1. OBJECTIVE

These guidelines have been prepared to provide guidance for collecting, validating and presenting adverse event or reaction reports occurring in the clinical trials of drugs, biological, medicinal and herbal products conducted in our country, and for code breaking methods.

2. DEFINITIONS

The definitions in the Good Clinical Practice Guidelines and relative regulations are applicable.

3. RESPONSIBILITIES

3.1. The responsibilities of investigators in charge, or investigators or sponsors appointed by said investigators regarding safety reports are disclosed in the Good Clinical Practice Guidelines and relative regulations.

3.2. The sponsor is responsible for the safety evaluation of the investigational product.

3.3. In cases which could adversely affect the health of the subjects or the trial, or could change the Turkish Drug and Medical Device Institution's approval for the continuation of the trial, the sponsor must immediately inform all investigators, the coordinator, administrative authority, the relative Ethics Committee and Turkish Drug and Medical Device Institution about the trial.

3.4. The sponsor is responsible for arranging systems and written standard operating procedures to ensure that the necessary quality standards are observed in every step of the case documentation, data collection, validation, evaluation, archiving and reporting.

3.5. Reports concerning clinical trials conducted with advanced medical treatment products are found in the relative guidelines.

4. RECORDING, EVALUATION AND REPORTING OF ADVERSE EVENTS AND REACTIONS

4.1. This encompasses processing adverse events into case report forms, determining and evaluating data in each case, identifying and processing alerts requiring specific handling, and investigating all other cases.

4.2. Case report processing concerns the evaluation of data in individual cases, identification of individual cases requiring specific handling, recognition and processing of alerts, and any other data processing of aggregated cases.

4.3. Individual adverse events should be evaluated by the investigator in charge. This includes the evaluation of the advers event's seriousness and the causality between the investigational products or other concomitant therapies and the adverse event.

4.4. The sponsor must retain detailed records of all adverse events reported to him by the investigator and perform an evaluation with respect to the seriousness, causality and expectedness or unexpectedness of the adverse event or reaction, and should submit these records upon request.

4.5. The assessment of whether an events is serious shall generally be determined by the investigator conducting the reporting process. Seriousness shall be determined taking into account the comments presented in the annex of the guidelines.

4.6. The assessment of whether the causality relationship has a logical probability is generally determined by the investigator in charge. Causality shall be determined taking into account the comments presented in the annex of the guidelines.

4.7. All adverse events judged by either the investigator or the sponsor as "having a reasonable suspected causal relationship to an investigational product" are defined as adverse reactions.

4.8. The causality assessment performed by the investigator should not be refused by the sponsor. If the sponsor disagrees with the investigator's causality assessment, both, the opinion of the investigator and the sponsor should be provided in the report.

4.9. The investigator is responsible for reporting all serious adverse events occurring in the subjects taking part in the clinical trial to the sponsor. Unless indicated otherwise in the protocol or unless the investigator requests an extended follow-up on account of the relative Ethics Committee or Turkish Drug and Medical Device Institution, the investigator does not necessarily have to actively follow the subjects in terms of adverse events after the trial has ended.

4.10. The investigator should report to the sponsor when made aware of serious adverse events occurring in subjects after the trial has been terminated.

4.11. The investigator should immediately notify the sponsor of all adverse events not present in the protocol or Investigator's Brochure.

4.12. Adverse events or laboratory abnormalities identified in the protocol as critical to safety evaluation shall be reported to the sponsor according to the reporting requirements within the time periods specified in the protocol and relative regulations.

4.13. The investigator must submit any requested information (particularly in the case of death of a subject) to the relative Ethics Committee, Turkish Drug and Medical Device Institution, and sponsor.

4.14. The sponsor should enable the recording of all information regarding suspected unexpected serious adverse reactions, and the notification of these to the relative Ethics Committee and Turkish Drug and Medical Device Institution within the specified periods, and should inform the investigator responsible for this matter.

4.15. If the nature, seriousness, severity or outcome of the adverse reaction does not comply with the reference information, it shall be considered as "unexpected".

