must ensure control of the assignment status of site staff members and of site activities, and must submit to the Turkish Medicines and Medical Devices Agency (TİTCK) the monitoring activity report, prepared every 6 (six) months following the initial project assignment of the site staff member, in a site staff member-specific manner. 3.8. The contract research organisation must submit to the Turkish Medicines and Medical Devices Agency (TİTCK) the current status table of site staff member projects set out in the annex to this guideline. 3.9. Site staff members must receive the relevant training on basic good clinical practice and on the clinical trial in which they will take part.

3.10. Within the scope of this guideline, site staff members may take part only in clinical trials covered by the "Regulation on Clinical Trials of Pharmaceuticals and Biological Products" and conducted in accordance with the relevant legislation. 3.11. At a site where the studies defined in the observational drug studies guideline are conducted, data entry support personnel may be authorised by the coordinator or participating physician of the study. It is not necessary for each participating physician to authorise personnel separately. 3.12. In order for the data entry support services to be performed, the coordinator or participating physician may make a request to this effect to the contract research organisation, independently of the sponsor. This request must be documented by means of a data entry support personnel request letter for the data entry support

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service. 3.13. A person working as data entry support personnel must be authorised by the contract research organisation by which he/she is employed. 3.14. Data entry support personnel must receive the relevant training on basic good clinical practice and on the observational drug study in which they will take part.

4. RESPONSIBILITIES 4.1. Responsibilities of the Coordinator or Principal Investigator 4.1.1. The coordinator or principal investigator of the trial site or institution where the site staff member will be included must document that the sponsor of the trial has been informed. 4.1.2. Only the coordinator or principal investigator may direct the site staff member. The coordinator or principal investigator must submit the site staff member to be assigned to the sponsor for approval. 4.1.3. He/she must undertake that the person assigned as a site staff member acts independently of the sponsor, complies with the task descriptions specified in the authorisation list, and has no authority whatsoever to alter the clinical trial data. 4.1.4. The coordinator or principal investigator is responsible for making, where necessary, the administrative notifications required at his/her institution in relation to the site staff member he/she has assigned. 4.2. Responsibilities of the Coordinator or Participating Physician 4.2.1. The coordinator or participating physician of the study in which the data entry support personnel will be included must document that the sponsor of the study has been informed. 4.2.2. He/she must undertake that the person assigned as data entry support personnel acts independently of the sponsor, complies with the task descriptions specified in the authorisation list, and has no authority whatsoever to alter the observational drug study data. 4.2.3. The coordinator or participating physician is responsible for making, where necessary, the administrative notifications required at his/her institution in relation to the assigned data entry support personnel. 4.3. Responsibilities of the Sponsor 4.3.1. The sponsor must enter into the necessary commercial agreements with the relevant parties for the financing of the services to be procured in accordance with this guideline. 4.3.2. Apart from the financing, the sponsor may provide training to the site staff member or data entry support personnel only in trial-specific trainings given to the trial team and in basic good clinical practice training, and may not be involved otherwise. 4.3.3. The sponsor must inform the contract research organisation in advance of the trainings to be provided to the site staff member or data entry support personnel and must transmit the training records. 4.4. Responsibilities of the Contract Research Organisation 4.4.1. When providing the site organisation management service, it may not assign its personnel at the same time to trials conducted by different investigators having different sponsors. However, if the Turkish Medicines and Medical Devices Agency (TİTCK) deems it appropriate and it is justified by the applicant

if justified, the relevant personnel may also serve simultaneously in trials with a different sponsor, and this matter must be notified to the sponsor. 4.4.2. The assignment or assignment termination notifications to be made in accordance with the relevant legislation for the personnel to be assigned to the site management organization service are the responsibility of the contract research organization. 4.4.3. It must be ensured that site staff or data entry support personnel have received the relevant training on basic good clinical practice and the trial in which they will serve, and their records must be kept. 4.4.4. The contract research organization must guarantee that it provides the necessary training for site staff or data entry support personnel to properly fulfill their responsibilities. 4.4.5. The contract research organization must make the notifications regarding the site staff or data entry support personnel in accordance with the relevant legislation. 4.4.6. Regarding data entry, the sponsor, coordinator, or participant's physician must be informed by regular reporting at regular intervals. 5. NOTIFICATION 5.1. Applications must be made in accordance with the application forms and cover letter templates published on the website of the Turkish Medicines and Medical Devices Agency (TİTCK). 5.2. In order for the site management organization services to be provided by the contract research organization, the personnel to be assigned must be notified by the contract research organization to the TİTCK and the ethics

