1. PURPOSE

This guideline is about the collection, verification, and submission of the reports of adverse events / reactions occurring in clinical drug trials, and code breaking methods.

2. DEFINITIONS

Definitions specified in the Good Clinical Practices Guideline and in the related legislation are valid.

3. RESPONSIBILITIES

3.1. The responsibilities of principal investigator or the investigator who is designated by the principal investigator or sponsor related to adverse event / reaction notifications are explained in the Good Clinical Practices Guideline and in the related legislation.
3.2. Sponsor is responsible for safety assessment regarding investigational product.
3.3. In cases that might affect adversely the health of volunteer and the conduct of the trial or that might alter the permission of Turkey Pharmaceuticals and Medical Device Agency regarding the continuation of the trial, sponsor is responsible for informing immediately all investigators related to the trial, the concerned Ethics Committee, and Turkey Pharmaceuticals and Medical Device Agency.
3.4. Sponsor is responsible for organizing systems and written standard operating procedures that will ensure the required quality standards at every stage related to documentation pertaining to the case, data collection, validation, assessment, archiving, and reporting.
3.5. Notifications related to clinical trials conducted with advanced therapy medicinal products are included in the related guidelines.

4. RECORDING, ASSESSMENT, AND REPORTING OF ADVERSE EVENTS / REACTIONS

4.1. Recording of adverse events on case report form includes the determination and assessment of data in each case, and the identification and recording of alerts requiring specific handling, and the investigation of all other cases.
4.2. Recording case report concerns the assessment of data in individual cases and the determination of individual cases required to be considered specially, the recognition and recording of alerts, and other data recording of cases collectively.
4.3. Individual adverse events should be evaluated by the principal investigator. This evaluation should contain the seriousness of the adverse event and the assessment of causality between investigational product and other concomitant treatments.
4.4. Sponsor should keep the detailed records of all adverse events reported to itself by investigator and should evaluate the seriousness, the causality, and the expected / unexpected status of the adverse event.
4.5. Sponsor should keep the detailed records of all adverse events and should submit these records upon request.
4.6. If Turkey Pharmaceuticals and Medical Device Agency or the concerned Ethics Committee request, sponsor should submit the detailed records of all adverse events reported to itself by concerned investigator.
4.7. The assessment regarding whether an event is serious or not is generally made by the reporting investigator. Seriousness should be determined by considering the comments provided in Appendix-1.
4.8. The assessment whether a causality relationship has a logical possibility or not is generally made by the principal investigator. Causality should be determined by considering the comments provided in Appendix-1.
4.9. All adverse events evaluated as “having a suspected reasonable causal relationship with the

investigational product" by the investigator or sponsor are defined as adverse reactions.

4.10. The causality assessment made by the investigator should not be refused by the sponsor. If sponsor does not agree with the causality assessment of the investigator, both the opinions of investigator and sponsor should be indicated in the report.

4.11. Investigator is responsible for reporting to sponsor all serious adverse events occurring in clinical investigation volunteers. Unless otherwise indicated in the protocol, after termination of the trial, the active follow-up of volunteers with respect to adverse event by investigator is not required.

4.12. After termination of the trial, when the investigator is informed of serious adverse events occurring in the volunteer, he/she should report to sponsor.

4.13. Investigator should report to sponsor immediately all adverse events not included in the protocol or in the Investigator's Brochure.

4.14. Adverse events defined as critical for safety assessments in the protocol or laboratory abnormalities should be reported to sponsor pursuant to reporting requirements and within the time frame indicated in the protocol and in the related legislation.

4.15. The investigator must report to the concerned Ethics Committee, to Turkey Pharmaceuticals and Medical Device Agency, and to sponsor any information requested (especially in case of death of the volunteer).

4.16. Sponsor should ensure the recording of all information about suspected unexpected serious adverse reactions and should ensure their notification to the concerned Ethics Committee and to Turkey Pharmaceuticals and Medical Device Agency within the indicated periods; sponsor should inform the principal investigator about this subject.

4.17. If the nature, seriousness, severity, or reaction outcome of the adverse reaction is not consistent with reference information, it should be assessed as "unexpected".