4.16. The expectedness of an adverse reaction shall be determined by the investigator's brochure for a non-authorised investigational product in our country, and reference document which is the summary of product characteristics or package insert for an authorised product in our country. The reference document should be specified in the trial protocol and should be present in the application document.

4.17. The standards of confidentiality must always be maintained and any relevant legislation on data protection must be followed during the notification and recording process.

4.18. The sponsor should report suspected unexpected serious advers reactions (SUSARs) according to the following situations through specifying the trial coordination centre and the public name of the trial:

4.18.1. All suspected unexpected serious advers reactions relating to the investigational product and comparator, arising in the relative trial,

4.18.2. SUSARs occurring in other trials conducted by the same sponsor with regard to the investigational product in our country or other countries; spontaneous reports from outside our country; SUSARs identified in a scientific journal; or SUSARs transferred from another regulatory authority to the sponsor should only be reported every 6 months as a *foreign based SUSARs* line listing.

4.19. Safety issues which could change the current benefit-risk assessment of the investigational product, or could require changes to be made in administering the investigational product or conducting the entire trial. For example:

4.19.1. An increase or qualitative change in the incidence of the clinically significant, expected serious adverse reaction,

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

4.19.3. New events that develop depending on conducting the trial or the developing the investigational product, and have a possibility of affecting subject safety. For example:

4.19.3.1. Serious advers event that could be related to the trial methods and could change how the trial is conducted,

4.19.3.2. Causing a serious risk for the subject population e.g., lack of efficiency in the investigational product used in the treatment of a life-threatening disease,
4.19.3.3. The presence of a major safety finding belonging to a newly completed animal trial,
4.19.3.4. All safety findings causing the trial to be suspended or temporarily suspended in trials conducted with the same investigational product in a different country by the same sponsor,
4.19.4. Independent Data Monitoring Committee suggestions, if available, which are applicable for the safety of the subjects.
4.20. Expedited reporting is not usually required for non-serious adverse reactions.
4.21. The sponsor should report the relevant information regarding the SUSARs which could adversely affect the safety of subjects to all the investigators enrolled in the trial.
4.22. The investigator should report the relevant information regarding the SUSARs which could affect the safety of subjects.
4.23. The sponsor must report to the relative Ethics Committee and Turkish Drug and Medical Device Institution all SUSARs associated with a comparator product in the concerned clinical trial even if this product is authorised in our country.
4.24. When SUSARs are associated with the placebo (e.g. reaction due to an excipient), it is the sponsor's responsibility to report such cases.
4.25. The sponsor should inform the Turkish Drug and Medical Device Institution within the periods specified in the relative regulations after being initially informed of the minimum reporting criteria.
4.26. The follow-up information of each case should be sought and the report should be completed as fast as possible. The sponsor should communicate the follow-up information to the relevant Ethics Committee and Turkish Drug and Medical Device Institution within eight days of receiving it.
4.27. The sponsor should inform the relevant Ethics Committee and Turkish Drug and Medical Device Institution about all the statements and reports regarding safety issues within the periods specified in the relative regulations. Additional follow-up information should be provided in the shortest period. The sponsor should also inform all investigators about the issue. However, foreign based SUSARs must be reported at least once every 6 months as a line listing.
4.28. Information on the final description and evaluation of an adverse reaction report may not be complete within the required time frames for reporting. For regulatory purposes, initial reports should be submitted within the specified periods as soon as the following minimum criteria are met:
4.28.1. a suspected investigational product
4.28.2. an identifiable subject (e.g. subject code number)
4.28.3. an adverse event assessed as serious and unexpected, and for which there is a reasonable suspected causal relationship
4.28.4. an identifiable reporting source
4.28.5. a protocol number, if applicable.
4.29. In case of incomplete information during the initial reporting, all the appropriate information for an adequate analysis of causality should be sought from the reporter or other available sources. The sponsor should report further information after receiving it as follow-up reports. In certain cases, it may be appropriate to conduct a follow-up of the long-term outcome of a particular reaction.
4.30. The preferred method for reporting to the relevant Ethics Committee and Turkish Drug and Medical Device Institution should be via fax or written reports. The reports made via fax are then required to be submitted as a written report. An exemplary letter regarding the

notification of these reports is found on the website of the Turkish Drug and Medical Device Institution.