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committee. These notifications may be made simultaneously. The ethics committee and TİTCK notifications regarding the relevant personnel must be made after the TİTCK authorization letter has been obtained in order for the clinical trial to commence. However, the ethics committee or TİTCK may cancel this assignment with justification. The relevant personnel may commence their duty at the trial site as of the date of the TİTCK notification. 5.3. The relevant personnel may attend the investigators' meetings to be held prior to the trial, provided that the contract research organization holds internal authorization documents for them and that the required authorization is obtained from TİTCK in accordance with the relevant legislation. If such person is a staff member of the center or institution where the clinical trial is being conducted, they may also be included in the trial team in the status of sub-investigator. 6. DUTIES AND RESPONSIBILITIES OF SITE STAFF WITHIN THE SCOPE OF THE SITE MANAGEMENT ORGANIZATION SERVICE 6.1. The duties and responsibilities of the site staff within the scope of the site management organization service are set out below: 6.1.1. If there are referral centers that will ensure that patients meeting the trial criteria are referred to the trial site, to visit these centers and physicians and to remind them of the volunteer screening conditions, 6.1.2. During the enrollment (recruitment) period, to review hospital files under the supervision of the responsible investigator, provided that the necessary permissions are obtained for the purpose of assisting in volunteer pre-screening procedures when necessary and in compliance with confidentiality principles, and to seek to identify suitable volunteers, 6.1.3. To assist the personnel involved in the trial in the screening of volunteers whom the responsible investigator considers to be in accordance with the trial protocol (such as organizing the volunteers' appointments and assisting the personnel involved in the trial with non-invasive procedures authorized by the responsible investigator),

6.1.4. To ensure the filing of the informed consent forms (ICF) obtained from volunteers and to remind the responsible investigator to provide a copy to the volunteer, 6.1.5. To ensure the organization and follow-up of appointments so that volunteer visits are conducted on time, 6.1.6. To make the necessary preparations for the responsible investigator to carry out the procedures in accordance with the trial protocol during visits (for example, to prepare a list of the procedures to be performed and to remind the responsible investigator or other investigators), 6.1.7. To send blood samples obtained from volunteers to the central or local laboratory in accordance with the trial protocol, to organize and follow up on courier procedures, to follow up on laboratory reports, to ensure their review by the responsible investigator or an investigator who is a physician or dentist, to file them, and to ensure that, if there is an abnormal finding noted or flagged in the report, the relevant persons are informed so that immediate action is taken, 6.1.8. To ensure that complete records are kept of the procedures performed by the responsible investigator or an investigator who is a physician or dentist and to assist in the filing of documents, 6.1.9. To assist in ensuring that information pertaining to volunteers is completely recorded in hospital source documents (patient file, trial file), 6.1.10. To assist, within the scope of their authority, the responsible investigator or an investigator who is a physician or dentist in completely and in no way altering the entry of volunteer data into the paper or electronic case report form (e-CRF), its file, or screening cards, 6.1.11. To ensure that documents specific to the trial that vary, such as laboratory results, ECG assessments, IVRS confirmation faxes, and scales, are reviewed and signed in a timely and complete manner by the responsible investigator or an investigator who is a physician or dentist, and to ensure that these are filed as required, 6.1.12. To take the necessary measures to ensure that trial materials, patient diaries, laboratory kits, and patient identification cards are available in sufficient quantities throughout the trial, 6.1.13. To ensure that the relevant form for safety reports reported by volunteers that meet the definition of a serious adverse event is completed by the responsible investigator or an investigator who is a physician or dentist and immediately reported to the sponsor, and to follow up on these events (for example, to ensure the procurement of patients' discharge summaries, hospital admission records, or death reports),

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6.1.14. During the trial, to ensure that all documents that must be notified to the ethics committee and TİTCK regarding the trial, such as investigator's brochure amendments, protocol amendments, and investigator notifications, are notified and to follow up on the decisions, 6.1.15. To place all correspondence received from the sponsor and the ethics committee in the responsible investigator's file, 6.1.16. To ensure that questions formulated regarding volunteer information matters requiring clarification are answered in a timely manner by the responsible investigator, 6.1.17. To ensure the provision of the necessary volunteer information requested by the unit performing data analysis or other assessment committees during the interim analysis periods conducted while the trial is ongoing, 6.1.18. To ensure that the letter indicating the conclusion of the trial is submitted to the ethics committee, 6.1.19. To assist in establishing the environment in which the trial files will be stored. 7. DUTIES AND RESPONSIBILITIES OF DATA ENTRY SUPPORT PERSONNEL WITHIN THE SCOPE OF THE DATA ENTRY SUPPORT SERVICE

