1. AIM AND SCOPE

This guideline is prepared for regulating minimum conditions in order to plan, conduct and review observational drug studies.
Retrospective studies are out the scope of this guideline.

2. DEFINITIONS

2.1. **Observational Drug Study:** These are epidemiologic studies where data on spontaneously prescribed drugs in patients with ongoing treatment in accordance with current diagnosis and treatment guidelines of the Ministry for indications, posology and administration forms of drugs authorized in Turkey.
2.2. **Coordinator Physician or Dentist**: The physician or dentist with doctorate or specialist degree who is assigned in order to be responsible for ensuring coordination between participant physician, institution/organization where the study is conducted and the sponsor.
2.3. **Participant Physician**: The physician collecting data from patients in conformity with observational drug study plan/protocol.

3. GENERAL CONDITIONS

3.1. In observational drug studies, it is the principle that treatment of the patient should be started when the decision is made for enrolling the patient to the study. The drug started before the patient is enrolled to the study can be prescribed by coordinator physician or participant physician during or after the study.
3.2. In observational drug studies, it is necessary to plan, conduct and review in accordance with current diagnosis and treatment guidelines of the Ministry related with relevant disciplines.
3.3. These studies should have medical and scientific aim which is formulated with regards to a previously designed question. The design selected (basis of the comparison, interval and scope of patient's examination, number of patients) and the method planned in relation with collection and review of data should be suitable for finding an answer to said question.
3.4. In order for a study to be regarded as observational drug study, the prescribing physician should not be under any influence. The drug should not be prescribed in order to enroll the patient to the observational drug study. Prescription of the drug and enrolling a patient to the observational drug study are two issues which should be regarded as independent from each other. This differentiation is ensured in accordance with the example that a patient is enrolled into the study only after the decision of treatment is made.
3.5. These studies cannot be planned or conducted in order to promote use of a preparation.
3.6. Observational drug studies cannot be conducted for promotional purposes.

4. METHODOLOGY

4.1. Observational drug study is one of many methodological tools which serve for collecting information on drugs found in the market. Selection of suitable tool depends on target of observations. Therefore, the tools selected for a particular question should be methodologically suitable for answering the question and it should provide information and be adequate with regards the number of patients.
4.2. In the plan/protocol of observation drug study, the justification of the study and size of the sample as well as literature and other information should be explained in details.
4.3. There are different designs and forms of observational drug studies and observation conditions may also vary depending on the question to be answered. Therefore, scope of diagnostic examinations should be determined or the study should take published guidelines as reference.
4.4. The population subject to the study should normally represent the overall user population as much as possible and it should be a population which is not undergone a selection procedure for purposes other than the specifically targeted aims of the study.

5. AIM OF THE STUDY

Possible aims of observational drug studies can be some of below written issues:
5.1. Determining safety questions of drugs or determining risk factors in order to verify the safety profile expected under marketing conditions,
5.2. Collecting information on prescription habits, consent to the treatment and the compliance,
5.3. Collecting more data on efficiency (for example, characterizing non-responders in groups and sub-groups not included in clinical studies under conditions of routine use)
5.4. Severity of the disease, revealing out the comorbidities, collecting data on special groups (such as elderly, children),
5.5. Collecting data on effects of drugs on life quality.

6. COORDINATOR AND PARTICIPANT PHYSICIANS

6.1. The multi-center observational drug studies, which shall be conducted in healthcare institutions/organizations, are conducted by a study team suitable for quality of the study under presidency of a coordinator physician or dentist.
6.2. Coordinator and participant physician may not be interfered in following issues; which drugs will be used in medical treatment or the conditions requiring discontinuation of the treatment or the conditions necessitating change of the treatment.

7. STUDY PLAN/PROTOCOL

7.1. Before observational drug study is started, an observation and review plan should be prepared which represents most recent advances in medicine and statistics.
7.2. Study plan should include at least following issues;
7.2.1. Justifications about why the observational drug study is a suitable tools for answering questions
7.2.2. Criteria for selecting participant physicians or sites for the study

7.2.3. Inclusion and exclusion of patients to be enrolled into the study,
7.2.4. Target parameters, their relations with the study and their role in answering questions,
7.2.5. Possible cofactors/covariants and the way they will be controlled,
7.2.6. Study period and discontinuation criteria,
7.2.7. Data collection tools required for observation
7.2.8. Number of patients to be included in the study and the countries and number of patients in each country if the study is an international one,
7.2.9. Statistical methods to be used,
7.2.10. Clarification of responsibilities (such as auditing the study, coordination).