4.31. The CIOMS-I (Council for International Organizations of Medical Sciences) form is the standard form for the reports. Furthermore, other forms may be used through being stated in the trial application but the basic information or data specified in the annex of the guidelines should be present in the report.

4.32. All SUSARs from other countries are submitted to the relevant Ethics Committee and Turkish Drug and Medical Device Institution at least every 6 months as a line listing accompanied by a brief report by the sponsor highlighting the main points of concern.

4.33. All kinds of changes which increase the subjects' risk, and all kinds of new cases which could adversely affect the subjects' safety or conduct of the trial should be submitted to the relevant Ethics Committee and Turkish Drug and Medical Device Institution as soon as possible, i.e. no later than 15 days.

4.34. Each SUSAR report (initial report and follow-up report) should contain information to enable understanding whether the report is the same (duplicate) or not. The identification code of the subject who experienced a SUSAR should be unique in the same trial whatever the number of SUSARs and the time at which they occurred. If duplicates are identified by the sponsor, the relevant Ethics Committee and Turkish Drug and Medical Device Institution shall be informed accordingly.

4.35. The sponsor must inform all the concerned investigators of findings which could adversely affect the safety of the subjects. If appropriate, said information may be gathered in a SUSAR line listing. A brief summary of the safety profile to be released regarding the investigational product should be added to this line listing.

4.36. In the case of blind/masked trials, the line listing should include data concerning all SUSARs regardless of which investigational product is administered. Thus, the blindness is maintained if possible and applicable, and the risk of informing the investigators about the identity of the investigational product is avoided.

4.37. If a significant safety issue is identified in the analysis of an individual case report or aggregate data, the sponsor must inform all investigators as quickly as possible. The temporary suspension of the trial or the course of a clinical trial including amendments regarding safety in the trial protocol or a safety issue which has an effect on the development project should be reported to the investigators.

4.38. The expectedness of an adverse reaction is determined by the sponsor's reference safety information. This should not be conducted based on what could be expected from the pharmacological properties of a medicinal product, but previously observed events.

4.39. The reference safety information is found in the summary of product characteristics (SPC)/package insert or investigator's brochure. The application along with the letter submitted to the Turkish Drug and Medical Device Institution and relative Ethics Committee should refer to the reference safety information.

4.40. If the reference safety information is present in the investigator's brochure, the investigator's brochure should include a section clearly describing these effects. This section should include information regarding the frequency and nature of adverse reactions.

4.41. Reference safety information may change during the conduct of the trial. This is a typical significant change. The reference safety information version from when the SUSAR occurred is valid for the SUSAR report. Thus, a change in the reference safety information affects the number of adverse events to be reported as a SUSAR.

5. MANAGING REPORTS OF ADVERSE EVENTS OR REACTIONS IN BLINDED/MASKED TRIALS

5.1. It is desirable to retain the blindness for all subjects enrolled in the trial prior to the results analysis of the trial. However, a serious adverse event may become to be a serious

adverse reaction. In this case, the blind may be broken only for that subject by the sponsor even if it has not been removed by the investigator.

5.2. If possible, the blind should be maintained for the personnel responsible for data-analysis and interpretation of the results once the study has been completed.

5.3. The unblinding of a single subject by investigators can be performed if it is related to the safety of the subject.

5.4. In a blind/masked trial, the seriousness, expectedness and causal relationship of the adverse event should be evaluated assuming that the investigational product caused said reaction. If the case appears to meet the SUSAR criteria, the blinding should be broken and one of the following three possibilities must be considered:

5.4.1. *If the product administered to the subject is the investigational product used in the trial,* the case should be reported as a SUSAR to the relevant Ethics Committee and Turkish Drug and Medical Device Institution.