4.18. The expected / unexpected status should be evaluated according to reference document; for investigational product not registered / permitted in our country, it should be referred to Investigator's Brochure; and for products registered / permitted in our country, it should be referred to summary of product characteristics or information leaflet. Reference document should be specified in the trial protocol and should be included in the application file.

4.19. During the notification and recording procedure, confidentiality standards should be always maintained and the legislation related to data protection should be complied with.

4.20. Sponsor should report suspected unexpected serious adverse reactions (SUSAR) according to the conditions below by indicating the trial coordinator site and the full trial title;

4.20.1. All investigational product and comparator products related suspected unexpected serious adverse reactions occurring in the related trial, ,

4.20.2. SUSARs occurring in other trials being conducted by the same sponsor in our country and in other countries related to the investigational product, spontaneous notifications outside our country, SUSARs defined in a scientific publication, or SUSARs communicated to sponsor by another regulatory authority should be reported at least once every 6 (six) months only in the form of line listing of *SUSARs of foreign origin*.

4.21. Safety issues, that might change the available benefit-risk assessment of the investigational product or that might require to make an amendment in the administration of the investigational product or in the conduct of the trial from beginning to end, should also be reported. For example:

4.21.1. Increase in the prevalence or qualitative change of expected serious adverse reaction that has been evaluated as clinically significant,

4.21.2. Post-trial SUSARs occurring after the volunteer's completion of the clinical trial and reported to sponsor by investigator,

4.21.3. New events developing related to the conduct of the trial or to the development of the investigational product and having the possibility to affect volunteer safety. For example:

4.21.3.1. A serious adverse event that might be related to trial methods and that might change the conduct of the trial,

4.21.3.2. Causing serious risk for volunteer population, for example, the ineffectiveness of the investigational product used in the treatment of a life-threatening disease,
4.21.3.3. Presence of major safety finding pertaining to newly completed animal studies (for example, carcinogenicity),
4.21.3.4. In trials conducted by the same sponsor also in another country with the same investigational product, discontinuation of the trial or all safety findings causing temporary discontinuation
4.21.4. If any, suggestions of the Independent Data Monitoring Committee, valid for the safety of the volunteers.
4.22. Expedited report is generally not required for non-serious adverse reactions.
4.23. Sponsor should notify all investigators participating in the trial concerning the information related to SUSARs that might affect adversely the safety of volunteer.
4.24. Investigator should notify sponsor concerning the information related to SUSARs that might affect the safety of volunteer.
4.25. Sponsor should report SUSARs occurring in the related clinical trial related to the comparator product to the relevant Ethics Committee and to Turkey Pharmaceuticals and Medical Device Agency, also in the case that this product is licensed / permitted in our country.
4.26. When SUSARs are related to placebo (for example, a reaction related to an excipient), the reporting of such cases is of sponsor's responsibility.
4.27. Sponsor should inform Turkey Pharmaceuticals and Medical Device Agency within the periods indicated in the related legislation after obtaining first information related to minimum reporting criteria.
4.28. In each case, the follow-up information should be monitored and the report should be completed as promptly as practicable. The follow-up information should be communicated to the concerned Ethics Committee and to Turkey Pharmaceuticals and Medical Device Agency by sponsor within eight days after it reaches to sponsor.
4.29. Sponsor should notify the concerned Ethics Committee and Turkey Pharmaceuticals and Medical Device Agency concerning all notifications and reports related to safety issues within the periods indicated in the related legislation. Additional follow-up information should also be submitted as soon as possible. Sponsor should also inform all investigators about the subject. However, SUSARs of foreign origin should be reported in a form of line listing at least once every 6 (six) months.
4.30. The information related to the final definition and assessment of an adverse reaction report might not be completed within the period required for reporting. Due to the related legislation, the initial reports should be submitted within the periods specified, as soon as the minimum criteria indicated below are met:
4.30.1. Suspected investigational product,
4.30.2. A definable volunteer (for example; volunteer code number),
4.30.3. Adverse event evaluated as serious and unexpected, where a reasonable, suspected causal relationship is observed,
4.30.4. A definable report source,
4.30.5. If any, trial protocol number.
4.31. If there is deficient information during initial reporting, all appropriate information required for a sufficient causality analysis should be requested from the person writing the report or should be obtained from other available sources. Sponsor should report additional information in the form of follow-up reports after it reaches to sponsor. In some cases, conducting the follow-up of the long term outcome of a certain reaction might be appropriate.
4.32. The preferred method for the notifications to be made to the concerned Ethics Committee and to Turkey Pharmaceuticals and Medical Device Agency should be by fax or in the form of written reporting. The cover letter template related to the notification of these reports is included at the website of Turkey Pharmaceuticals and Medical Device Agency.
4.33. CIOMS-I (Council for International Organizations of Medical Sciences) form is a standard