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7.1. The duties and responsibilities of data entry support personnel within the scope of data entry support services are set out below: 7.1.1. During the enrollment (recruitment) period, subject to obtaining the necessary permissions, to review hospital files under the supervision of the participant's physician, in compliance with confidentiality principles, in order to assist with participant screening procedures when necessary, and to attempt to identify suitable participants (volunteers), 7.1.2. To ensure that the informed consent forms (ICF) obtained from participants (volunteers) are filed, and to check the suitability of the informed consent forms or data usage permission forms of patients whose data will be entered, 7.1.3. To check whether the necessary permissions required for the commencement of the trial have been obtained, 7.1.4. To check the conformity of the patient data entered during visits to the trial protocol and to assist, under the supervision of the participant's physician, in transferring them to the relevant forms, 7.1.5. To assist, within the scope of the authority granted, the coordinator or the participant's physician in entering participant data completely and without making any alterations whatsoever onto paper or electronic case report forms (e-CRF), into files, and onto screening cards, 7.1.6. During the interim analysis periods conducted while the trial is ongoing, to ensure the provision of the necessary participant (volunteer) information requested by the department performing the data analysis or by other evaluation committees, to respond to data query forms relating to the trial data, and to send them to the relevant data processing units. 8. REPEALED PROVISIONS The "Guideline on the Principles of Site Management Organization in Clinical Trials", which was put into effect by the Approval of the Presidency No. 95052 dated 06.08.2014, has been repealed. 8. ENTRY INTO FORCE This Guideline enters into force on the date of its approval.

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ANNEX–1: SITE PERSONNEL REQUEST FORM BY THE COORDINATOR/PRINCIPAL INVESTIGATOR FOR SITE MANAGEMENT ORGANIZATION SERVICES ___/___/20__ We request that "ENTER THE NAME OF THE SITE PERSONNEL", on whom we have agreed with "ENTER THE NAME OF THE ORGANIZATION", join our trial team in order to assist in the conduct of trial procedures at our trial site, when necessary and in accordance with the authorities granted by the relevant legislation, within the scope of the clinical trial with protocol number "ENTER THE PROTOCOL NUMBER" titled "ENTER THE TITLE OF THE CLINICAL TRIAL", for which I serve as coordinator/principal investigator and of which "ENTER THE NAME OF THE SPONSOR" is the sponsor. I undertake that the site personnel assigned for site management organization services performs their duties independently of the sponsor, complies with the job descriptions specified in the authorization list prepared in accordance with the relevant legislation, and has no authority to alter the clinical trial data in any way whatsoever. I acknowledge that the sponsor of the trial is informed of this participation and that, if necessary, I will make the administrative notifications at our site. Name/Surname of the Coordinator/Principal Investigator: Institution: Date/Signature: The

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investigator's request for site management organization services is within our knowledge. Name/Surname of the Sponsor's Authorized Representative: Date/Signature:

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ANNEX–2: INTRA-COMPANY AUTHORIZATION DOCUMENT OF THE CONTRACT RESEARCH ORGANIZATION ___/___/20__ Within the scope of the clinical trial with protocol number "ENTER THE PROTOCOL NUMBER" titled "ENTER THE TITLE OF THE CLINICAL TRIAL", of which "ENTER THE NAME OF THE SPONSOR" is the sponsor, "ENTER THE NAME OF THE SITE PERSONNEL" has been authorized by "ENTER THE NAME OF THE ORGANIZATION" as site personnel for the site "ENTER THE NAME OF THE SITE WHERE THE SITE PERSONNEL WILL SERVE", in order to assist in the conduct of trial procedures when necessary and in accordance with the authorities granted by the relevant legislation. On behalf of the Contract Research Organization, Name/Surname of the Authorized Person: Date/Signature: Note: This document must be on the institution/organization's letterhead. A copy of the authorized person's intra-company signature circular must be attached.