5.4.2. *If the product administered to the subject is a comparator with a marketing authorisation in our country,* the adverse reaction should be reassessed for expectedness according to the summary of product characteristics or package insert.

5.4.3. *If the adverse reaction is unexpected,* it should be reported as a SUSAR.

5.5. Reporting the SUSARs are associated with a placebo after unblinding is the sponsor's responsibility.

6. MANAGING REPORTS OF ADVERSE EVENTS OR REACTIONS IN CLINICAL TRIALS CONCERNING HIGH MORBIDITY AND HIGH MORTALITY DISEASES

6.1. In clinical trials concerning high morbidity and high mortality diseases, efficacy end-points or mortality could be reported as adverse reactions and the integrity of the trial may be compromised when the blind is broken. Under such circumstances, it may be appropriate to reach an agreement to not unblind through considering the adverse reaction disease-related on condition that the Turkish Drug and Medical Device Institution and relevant Ethics Committee are informed in advance and that consent is received from the Turkish Drug and Medical Device Institution and relevant Ethics Committee. Methods for reporting such adverse reactions must be clearly defined.

6.2. In clinical trials concerning high morbidity and high mortality diseases, sponsors are encouraged to appoint an Independent Data Monitoring Committee (IDMC) to give advice on reviewing safety data on the ongoing trial on a regular basis and when necessary recommending to the sponsor whether to continue, modify or terminate the trial.

6.3. The composition and operation of an Independent Data Monitoring Committee must be described in the protocol. The opinion and recommendations of the Data Monitoring Committee should be notified the sponsor to the relevant Ethics Committee and Turkish Drug Medical Device Institution as a report. However cases of SUSARs, in these same studies, that are not efficacy endpoints should be reported as usual.

7. ANNUAL SAFETY REPORTS

7.1. The sponsor shall submit all current new safety information which will emerge during the reporting period as well as reports of adverse events or reactions to a relevant Ethics Committee and the Turkish Drug and Medical Device Institution once a year throughout a clinical trial, or upon request as a safety report with the exemplary letter published on the website of the Turkish Drug and Medical Device Institution.

7.2. If the sponsor conducts numerous trials with the same investigational product, the annual safety report should include a brief general analysis of the actual safety profile of the investigational product based on experience gained from all trials conducted by the sponsor and all current data.

7.3. The reference safety information in force at the beginning of the reporting period should be provided in the report annex.

7.4. The reference safety information in force at the beginning of the reporting period is considered as reference safety information throughout the reporting period.
7.5. If significant changes are made to the reference safety information throughout the reporting period, these should be provided as a list in the annual safety report.
7.6. The annual safety report should consist of three parts:
7.6.1. *Part 1:* Report of the subjects' safety in the concerned trial.
7.6.1.1. Along with his/her personal view, the sponsor should present a brief safety analysis and benefit-risk assessment regarding the clinical trial; should notify all new (not previously present in the investigator's brochure or package insert/summary of product characteristics) findings concerning the safety of the treatments, and known by the sponsor; and should provide an analysis assessing the effects of these in terms of the subjects. Views and suggestions from the Independent Data Monitoring Committee, if any, should also be attached to the report.
7.6.1.2. The possible effects for the clinical trial population should be analysed as well as the safety profile of the tested investigational product and its implication for subjects, taking into account all available safety data. The following points should be considered:
- relation of the dose and duration of the treatment
- reversibility of the effect
- evidence of previously unidentified toxicity in the subjects
- increased frequency of toxicity
- overdose and its treatment
- interactions or other associated risks factors
- any specific safety issues related to special populations, such as the elderly, children or any other at risk groups
- positive and negative experiences during pregnancy or lactation
- abuse
- risks which might be associated with the investigation or diagnostic procedures used in the clinical trial
- risks which might be associated with insufficient quality of the investigational product.