form for notifications. Nonetheless, other forms may also be used, provided that they are specified in the trial application. However, basic information / data indicated in Appendix-2 should be included in the report.

4.34. All SUSARs occurring outside our country should be reported to the concerned Ethics Committee and to Turkey Pharmaceuticals and Medical Device Agency in a form of line listing and at least once every six months along with a short report of sponsor emphasizing the important main topics.

4.35. Every kind of amendment increasing volunteer risk and every kind of new condition that might affect adversely the safety of volunteer or conduct of trial should be reported to the concerned Ethics Committee and to Turkey Pharmaceuticals and Medical Device Agency as promptly as practicable not exceeding fifteen days.

4.36. In each SUSAR report (initial report and follow-up report), information ensuring to understand whether the report is the same (repetitious) or not should be included. The code of the volunteer where SUSAR is observed, the number of SUSARs, and the time of occurrence, no matter what, should be unique for the same trial. If dual reports are noticed by sponsor, this should be communicated appropriately to the concerned Ethics Committee and to Turkey Pharmaceuticals and Medical Device Agency.

4.37. Sponsor should inform all concerned investigators about the findings that might affect adversely the safety of the volunteers. If appropriate, the said information can be collected in a SUSAR line listing. A short summary of the safety profile that will appear related to investigational product should be added to this line listing.

4.38. In case of blind / masked trials, the line listing should include data related to all SUSARs, no matter what the applied investigational product is (for example, active substance / placebo). Thus, when possible and appropriate, blindness (masking) is preserved and the risk of informing investigators on the identity of the investigational product is prevented.

4.39. If a significant safety issue is detected in the analysis of individual case report or collective data, sponsor should inform all investigators as promptly as practicable. A safety issue that has an effect on the course of the clinical trial or on the development project, including corrections related to temporary discontinuation of the trial or to the safety in the trial protocol, should also be reported to investigators.

4.40. The expectedness of the adverse reaction is determined by the reference safety information of the sponsor. This should be done on previously observed events, not on the basis of the expected from the pharmacological characteristics of a medical product.

4.41. Reference safety information is included in Summary of Product Characteristics (SmPC) / information leaflet (IL) or in Investigator's Brochure. The cover letter submitted together with the application made to Turkey Pharmaceuticals and Medical Device Agency and to the concerned Ethics Committee should refer to the reference safety information.

4.42. If the reference safety information is included in the Investigator's Brochure, the Investigator's Brochure should contain a section of these effects that is clearly explained. This section should contain information about the frequency and the nature of adverse reactions.

4.43. Reference safety information may change during the conduct of the trial. This is a typically important change. For SUSAR reporting, the version of reference safety information at the time of the formation of SUSAR is valid. Thus, a change in the reference safety information affects also the number of adverse events to be reported as SUSAR.

5. THE ORGANIZATION OF THE NOTIFICATIONS OF ADVERSE EVENTS / REACTIONS IN BLIND / MASKED TRIALS

5.1. Before outcome analysis of the trial, the maintenance of the blinding for all subjects participating in the trial is a desired condition. However, a serious adverse event might be an unexpected serious adverse reaction, in this case, the blinding might be broken by sponsor only for that subject, although it is not broken by the investigator.