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ANNEX-3: INTRA-COMPANY ACCEPTANCE OF DUTY DOCUMENT OF THE CONTRACT RESEARCH ORGANIZATION ___/___/20__ Within the scope of the clinical trial with protocol number "ENTER THE PROTOCOL NUMBER" titled "ENTER THE TITLE OF THE CLINICAL TRIAL", of which "ENTER THE NAME OF THE SPONSOR" is the sponsor, I, "ENTER THE NAME OF THE SITE PERSONNEL", have been authorized by "ENTER THE NAME OF THE ORGANIZATION" as site personnel at the site "ENTER THE NAME OF THE SITE WHERE THE SITE PERSONNEL WILL SERVE", in order to assist in the conduct of trial procedures when necessary and in accordance with the authorities granted by the relevant legislation. I declare that I accept the duty given to me for the performance of the specified procedures throughout the clinical trial. Name/Surname of the Site Personnel Date/Signature Note: This document must be on the institution/organization's letterhead.

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ANNEX-4: CURRENT STATUS TABLE OF SITE PERSONNEL PROJECTS 1 Name and Surname of the Principal Investigator: Clinical Trial Code Site/Institution Name

2 Name and Surname of the Principal Investigator: Clinical Trial Code Site/Institution Name

3 Name and Surname of the Principal Investigator: Clinical Trial Code Site/Institution Name

4 Name and Surname of the Principal Investigator: Clinical Trial Code Site/Institution Name

5 Name and Surname of the Principal Investigator: Clinical Trial Code Site/Institution Name

On behalf of the Contract Research Organization;

Signature/Date: Name/Surname (Authorized Representative of the Contract Research Organization): Signature/Date: Name/Surname (Site Personnel):

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ANNEX–5: DATA ENTRY SUPPORT PERSONNEL REQUEST FORM BY THE COORDINATOR/PARTICIPANT'S PHYSICIAN FOR DATA ENTRY SUPPORT SERVICES ___/___/20__ We request that "ENTER THE NAME OF THE DATA ENTRY SUPPORT PERSONNEL", on whom we have agreed with "ENTER THE NAME OF THE ORGANIZATION", take part in the study titled "ENTER THE TITLE OF THE STUDY" with protocol number "ENTER THE PROTOCOL NUMBER" (if any), within the scope of which I serve as coordinator/participant's physician and of which "ENTER THE NAME OF THE SPONSOR" is the sponsor, in order to provide assistance at our trial site when necessary in accordance with the relevant legislation. I undertake that the personnel assigned for data entry support services perform their duties independently of the sponsor, comply with the job descriptions, and have no authority to alter the study data in any way whatsoever. I acknowledge that the sponsor of the study is informed of this participation and that, if necessary, I will make the

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administrative notifications at the relevant places. Name/Surname of the Coordinator/Participant's Physician: Institution: Date/Signature: The investigator's request for data entry support services is within our knowledge. Name/Surname of the Sponsor's Authorized Representative Date/Signature:

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ANNEX–6: INTRA-COMPANY AUTHORIZATION DOCUMENT OF THE CONTRACT RESEARCH ORGANIZATION ___/___/20__ Within the scope of the study titled "ENTER THE TITLE OF THE STUDY" with protocol number "ENTER THE PROTOCOL NUMBER" (if any), of which "ENTER THE NAME OF THE SPONSOR" is the sponsor, "ENTER THE NAME OF THE DATA ENTRY SUPPORT PERSONNEL" has been authorized to provide assistance in accordance with the relevant legislation. On behalf of the Contract Research Organization, Name/Surname of the Authorized Person: Date/Signature: Note: This document must be on the institution/organization's letterhead. A copy of the authorized person's intra-company signature circular must be attached.

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ANNEX-7: INTERNAL DUTY ACCEPTANCE DOCUMENT OF THE CONTRACT RESEARCH ORGANIZATION ___/___/20__ Within the scope of the trial titled "ENTER TRIAL NAME" with protocol number "ENTER PROTOCOL NUMBER" (if any), sponsored by "ENTER SPONSOR'S NAME", I, "ENTER THE NAME OF THE DATA ENTRY SUPPORT PERSONNEL", have been authorized as data entry support personnel by "ENTER ORGANIZATION NAME" in order to provide assistance in accordance with the relevant legislation, under the supervision and control of the coordinator/investigator physician. I declare that I accept the duty given for the execution of the procedures to be carried out in compliance with the relevant legislation throughout the trial. Name/Surname of the Data Entry Support Personnel: Date/Signature: Note: This document must be on the letterhead of the organization.

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Dates and Issue Numbers of the Publication of Amendments Made to the Guideline Date Issue Number 1. 21.02.2011 1491 2. 11.05.2011 4196 3. 23.08.2011 7481 4. 17.04.2013 43020 5. 06.08.2014 95052

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