8. STUDY APPLICATION AND APPROVAL

8.1. The Sponsor or the coordinator physician (the participating physician in single center studies), if there is no sponsor, should apply to and take the permission from Turkey Pharmaceuticals and Medical Device Agency after approval of ethics Committee is obtained. The study cannot be started before the ethics committee's approval and permission of Turkey Pharmaceuticals and Medical Device Agency are obtained.
8.2. The applicant should prepare a preliminary letter in order to be presented together with the application and he should undersign this letter. Final name of the study should be indicated on the title of preliminary letter. In the text of the letter, attentions should be attracted to special issues about the application such as the special population undergoing the study and the localization of relevant information and documents in the application file should be indicated.
8.3. If the observational drug study will be registered to a public database, it should be committed by the applicant on preliminary letter that the information registered on the database is compatible with the information about the study, which is approved in Turkey.
8.4. Application should be made using the application forms and its attachments published in the web site of Turkey Pharmaceuticals and Medical Device Agency.

8.5. Original copy and a photocopy of the bank receipt indicating the payment of application fee, which is published in the web site of Turkey Pharmaceuticals and Medical Device Agency, should be attached to the application file.
8.6. There is no need to deposit application fee for specialism thesis or studies conducted for academic purposes. However, the document approved by the Head of relevant Department or training officer of the clinic should be attached to the application file, indicating that said study is a specialism thesis or a study for academic purposes.
8.7. Correspondences about the study should be conducted with the sponsor, if available, or with the coordinator physician, if there is no sponsor.
8.8. After approval of ethics committee is obtained in any kind of studies which are for collecting the data of indications, posology and administration forms of the drugs authorized in Turkey, application should be performed and permission should be obtained from Turkey Pharmaceuticals and Medical Device Agency.
8.9. In first application to be performed for Turkey Pharmaceuticals and Medical Device Agency and in substantial amendments, application fee is paid in the way that is not to exceed the application fee which is determined by the Institution and published at web site of institution, and original receipt and copy of it are added to the application dossier. Application fee is not requested for dissertations and studies for academic purposes.

9. DATA COLLECTION PROCESS

The data collection procedure within scope of observational drug study can be conducted in health institutions/organizations and it may be conducted in the form of field screening by directly accessing to study participant, should necessary approvals are obtained, or it may conducted via relevant databases.

10. OBLIGATION OF NOTICE

10.1. The sponsor or the coordinator physician (participant physician in single center studies), if there is no sponsor, findings to be provided from the studies should be notified to Ethics Committee and Turkey Pharmaceuticals and Medical Device Agency, with using annual report form published at web site of Turkey Pharmaceuticals and Medical Device Agency. When it is regarded as necessary, Turkey Pharmaceuticals and Medical Device Agency may request a report earlier.
10.2. Notification regarding completion of the study should be submitted to Ethics Committee and Turkey Pharmaceuticals and Medical Device Agency, with using notification form of termination published at web site of Turkey Pharmaceuticals and Medical Device Agency.
10.3. The sponsor or the coordinator physician (participant physician in single center studies), if there is no sponsor, is responsible for submitting notifications regularly to Ethics Committee and Turkey Pharmaceuticals and Medical Device Agency.
10.4. After the permission is obtained from Turkey Pharmaceuticals and Medical Device Agency, permission should be obtained from Ethics Committee and Turkey Pharmaceuticals and Medical Device Agency for amendments made in only study plan/protocol, patient consent form if any, or form of permission on use of data To obtain permission only from Turkey Pharmaceuticals and Medical Device Agency is adequate for amendments apart from these.
10.5. Any and all types of changes made following commencement of the study are notified to the Turkey Pharmaceuticals and Medical Device Agency in order to obtain permission and the study cannot be continued until the permission is obtained.
10.6. Safety notifications which occur during the study should be submitted as an annual safety report to Ethics Committee and Turkey Pharmaceuticals and Medical Device Agency.

11. INFORMING THE PATIENT AND PATIENT'S CONSENT

11.1. The patient should be at least informed orally other than the normal informing process which is the duty of the physician with regards the treatment decisions. Documentation of patient data should be in conformity with the legislation about confidentiality of data.
11.2. If the patient to be enrolled for the study is a child, if the child is able to explain his/her consent, if the child is under custody of his/her mother or father, informed consent form is taken after legal representative is informed in accordance with relate regulation, in addition of his/her consent.

11.3. If the patients to be enrolled for the study are restricted, if the patient is able to explain his/her consent, informed consent form is taken after legal representative is informed in accordance with relate regulation, in addition of restricted patient's consent.