7.6.1.3. The report should also consider results of non-clinical studies or other experience with the investigational product and other experiences that are likely to affect the subjects' safety.
7.6.1.4. Measures previously or currently proposed to minimise present risks, if available, should be elaborated.
7.6.1.5. A detailed rationale for whether or not it is necessary to amend or update the protocol, consent form, patient information insert and the investigator's brochure should be given. This report will not replace the request for protocol amendments.
7.6.1.6. Finally, the risk-benefit evaluation of the clinical trial should be provided.
7.6.2. *Part 2:* A line listing of all suspected serious adverse reactions (including all SUSARs) that occurred in the concerned trial.
7.6.2.1. The annual report should include a line listing regarding all suspected serious adverse reaction reports reported during the trial.
7.6.2.2. The line listing provides key information but not necessarily all the details usually collected on individual cases.
7.6.2.3. It should include each subject only once regardless of how many adverse reactions are reported for the case. If there is more than one reaction in a subject, they should all be mentioned but the adverse reactions should be listed in terms of severity (sign, symptom or diagnosis) as judged by the sponsor. It is possible that the same subject may experience different adverse reactions on different occasions.

Such experiences should be treated as separate reports. Under such circumstances, the same subject might be included in a line listing more than once. This case should be specified in the line listings.

7.6.2.4. Cases should be tabulated by body system (standard organ system classification scheme).

7.6.2.5. There should be one listing for each trial, but separate listings might be provided for the active comparator or placebo, or when appropriate and relevant for other reasons (e.g. in cases where different formulations, indications or routes of administration are studied in the same trial).

7.6.3. *Part 3:* An aggregate summary tabulation of suspected serious adverse reactions that occurred in the concerned trial.

7.6.3.1. In addition to individual cases' line listings provided in part 2, summary tabulations of all serious adverse reactions that occurred during the trial should be provided to allow an overview of the trial. In said tabulations, serious adverse reaction terms for signs, symptoms or diagnoses should be presented. When the number of cases is very small, a narrative description would be more suitable.

7.6.3.2. The aggregate summary tabulation should specify the number of reports:

- for each body system
- for each adverse reaction term
- for each treatment arm, if applicable (investigational product, comparator or placebo).

7.6.3.3. The unexpected adverse reaction terms should be clearly identified in the tabulation. The table in the annex of the guidelines can be used.

7.7. The reporting time frame for annual reports starts with the date of the first authorisation of the clinical trial by the Turkish Drug and Medical Device Institution. The data cut off point should be prepared based on the approval date of the clinical trial conducted in our country with the relative investigational product.

7.8. The anniversary of this date is designated as the cut off for data to be included in the annual safety report. The sponsor should submit the annual reports within 70 days of the data lock point.

7.9. Even if the sponsor is conducting numerous clinical trials with the same investigational product, the sponsor should separately prepare the safety reports for each trial, including necessary information regarding all these trials.

7.10. The first-in-man trial, bioequivalence and bioavailability studies and subsequent safety report in the short term metabolism or pharmacokinetic studies should be notified within 90 days of the end of trial. This report should contain the minimum line listing, aggregate summary tabulations, if appropriate, and a statement regarding the subjects' safety.

8. REPEALED REGULATIONS

"Guidelines on the Collection, Verification and Submission of Reports on Adverse Events/Reactions Arising During Clinical Trials of Drugs and Biological Products" which was enforced with the Official Approval no. 95052 on 06.08.2014 has been repealed and changed to "Guidelines for Safety Reports in Clinical Trials".

9. ENFORCEMENT

These Guidelines are enforced on their approval date.

10. ANNEXES

ANNEX -1: COMMENTS ON DEFINITIONS AND ABBREVIATIONS

Relevant Investigators: Investigators which are actively involved in conducting clinical trials.

Severe-serious: The term "severe" is generally used to describe the intensity (severity) of a specific event.