5.2. If possible and appropriate, the blindness of the personnel that will perform data analysis and that will assess the results when the trial is completed, should be maintained.
5.3. The breaking of the blinding of a single subject by investigator might be performed if it is related to subject safety.
5.4. In a blind/masked trial, the seriousness, the status of expected / unexpected, and the causality relationship of the adverse event should be evaluated by assuming that the investigated product causes the said reaction. If the event meets SUSAR criteria, the blinding should be broken and one of the following three possibilities should be implemented:
5.4.1. *If the product applied to the subject is the investigational product used in that trial*, it should be reported to the concerned Ethics Committee and to Turkey Pharmaceuticals and Medical Device Agency as SUSAR.
5.4.2. *If the product applied to the subject is the comparator product registered / permitted in our country*, the adverse reaction should be reevaluated as expected or unexpected according to summary of product characteristics or information leaflet.
5.4.3. *If it is an unexpected adverse reaction*, it should be reported as SUSAR.
5.5. After breaking of the blinding, the reporting of SUSARs related to placebo is of sponsor's responsibility.

6. THE ORGANIZATION OF THE NOTIFICATIONS OF ADVERSE EVENTS / REACTIONS IN CLINICAL TRIALS RELATED TO DISEASE WITH HIGH MORBIDITY AND HIGH MORTALITY

6.1. In clinical trials related to disease with high morbidity or high mortality, efficacy endpoint or death status might be reported as adverse reaction and the breaking of the blindness might endanger the trial integrity. In such cases, Turkey Pharmaceuticals and Medical Device Agency should be informed beforehand, and provided that it is approved by Turkey Pharmaceuticals and Medical Device Agency, the adverse reaction will be accepted as related to the disease and the unblinding might be accepted. The methods for reporting such adverse reactions should be clearly defined in the protocol.
6.2. In clinical trials related to diseases with high morbidity or mortality, in order to analyze regularly and to analyze the safety data of the on-going trial, to recommend in subjects of whether to continue the trial or not, to amend the trial or not, or to terminate or not, the composition of Independent Data Monitoring Committee (IDMC) is recommended to sponsor.
6.3. The structure and the operation of Independent Data Monitoring Committee should be defined in the protocol. The opinion and recommendations of Independent Data Monitoring Committee should be notified to the related Ethics Committee and to Turkey Pharmaceuticals and Medical Device Agency by sponsor in a report form. However, SUSARs with no efficacy endpoint in the same study should be reported as required.

7. ANNUAL SAFETY REPORTS

7.1. Additional to adverse event / reaction reports, once a year during the clinical trial or upon request, sponsor should submit all available new safety information that will arise during the reporting period in the form of safety report to the related Ethics Committee and to Turkey Pharmaceuticals and Medical Device Agency along with the cover letter sample published at the website of Turkey Pharmaceuticals and Medical Device Agency.
7.2. In case of sponsor's conducting several trials with the same investigational product, annual safety report should include a short general analysis of the actual safety profile of the investigational product based on the experience obtained from all trials conducted by sponsor and from all available data.
7.3. The reference safety information which is in force at the beginning of the notification period should be presented in the attachment of the report.
7.4. The reference safety information which is in force at the beginning of the notification period

is considered as reference safety information during the notification period.

7.5. In the case of significant amendment in the reference safety information during the notification period, they should be submitted in a list in the annual safety report.

7.6. Annual safety report should be formed of three sections:

7.6.1. Section 1: A report related to the safety of the volunteers in the related trial;

7.6.1.1. Sponsor should submit a short safety analysis and benefit-risk assessment regarding the related clinical trial along with its own opinion, should define all new (not previously included in the Investigator's Brochure and/or information leaflet/summary of product characteristics) findings that are related to the safety of the treatments performed with the investigational product and that are known by sponsor, and should submit an analysis evaluating the effect of these with respect to volunteers. If available, sponsor should also add the opinion and recommendations of Independent Data Monitoring Committee to its report.

7.6.1.2. The analysis of possible effects for clinical trial population should be completed and at the same time, the safety profile and the possible effect on the volunteers of the investigational product should also be analyzed by considering all available safety data. The following subjects should be considered:

- The relationship with the treatment dose and duration,
- Reversibility of the effect,
- Observation of not previously defined toxicity in volunteers,
- Increase in the frequency of toxicity observed,
- Overdose and its treatment**,**
- Interactions or other related risk factors,
- Every kind of special safety issue related to special populations such as elderly, children, or any other risk group,
- Favorable and unfavorable experiences during pregnancy or breastfeeding,
- Misuse,
- Risks that might be related to the diagnosis and trial methods used in the clinical trial,
- Risks that might be associated with insufficient quality of the investigational product.