12. GENERAL AND ETHICAL PRINCIPLES ON PROTECTION OF PATIENTS PARTICIPATING TO THE STUDY

12.1. It is essential to have maximum care for protecting rights of patients participating to the study and to follow ethical rules.
12.2. Before the medical information about patients participating to the study are recorded to relevant form, the subject requested to enroll into the study (or the legal representative, if the patient has not the capacity to consent) should be adequately and understandably (about aim of the study, duration and patient rights) informed by coordinator physician or participant physician.
12.3. The participant patient may leave the study at any time. It is necessary that s/he shall not suffer any loss of normal rights in the future treatment and follow-up due to decision of discontinuation.
12.4. No convincing promotion or financial offer can be made by sponsor, coordinator physician or participant physician in order to ensure patients participate to and continue to stay in the study. However, additional expenses such as transportation, meal arising from participation of patients to the study shall be indicated in the study budget and they are undertaken by sponsor or the coordinator physician (or participating physician in single center studies), if there is no sponsor.
12.5. The Sponsor, coordinator physician or participating physician should guarantee the confidentiality of details about the patient (such as disease and identity details). If the information obtained as a consequence of the study is published, identity details of patients participating to the study may not be disclosed.

13. DATA SAFETY

13.1. It is necessary that standards and advanced methods should be used for safely storing data.
13.2. Outlines of data handled by the sponsor, coordinator physician or participating physician as well as plans about protecting their copies should be included in the study plan. For access restraints and explanation, outlines of legal obligations, if available, should be clearly indicated in study plan.

14. STATISTICAL EVALUATION

Data on observational drug study should be assessed using suitable statistical methods. The planned approach should be previously determined in the study plan; if there is a deviation from this approach in the evaluation, reasons underlying the deviation should be stated.

15. BUDGETING AND INSURANCE

15.1. In observational drug studies, all procedures which may be possibly required other than standard medical care should be undertaken by sponsor or the coordinator physician (the participating physician in single center studies), if there is no sponsor, and a detailed budget should be prepared.
15.2. Presence or absence of patient's social insurance coverage should not influence the scientific aim of the study when patients to be enrolled into the study are selected.
15.3. In observational drug studies, there is no need to insure patients participating to the study.

16. PROVIDING INFORMATION IN THE EVENT THAT STUDY CANNOT BE CONDUCTED

If the study cannot be commenced due to whatsoever reason although approval is obtained or it is prematurely stopped, it is notified to the Ethics Committee and Turkey Pharmaceuticals and Medical Device Agency together with justifications.

17. SHARING DUTY AND RESPONSIBILITY

The sponsor may transfer a part of its duties to contracted research institutions, should a written contract is made. Transfer of duties to contracted research institutions does not release possible legal and penal

responsibility of the sponsor about the issues transferred. The sponsor and the contracted research institution are severally responsible for outcomes of works and procedures subject to the contract.

18. AUDIT

Turkey Pharmaceuticals and Medical Device Agency audits observational drug studies conducted locally or internationally, the localizations where studies are conducted, the sponsor and the contracted research institution, if available with regards the conformity with this guidelines and provisions of other relevant legislation.

19. ARCHIVING AND CONFIDENTIALITY

19.1. After the observational drug study is completed, it is necessary that all documents related with the study should be retained by the sponsor or the coordinator physician (or participating physician in single center studies) for at least four years.
19.2. Confidentiality of study records is fundamental. Such records are only presented to legally authorized subjects or if they are requested by competent authorities.

20. TEMPORARY DISCONTINUATION OR PROHIBITION OF THE STUDY

If it is found during execution of the study that conditions stated when the study is approved are not met or such conditions are violated, Turkey Pharmaceuticals and Medical Device Agency warns the sponsor, the coordinator physician or participating physician and it may temporarily discontinue or prohibit the study, if necessary.

21. PROHIBITIONS AND SANCTIONS

21.1. Observational drug studies cannot be designed and conducted by marketing and sales departments of companies. Such type of studies designed and/or monitored by marketing departments is regarded as non-ethical promotion activity and procedures are applied in accordance with relevant legislation.
21.2. In the event that a study plan / protocol violation is found for marketing and insemination in the study plan / protocol, sale price of said drugs and other expenses related with administration of them to the patient, if available, should be paid by the sponsor.

22. REGULATIONS SUPERSEDED

The Observational Drug Studies Guideline, which was put into for force based on the Authority Consent Numbered 7481 and dated 23.08.2011, is superseded.

23. EFFECTIVE DATE

This guideline comes into effect on the date of approval.