ANNEX -2: SUSAR REPORT DATA

1. Clinical trial:

1.1. Protocol number of the clinical trial, if available

2. Subject's details:

2.1. Sponsor's subject identification number

2.2. Subject initials

2.3. Gender

2.4. Age or date of birth

2.5. Weight

2.6. Height

3. Suspected investigational product:

3.1. Name of the investigational product or brand name as reported

3.2. International Non-proprietary Name (INN)

3.3. Batch number

3.4. Indication(s) for which suspected investigational product was used

3.5. Dosage form and strength

3.6. Daily dose and regimen (specify units e.g. mg, ml, mg/kg)

3.7. Route of administration

3.8. Starting date and time of day

3.9. Stopping date and time, or duration of treatment

3.10. Unblinding: yes/no/not applicable. The results thereof if the answer is yes.

4. Other treatment(s):

4.1. For concomitant medicinal products (including non-prescription/OTC medicinal products) and non-medicinal products provide the same information as listed for the third article.

5. Evaluation of causality:

5.1. Investigator's evaluation of causality

5.2. Sponsor's evaluation of causality

5.3. Remarks

6. Details of suspected Adverse Drug Reaction(s):

6.1. Full description of reaction(s) including body site and severity, as well as the criteria for regarding the report as serious should be given. In addition to a description of the reported signs and symptoms, attempts should be made to establish the reaction as soon as possible.

6.2. Reactions in MedDRA terminology (lowest level term)

6.3. Start date and time of onset of the reaction

6.4. End date and duration of the reaction

6.5. De-challenge and re-challenge information of the drug

6.6. Setting (e.g. hospital, out-patient clinic, home) where the adverse reaction is observed

6.7. Outcome: Information on recovery and any sequelae; which specific tests or treatment may have been required and their results; cause of death for a fatal outcome, and information on its possible relationship with the suspected reaction should be provided. Any autopsy or other post-mortem findings should also be provided when available.

6.8. Other information: Any relevant information to facilitate the assessment of the case. For example, medical history including allergy, drug or alcohol abuse, family history, findings from special investigations.

7. Details on the reporter of the event or suspected adverse reaction:
7.1. Name
7.2. Address
7.3. Telephone number
7.4. Profession (speciality)
8. Sponsor details and other details:
8.1. Date of this report
8.2. Source of report: Clinical trial/literature information/other (provide a copy if the source of the report is literature)
8.3. Date on which the report was first received by the sponsor
8.4. Country in which the reaction occurred
8.5. Type of report filed to authorities: initial or follow-up (first follow-up, second follow-up, etc.)
8.6. Name and address of sponsor/manufacturer/company
8.7. Name, address, telephone number and fax number of the person responsible for reporting to the sponsor
8.8. Case reference number (ID number of the sponsor/manufacturer for the case. This number must be the same for relative initial and follow-up reports on the same case.)

ANNEX -3: CONTENT OF LINE LISTING

The line listing should include the following information in each case:

1. Public name of the clinical trial
2. Subject's identification number in the trial
3. Case reference number (Case-ID Information-Number) in the sponsor's safety database for medicinal products
4. Country in which the case occurred
5. Age and sex of trial subject
6. Daily dose of investigational product (dosage form and route of administration)
7. Date of onset of the adverse reaction (if not available, best estimate of time to onset from therapy initiation) (Calculation of time lag for an adverse reaction known to occur after cessation of therapy, if possible)
8. Dates of treatment (if not available, estimate of closest time of treatment)
9. Adverse reaction: Description of the reaction as reported, and making a diagnosis with the signs and symptoms, if possible
10. Patient's outcome (recovery, sequelae, death, unknown)
11. Comments
12. The evaluation of results regarding no blinding/masking as per the reference document in force at the beginning of the period covered by the report, in the case of SUSARs without there being blinding/masking.

ANNEX -4: EXAMPLE FOR AN AGGREGATE SUMMARY TABULATION

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

* indicates an example of a SUSAR

** indicated the number of reports according to the terms (signs, symptoms and diagnoses)

The Dates and Issues on Which the Changes to the Guidelines Were Published

	Date	**Issue**
1.	28.01.2009	616
2.	20.04.2009	2716
3.	22.10.2009	6829
4.	16.03.2010	1577
5.	24.12.2010	8066
6.	05.09.2011	7668
7.	19.04.2013	43659
8.	10.05.2013	50838
9.	06.08.2014	95052