7.6.1.3. The results obtained from non-clinical research related to the investigational products and other experiences having the possibility to affect the safety of the patients should also be evaluated in the report.

7.6.1.4. If any, in order to minimize available risks, the measures suggested in the past or current should also be detailed.

7.6.1.5. A detailed justification about whether amending or updating protocol, volunteer informed consent form, and Investigator's Brochure is required or not should be submitted. This report does not replace the request for protocol amendment.

7.6.1.6. The risk-benefit assessment of the clinical trial should be evaluated as an outcome.

7.6.2. Section 2: A line listing related to all suspected serious adverse reactions (including all SUSARs) arising in the related trial;

7.6.2.1. Annual report should include the line listing related to all suspected serious adverse reaction reports reported during the trial.

7.6.2.2. Line listing includes key information. It is not required that it contains each detail related to cases.

7.6.2.3. No matter how many adverse reactions are reported for a case, it should include each volunteer only once. Namely, if more than one adverse reaction has occurred in a volunteer, all of these should be mentioned. However, adverse reactions should be listed according to the assessment of sponsor with respect to seriousness (finding, symptom, and diagnosis). It is possible that the same volunteer might experience different adverse reactions in different cases. Such experiences should be handled in the form of separate reports. In such cases, the same volunteer might be in a line listing more than once. This case should be indicated in line listings.

7.6.2.4. Cases should be submitted in tables according to body system (standard system organ classification chart).

7.6.2.5. For each trial, there should be a list. However, for active comparator product or placebo, or due to other appropriate and related reasons (for example, cases where different formulas, indications, or administration routes are analyzed in the same trial), separate lists should be submitted.
7.6.3. Section 3: Aggregate summary table of suspected serious adverse reactions arising in the related trial;
7.6.3.1. In addition to line listings pertaining to each case submitted in Section 2, summary tables of all serious adverse reactions observed during the trial should be submitted to enable the general assessment of the trial. In the said tables, serious adverse reaction terms related to finding, symptom, or diagnosis should be submitted. When case numbers are low, submission in verbal expression is more appropriate.
7.6.3.2. Aggregate summary tables should specify the number of reports related to the following:
- For each body system,
- For each adverse reaction term,
- If appropriate, for each treatment arm (investigational product, comparator product, or placebo).
- Unexpected adverse reaction terms should be defined clearly in the table. As an example, table in Appendix-4 can be used.

7.7. The reporting time related to annual reporting starts as of date of first permission granted to the clinical trial by Turkey Pharmaceuticals and Medical Device Agency. Data lock point should be prepared based on the clinical birth date in the world (the approval date of the clinical trial conducted with the related investigational product in our country).
7.8. Starting from this date on, data until the end of the first year should be included in annual safety report. Sponsor should submit annual safety reports within 60 (sixty) days after data lock point.
7.9. Even though sponsor conducts several clinical trials with the same investigational product, sponsor should prepare safety reports, covering required information related to all these trials, separately for each trial.
7.10. Safety report in first-in-man, bioequivalence, and bioavailability studies, and in short term metabolism or pharmacokinetic trials is notified within 90 (ninety) days after the ending of the trial. This report should include minimum line listing, if appropriate, aggregate summary tables and an explanation related to volunteer safety.

8. SUPERSEDED REGULATIONS

"Guideline regarding Collection, Verification, and Submission of the Reports of Adverse Events / Reactions Occurring in Clinical Drug Trials" effective with the Consent dated 19.04.2013 and numbered 43659, has been superseded.

9. EFFECTIVE DATE

This guideline is effective as of date of approval.

10.APPENDIX

APPENDIX-1: EXPLANATIONS RELATED TO DEFINITIONS AND ABBREVIATIONS

Related Investigators: They are investigators actively participating in the conduct of the clinical trial.

Severe - serious: The term of severe is generally used to define the intensity (severity) of a certain event. It is not the same with the term of serious, which is based on patient / event outcome or on action criteria.

APPENDIX-2: SUSAR REPORT DATA

1. Clinical trial:
1.1. If any, protocol number of clinical trial,
2. Details related to volunteer:
2.1. Code number assigned for volunteer by sponsor,
2.2. Initials of volunteer,
2.3. Gender,
2.4. Age and/or date of birth,
2.5. Weight,
2.6. Height.
3. Suspected investigational product:
3.1. Name or notified trade name of investigational product,
3.2. International non-registered name (INN, International Nonproprietary Names),
3.3. Batch number,
3.4. Indication in which suspected investigational product is used,
3.5. Dosage form and amount,
3.6. Daily dose and regimen (please indicate in units of mg, ml, mg/kg, etc.),
3.7. Administration route,
3.8. Start date and time,
3.9. End date and time or treatment period,
3.10. Unblinding: should be indicated as yes/no/not applicable; if answer is yes, the results of this.
4. Other treatments:
4.1. Concomitant medicinal products (including non-prescription products), for non-medicinal products, please provide information indicated in third item).
5. Causality Assessment:
5.1. Causality assessment by investigator,
5.2. Causality assessment by sponsor,
5.3. Explanations.
6. Details of Suspected Adverse Reactions:
6.1. Full definition of reaction/reactions including body region and seriousness and at the same time required criteria for assessing the report as serious should be specified. In addition to description of reported findings and symptoms, the description of reaction should be provided as much as possible.
6.2. Reactions in MedDRA terminology (lowest level term),
6.3. Start date and time of reaction,
6.4. End date of reaction and its period,
6.5. Information on discontinuation and re-continuation of drug,
6.6. Environment where adverse reaction is observed (hospital, polyclinic, house),
6.7. Outcome: Information related to recovery and every kind of sequel; which special tests or treatment might be required and results of these; for a fatal outcome, information related to cause of death and its possible relationship with suspected reaction should be submitted. When possible, every kind of autopsy or other post-mortem findings should be submitted.
6.8. Other information: every kind of information that will facilitate the assessment of the case. For example: findings obtained from medical history including allergy, drug or alcohol addiction, from family history, and special trials.
7. Information related to the person reporting event/suspected adverse reaction:
7.1. Name,

7.2. Address**,**
7.3. Telephone number**,**
7.4. Occupation (specialty field)**.**
8. Information Pertaining to Sponsor and Other Information**:**
8.1. Date of this report**,**
8.2. Source of the report: Clinical trial/ literature review/other (if the source of the report is a literature, please add a copy of this)**,**
8.3. Date of the report initially received by sponsor**,**
8.4. Country where reaction has occurred**,**
8.5. Type of report submitted to authorities: Initial or follow-up (such as first follow-up, second follow-up)**,**
8.6. Name and address of sponsor/manufacturer/company**,**
8.7. Name surname, address, telephone number, and fax number of the responsible person reporting to sponsor**,**
8.8. Case reference number (identity number for the case by sponsor/manufacturer. This number must be the same in initial and follow-up reports related to the same case)**.**

APPENDIX-3: CONTENT OF LINE LISTING

Line listing should contain the following information for each case:
1. Full title of clinical trial**,**
2. Identity number of volunteer in the trial**,**
3. Case reference number in the safety database of sponsor for medicinal products (Case-Identity Information Number)**,**
4. Country where case has occurred**,**
5. Age and gender of volunteer**,**
6. Daily dose of investigational product (dosage form and administration route)**,**
7. Start date of adverse reaction (If not available, best time estimate for start as from initiation of adverse reaction treatment. For an adverse reaction known to occur after discontinuation of treatment, if possible, calculation of time delay)**,**
8. Treatment dates (if not available, nearest estimate of treatment period)**,**
9. Adverse reaction: Description of reaction in the form reported, and if possible, proceeding to diagnosis from findings and symptoms**,**
10. Outcome of volunteer (recovery, sequel, death, unknown)**,**
11. Explanations**,**
12. In case of SUSARs with no blinding/masking, the assessment of results concerning absence of blinding/masking according to the reference document (Investigator's Brochure) valid at the beginning of the period covered by the report**.**

APPENDIX-4: SAMPLE OF AGGREGATE SUMMARY TABLE

Body system/ADR term	Verum	Placebo	Blinded
CNS			
Hallucinations*	2**	2	0
Confusion*	1	1	0
……	……	……	……
Sub total	3	3	0
CV			
...			
……			
Sub total			

* Displays a SUSAR sample.

**Displays the number of reports according to terms (findings, symptoms, and diagnosis).